Guideline for PV activities in Digital Media (white paper)

Redatto da

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Index

1. SCOPE AND FIELD OF APPLICATION

This proposal of guideline applies to Company digital activities, including sponsored digital activities (i.e. Website, Web Apps, Social Media webpage, ChatBot) impacting pharmacovigilance.

The purpose of this guideline is to provide useful instructions on how to manage pharmacovigilance requirements for digital activities, including future applications such as digital marketing. If e-commerce activity is conducted, relevant sections of this guideline will apply.

2. INTRODUCTION TO DIGITAL MEDIA

The internet has become a central part of our everyday lives. In 2020, there were over 4 billion internet users and over 3.5 billion digital media users worldwide. Digital media is integrated in our daily routines and plays a critical role in the dissemination of public health information and disease prevention guidelines. The most striking feature of digital media, compared to static websites, is that of generating socialization among users who can contribute to the content generation sharing their contributions. For this reason, today the term digital media has been almost completely replaced by the term social media, however the 2 terms are not synonymous and social media must be considered a part of digital media. One thing that's changed since the early days of social media is that many platforms used to focus on one function, such as social networking or image sharing. Now, most established social media platforms have expanded to incorporate live streaming, augmented reality, shopping, social audio, and more. (*Audeh B, Bellet F, Beyens MN, Lillo-Le Louet A, Bousquet C. 2020. "Use of Social Media for Pharmacovigilance Activities: Key Findings and Recommendations from the Vigi4Med Project." Drug Saf 835-851*)

Today, patients compare clinical data on support groups, clinical trials, treatments, and even physicians and thus continue to take an active role in their healthcare. Social media is also a powerful medium to educate consumers about products regarding their benefits as well as side effects. Such awareness often contributes to building trust and acceptance. According to MedData Group, 72% of physicians surveyed were active on Facebook weekly and 38% were active on Instagram and LinkedIn weekly. Via social media, doctors connect with peers from all over the world, extending their network past their in-office or med school colleagues and gaining access to entirely new cohorts. The types of professional content on Facebook that physicians are most likely to engage with include continuing medical education opportunities (37%) and physician online community information (31%). The appeal of getting advice from trusted colleagues or sharing research has attracted millions of physicians worldwide. Of course, all the adverse event data collected in the public posts can be analyzed to identify the key unmet need of the market and help research to identify areas to improve or innovate the products. For these reasons, over the past five years, the pharmaceutical and healthcare industry has experienced widespread digitalization. A 2019 survey of over 100 pharma and bioscience companies found that nearly 30% of pharma companies planned to spend over 50% of their marketing budgets on digital channels by 2022. This number is only expected to increase thanks to the COVID-19 pandemic. Finally, we must take into consideration that all healthcare sectors are impacted by digital media, and scientific societies, academic institutions, patients' associations, hospitals and healthcare institutions are increasing their online presence generating tons of health-related discussions (*Convertino I, Ferraro S, Blandizzi C, Tuccori M. 2018 . "The usefulness of listening social media for pharmacovigilance purposes: a systematic review." Expert Opin Drug Saf 1081-1093 and Richard Sloane, Orod Osanlou, David Lewis, Danushka Bollegala, Simon Maskell, Munir Pirmohamed. 2015 Oct. "Social media and pharmacovigilance: A review of the opportunities and challenges." Br J Clini Pharmacol 910-20*).

There are several methods to classify digital media. One of the most useful is based on usage and function:

Blogs

Blogger, Livejournal, Wordpress are examples of online journals where authors share their opinions and/or experiences on various topics. Blogs can be personal, similar to an online diary, or professional, with opinions related to an area of expertise. Entries vary in length (often 200-1000 words) and frequency (some bloggers post daily or a few times a day, while others post 2-3 times/week) and readers can comment on posts. Entries can include photos, audio/video files. Examples in Healthcare are Sharing Mayo Clinic, American Red Cross, Mercy Health System, McLeod Health.

Microblogging and presence applications

A version of the blog. Twitter, Tumblr and Foursquare are examples. Posts are much shorter and more frequent. Twitter limits length to 280 characters and many users post several times a day. Posts can be sent via cell phone, text messaging, and can include images, audio/video files. St. Jude Children's Research Hospital and Aurora Health Care are 2 examples of institutions present on the web with a well-done twitter account.

Discussion forums

Reddit, Quora are used for asking and answering questions, networking, forming communities around niche- and interest-based topics. Colombia Health's wellness forum, Go Ask Alice!, allows young audiences to pose healthcare questions in an accessible, judgment-free environment. The community forum and casual writing style speaks to Colombia Health's own energy and culture. By attracting young audiences in this vibrant, open community, Colombia builds a loyal readership to draw talent. The blog's topics range from issues of puberty through adulthood, keeping the audience engaged from a young age and into their adult careers. When these readers seek jobs in the healthcare industry, the stickiness of this blog will keep Colombia at the top of mind.

Social audio platforms and formats

Clubhouse, Twitter space and Spotify are social audio platforms for listening to live conversations or podcasts on specific topics. They have thrived during COVID-19 lockdowns while people have been at home with more time to join live conversations. The New England Journal of Medicine is, arguably, the most important general medical publication in the world, drawing together stories on research, reviews, and opinion. The weekly podcasts are about 30 minutes long and are available on Apple, Android, and Windows devices. Second Opinion, is a 25-45 min regular podcast from celebrity physician, Dr Christian Jenner. His sessions take the form of interviews with studio guests on topics like addiction, detection dogs, mental health, death, and more.

Social networks

Facebook, MySpace, LinkedIn are examples of websites where users build online profiles, share updates about themselves, photos, links, etc. and comment on others' updates. A key function is the linking to other profiles, which builds one's social network on a site. Phyzforum and Veterans Health Administration on Facebook are clear examples of healthcare social networks.

PatientsLikeMe, as the name indicates, is a social network platform for patients to communicate and interact. The website offers functions such as 'find patients like you', 'explore the treatment reports', 'learn about symptoms' and 'check for your conditions', etc. It is a good platform for patients or even healthy people to do self-checking when encountering health problems, to explore what medicine would be

effective for the condition and seek peer mental support from those who suffer the same problems. According to the founder, PatientsLikeMe is committed to putting patients' rights and needs in the first place. In that way, social media helps the organization to show care and concern for the patients.

Social media live streams

Twitch, Periscope, YouTube Live streaming, Instagram Live Rooms, Facebook Live are examples of networks with broadcasting functions. Live video streams can range from one person showing themselves on their screen to professionally organized panels with multiple speakers. Livestreaming's popularity exploded during the pandemic when people were stuck at home during lockdowns. Live streams generally offer the opportunity for users to interact live with the hosts. A hospital system in Oklahoma uses its live stream channel to broadcast its own talk show, "OU Medicine Chat." Each episode has a single topic, geared towards either other medical professionals or lay people, and ranges anywhere from ten minutes to half an hour. The simple format (typically two people in a pleasant sitting area talking with each other) is a great place to start for live stream newbies. The added value of this live streaming is that you can take questions from the live stream audience.

Media sharing sites

YouTube, TikTok, Flickr, Instagram or SlideShare are examples of websites where users share photos, videos and files. Uploads are searchable and often can be downloaded and spread by linking to them in the other three types of social media. This linking could increase the reach of a video/photo exponentially and make it viral. Wellmont Health System and Duke University Medical Center on YouTube are good examples of this category. Inova Health System, a not-for-profit healthcare system based in Northern Virginia, has a YouTube page, a Facebook home page and a Twitter account. Its YouTube page