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Authors
The ABPI Pharmacovigilance Expert Network

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1. **Background**

There is a growing trend for pharmaceutical companies to run patient support programmes (PSP) (also known as patient assistance programmes or customer support programmes) to help patients and/or healthcare professionals better manage disease and optimise treatment. For the purposes of these guidance notes, the word ‘patient’ refers to any user of the medication. It is imperative that patient safety is a priority in such programmes and that the marketing authorisation holder (MAH) is able to meet ethical, legal and regulatory obligations including pharmacovigilance (PV) requirements.

Recent PV inspections have revealed that inspectors are particularly interested in PSPs and request evidence that the MAH and any MAH-contracted third party involved in the PSP have well documented processes in place particularly with respect to PV and that MAH PV departments are aware of PSPs and involved appropriately.

Other requirements may be relevant and must be complied with, for example, the ABPI Code of Practice for the Pharmaceutical Industry.

These notes have been developed by the ABPI Pharmacovigilance Expert Network (PEN) and shared with the Medicines and Healthcare Products Regulatory Agency (MHRA).

These notes have been put together as a compilation based on current legislative requirements and on inspection findings. It is up to each MAH to decide, in the context of their circumstances how to apply these notes. The ABPI PEN and MHRA reserve the right to adopt an alternative position should they be called upon to discuss PSPs.

2. **Scope**

These notes are intended to help companies address the PV obligations and regulatory authority expectations related to PSPs. They also provide general direction on how to categorise, and manage adverse event (AE) data collected from PSPs in order to achieve meaningful signal evaluation and meet regulatory requirements. PV departments should be involved at the design stages of a PSP so that PV obligations and regulatory authority expectations are addressed. These notes should be shared by PV departments with the relevant departments such as commercial and marketing so that the principles are considered and documented as formal processes to run all PSPs within the company.

If, however, after reference to these notes you remain unsure of how to categorise AEs for a specific programme, the relevant regulatory authority should be consulted prior to initiation of the PSP.

3. **Definition of a Patient Support Programme (PSP)**

For the purpose of this guidance, a PSP is defined as a service for direct patient or patient carer interaction/engagement designed to help management of medication and/or disease outcomes (e.g. adherence, awareness and education), or to provide healthcare professionals (HCPs) with support for their patients. A PSP definition will only apply if there is direct contact with patients or patient carers. The intention is to support patient care provided by the MAH or by a third party on the MAH’s behalf. Patients need to provide informed consent prior to enrolling on PSPs where they will be directly contacted.
From a broader perspective, PSPs may also include the MAH providing a service or arranging financial assistance for patients who cannot afford their medication (e.g. reimbursement or discount schemes).

For the purpose of this note, the development and/or distribution of patient-orientated material without any direct interaction between MAH and/or third party acting on behalf of the MAH and the patient (e.g. material passed to patients to discuss as part of their treatment) is not considered a PSP.

Common examples of PSPs include:

i. Compliance programmes where consenting patients on a medication are contacted to see how they are managing with their medication.
ii. Call centres where patients or patient carers can contact the MAH to obtain further information on medication or a particular disease area.
iii. “Nurse Educator” programmes where the MAH has hired third party nurses to interact directly with patients to help them properly administer medications and/or manage their disease.

A PSP may include proactive elements if the MAH is initiating contact with the patient or reactive elements if the patient is initiating contact with the MAH, although PSPs often have a combination of proactive and reactive elements. These elements determine safety reporting requirements, see Section 6.

Initiation and management of PSPs requires the involvement of the PV department to ensure appropriate monitoring and reporting of AEs.

4. Elements of PSP design which may impact PV processes

PSPs typically involve contact with the patient by phone, either incoming or outgoing calls, but can also be integrated / facilitated with mail, email or SMS text messaging which may or may not include involvement from HCP. Interactions may also be face to face with the patient.

Specific internet based programmes or website communication may also be a part of a PSP. In such instances there is a possibility that AE reports may be received via MAH sponsored or controlled websites where free text or other functionalities allow the user to submit comments. The MHRA Good Pharmacovigilance Practice Guide states:

‘The MAH must consider the mechanism by which incoming information is monitored to allow the identification and transfer of PV data to the correct person in an appropriate timeframe to meet regulatory reporting requirements’.

Processes should also consider internal reporting timelines to ensure compliance with legislative requirements. All those involved in monitoring websites must be trained in the identification and collection of AEs and aware of the process for forwarding reports to the PV department. From a PV perspective, consideration in the PSP design should be given to (see Section 6 for further details):

i. Whether it is interventional or non-interventional
ii. Solicited or spontaneous/stimulated AE report categorisation
iii. HCP confirmation

1 http://www.mhra.gov.uk/Publications/Regulatoryguidance/Medicines/Othermedicinesregulatoryguidance/CON028495
iv. Treatment of serious and non-serious AE reports
v. Following up AE reports

It is helpful to have a single point of accountability to take overall responsibility and to gain the necessary cross-functional co-operation and endorsement. If a third party will be commissioned to run the PSP on behalf of the MAH it is preferable that the single point of accountability is within the commissioning MAH, rather than the third party.

5. PV elements for documenting in PSPs

The documentation should outline how objectives will be achieved and define the responsibilities of each distinct stakeholder group applicable to the PSP. The documentation will be important in any regulatory authority inspection as evidence that safety requirements have been duly considered and appropriately actioned.

It is strongly recommended that the proposed design and execution of a PSP is fully documented and approved by PV and other relevant parties such as medical, marketing, commercial, business intelligence, market research, patient advocacy and compliance. All PV roles and responsibilities for PV need to be clearly documented. The following sections describe the items suggested for documentation.

5a. Background and purpose

The objective of the PSP should be stated clearly including the need for the PSP by looking at the possible benefit for each distinct stakeholder group e.g. patients, physicians, nurses and pharmacists.

5b. PSP Design

The design of a PSP should be defined following considered discussion and collaboration between key stakeholders (e.g. medical, marketing, commercial, business intelligence, market research, PV and patient advocacy and compliance).

The design is crucial to the overall success of a PSP, so it is important to consider all factors and barriers that may affect how a PSP will progress.

5c. PSP Description

This section should describe the patient flow through the PSP and the key processes that influence it. There should also be some detail on what decision points will be present that will trigger specific courses of action.

I Operational Details – The daily hours of PSP operation should be defined, including any predefined schedule for direct to patient interactions (e.g. home visits, telephone call service, online help etc.). Schematics may be incorporated into this section to aid in the explanation of the customer flow over specified timelines. There should also be consideration as to the suitability of individuals working on the PSP, such as HCP, non-HCP, and background experience, as deemed suitable for the specific PSP.

II Handling Customer Interaction – How patients register should be described, if appropriate, along with a detailed call script, process for follow-up calls, and handling non-contactable patients. This section should describe how call protocols will be used to direct the call flows and activity of the staff. It should be recognised that with phone lines, various company stakeholders
may call the patient; therefore there should be detail on the management of outbound calls. For websites the structure and interaction opportunities should be defined, in addition to the process flow for handling contact and free text information if required. For all interactions with customers, consideration must be given to relevant data privacy legislation and guidelines.

**III Safety Data Handling** – How patients will be able to report AEs and/or product complaints, or other safety related data (such as pregnancy, medication error, overdose etc.) should be detailed. A description of the responsibilities for detection and onward routing of safety reports to the PV group should be given, as well as the description of the responsibilities for the routing of product complaints. Any relevant performance measures, the management of any data capture (what systems and software will be used or required) should/must also be documented and any systems training to be conducted. Arrangements for out of hours safety reporting processes should be described.

**IV Patient Materials** – Details of any registration forms, patient information leaflets or any other materials intended to be sent to the patient should be included here.

**5d. Systems and Data Requirements**

PSPs involve data capture, and PSP documentation should describe its management. Consideration should be given as to whether a current in-house system or database will be used to record data, whether an in-house system requires customisation for the PSP, or whether the MAH will introduce a separate system or database for the PSP. Factors to consider include; the data requirements of the chosen database, what data points will be captured, data anonymisation, format for individual and aggregate data presentation, system performance requirements, storage, back up and continuity plans for any service disruptions.

**5e. Data Protection**

Since PSPs involve the data capture of potentially sensitive information, appropriate data protection must be ensured. You should consult your local Legal contact with regard to the inclusion of suitable confidentiality and data protection provisions and statements.

**6. Patient safety and handling AE data**

The MAH must ensure it complies at all times with both corporate policies and applicable legislation which place strict timelines for PV requirements in order to ensure patient safety.

When a programme involves direct interaction with patients, there is always the possibility that AEs or product complaints relating to any of the MAH’s products may be mentioned. AE report collection is a mandatory requirement when conducting PSPs due to the European wide legislation governing PV for pharmaceutical companies, Volume 9A² are the implementing guidelines for this legislation.

All AE reports must be forwarded to the company point of intake (e.g. local PV department) within internally defined timelines. It is important to note for outsourced PSPs the date of awareness, Day 0, which drives any expedited reporting of AEs, is the date the third party becomes aware not the date the report is passed to the MAH.

Volume 9A² also details special situations where safety data should be collected. These include:

- All side effects (both expected and unexpected)
- Pregnancies*

• Exposure to drug during lactation*
• Exposure via the father*
• Lack of effect*
• Overdose* / medication error* / dispensing error* / accidental exposure */ maladministration*
• Drug abuse* / drug misuse*
• Withdrawal reactions / rebound effects
• Disease progression / exacerbation of existing disease
• Drug - drug / drug - food interactions
• Suspected transmission of an infectious agent
• Product complaints associated with an adverse event
• Reports of unexpected benefit**
• Adverse event reports associated with the use of the product during compassionate use
• Use or in any unlicensed indications (off label use)**
• Counterfeits

*Should be collected even if reported without other signs or symptoms.
** Should be collected in accordance with your internal company policy and procedures.

These special situations and product complaints also fall under the scope of reporting to the PV department, therefore throughout this guidance, wherever reference is made to AEs, the reference also applies to special situations and product complaints as per Volume 9A².

PSPs may fall into several different categories for their management and the reports that they generate should be handled accordingly, as detailed below and summarised in the table in section 6e. The EU qualified person for PV (QPPV) must also be kept aware of significant safety data generated by PSPs.

Careful consideration should be given to the design and collation of data to ensure compliance with relevant PV legislation and reporting requirements. Therefore, it is strongly recommended PSPs are designed in collaboration with PV, medical and legal colleagues.

6a. Interventional or non-interventional

The majority of PSPs are non-interventional because the medicine is prescribed in the usual manner, in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within the current practice and prescription of the medicine is clearly separated from the decision to include the patient in the PSP. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the collected data.

Non-interventional post-authorisation activities are governed by the PV legislation for medicinal products in the EU, see Patient Safety section. Reports from PSPs that are non-interventional can be considered either solicited or (occasionally) spontaneous reports (see definitions below). Analysis of AE data from such studies should also be discussed in Periodic Safety Update Reports (PSURs) as appropriate.

On rare occasions PSPs may be classified as interventional which should be considered under the European Clinical Trials Directive 2001/20/EC.

6b. Solicited or spontaneous/ stimulated report

Adverse events may be actively sought during the conduct of a PSP, in which case they should be considered ‘solicited’ reports. Otherwise, reports arising from an PSP that have not been specifically solicited, i.e. they have been notified by a patient or HCP to the sponsor/MAH without having being actively sought, may be regarded as spontaneous/ stimulated reports. See examples below:

- Solicited report: The MAH phones a patient and asks if they have experienced a side effect associated with their product, the patient mentions an AE.

- Spontaneous/ stimulated reports: The MAH phones a patient for the purposes of refilling a prescription and the patient reports an AE; or the Company is informed that the patient has died. The MAH sets up a phone line for general advice on the product and a patient calls to report an AE.

Adverse drug reaction (ADR) reporting requirements should be determined according to whether an individual case safety report (ICSR) is solicited or spontaneous/ stimulated.

Solicited reports should be managed in the same manner as AE reports arising from interventional clinical trials, and should therefore have an appropriate causality assessment by an HCP or the sponsor/MAH in order to determine whether or not they qualify as suspected ADRs.

Spontaneous/ stimulated reports should be managed in the same manner as spontaneous reports, i.e. they do not necessitate specific individual causality assessment and are considered as suspected ADRs by default. For the remainder of this document, the term spontaneous report shall be used instead of spontaneous/ stimulated.

PSPs may generate both solicited and spontaneous reports. Careful consideration should be given on how the AE data should be collected and classified at each stage so that regulatory requirements can be met.

6c. Serious and non-serious report handling

According to Volume 9A², serious solicited and spontaneous reports must both be entered into the global safety database but non-serious report handling differs between solicited and spontaneous reports:

i. For non-interventional studies or solicited reports, non-serious adverse drug reactions are required in a final study report. Whether or not they have a final report, measures should be included in the PSP design to ensure non-serious data is collated and provided to the MAH in an appropriate time frame in accordance to internal company procedures. Solicited non-serious reports must be appropriately processed by the MAH to ensure adequate safety review by the company. The MAH may decide how best to process the data, by either entering it into the global safety database or by processing separately.

ii. Spontaneous non-serious reports should be entered into the MAH’s global safety database in a timely manner.

Consideration should be given to the handling and timely review of non-serious reports which are also cases of special interest and are defined in Risk Management Plans, for both reactive and proactive PSPs, in accordance with internal company procedures. These AEs should be mentioned in the protocol.

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6d. HCP Confirmation and causality assessment

HCP confirmation is required for all reports, serious and non-serious solicited and spontaneous. An AE report may be considered HCP confirmed if it is reported by an HCP or if it is handled by an HCP involved in a PSP (i.e. employed by the MAH or outsourced third party) where they have access to medical notes, or sufficient knowledge of or access to the patient, in order to make the confirmation. For example, an AE would be considered medically confirmed if a nurse visits a patient and can observe the occurrence of an AE (e.g. rash, injection site reaction). For cases considered non-HCP confirmed, follow-up will be required to be attempted with the reporter to seek HCP confirmation from the patient’s treating physician or other HCP. Where appropriate, the protocol and consent must mention to patients that follow-up will be required with their HCP.

An appropriate causality assessment assigned by the MAH or HCP is required for serious and non-serious solicited reports. Mechanisms for performing follow up must be described in the company SOPs.

6e. Summary of report handling in PSPs

<table>
<thead>
<tr>
<th>Report type</th>
<th>Seriousness</th>
<th>Requirement for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>HCP confirmation</td>
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<tr>
<td></td>
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<td>attempts</td>
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<tr>
<td>Spontaneous/</td>
<td>Serious</td>
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</tr>
<tr>
<td>stimulated</td>
<td>Non-serious</td>
<td>Yes</td>
</tr>
<tr>
<td>Solicited</td>
<td>Serious</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Non-serious</td>
<td>Yes</td>
</tr>
</tbody>
</table>

** Requirement to include this data in signal detection activities (see Section 9)
* Spontaneous reports have implied positive causality

7. Adverse event training

All those involved in running a PSP should undergo training on product information and AE training to support recognition of AEs and ensure appropriate and timely reporting of AEs to the MAH. It is particularly important when the PSP is outsourced that the MAH should ensure it has systems in place to monitor compliance of the outsourced provider. It is important that all training is clearly documented; including who received it, what was provided and the date the training was given. The MAH should ensure that there is a mechanism in place for the provider to receive any important updates on the product safety profile (e.g. new identified or potential risks added to the Risk Management Plan) and the provider staff involved in the PSP should receive additional training as appropriate. In the event of an external regulatory inspection, the inspectors may request to see such documents.
8. Outsourcing

If a third party is identified to run the PSP on behalf of the MAH, it should undergo detailed assessment (due diligence) by the MAH to determine whether it has the capabilities, processes and personnel in place to enable it to run the programme. The MAH should ensure that patient safety is a priority, that all PV regulatory requirements can be met and that third party staff are adequately trained prior to programme start and throughout the duration of the PSP. Provided the due diligence outcome is satisfactory a detailed contract or services agreement should be created (to be signed and agreed between both parties before any activities begin), describing all obligations under the scope of the PSP including all timelines, data protection and confidentiality provisions and back up or continuity plans for any systems employed.

PV and safety data exchange provisions should be defined in the contract between the MAH and the third party. It is important to involve the PV department in developing and finalising language for such contractual arrangements. Contractual arrangements should include:

- definitions
- the process for forwarding AEs, including required timelines
- an agreed reconciliation process between the MAH and the third party to ensure that all AEs have been identified by the third party and that all identified AEs have been forwarded to the MAH
- provision for the MAHs right to audit the third party
- the requirement for AE reporting training before the start of the PSP and training of third party personnel, training of PSP staff who join after the programme has been initiated and re-training of existing staff as applicable, throughout the conduct of the PSP
- the potential need for reports on specific project deliverables and standards of performance. This may incorporate key output findings for the PSP. Documentation of a clear communication process with contacts for both parties including the process for escalation of any issues.

9. Signal Detection

Ideally data from PSPs should be identifiable in the safety database such that signal detection may be carried out separately on the specific set of data, in order to avoid detection of false positive signals. The approach to “signal detection” for PSPs should be considered carefully, considering the source and the quality of the data. The CIOMS VIII report3 may be used to choose and document the most appropriate method, bearing in mind the PSP design and data generation. Non-serious solicited reports may also contain important safety data and therefore both serious and non-serious AE reports should be reviewed and analysed appropriately by the MAH.

3 http://www.cioms.ch/activities/wpviii.htm
Appendix 1 - Definitions

**Adverse event**
Any untoward medical occurrence in a patient or clinical-trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

**Lack of Efficacy**
The apparent failure of the medicinal product or medical technology to bring about the intended beneficial effect on individuals in a defined population with a given medical problem, under ideal conditions of use.

**Product Complaint**
A complaint specific to the product itself, its supporting devices or packaging, as opposed to its effect on the patient. Examples include damaged or missing tablets; wrong strength or colour of tablets; damaged packaging; a label that cannot be read; a liquid that should be clear but is cloudy or contains unexpected particles; a bent needle; a broken syringe; a missing patient information leaflet, or the identification of a potentially counterfeit medicine.

**Solicited report**
Organised data collection schemes which include clinical trials, registries, named-patients use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers or information gathering on efficacy or patient compliance.

For the purpose of safety reporting, solicited reports should be classified as Individual Case Safety Reports from studies and therefore should have an appropriate causality assessment by a Healthcare Professional or the Marketing Authorisation Holder.

**Spontaneous report**
An unsolicited communication by a Healthcare Professional or consumer to a company, regulatory authority or other organisation (e.g. WHO, a regional centre, a poison control centre) which fulfils the following three conditions:

- It describes one or more suspected adverse reactions in a patient
- The patient was given one or more medicinal products
- It does not derive from a study or an organised data collection scheme

Healthcare Professionals or consumers may be stimulated to report a suspected adverse reaction by several situations including:

- A Direct Healthcare Professional Communication
- Early Post-Marketing Phase Vigilance (EPPV), e.g. in Japan
- A report in the press
- Direct questioning of Healthcare Professionals by company representatives.

In these circumstances, provided the report meets the three conditions above, it should be considered a spontaneous report.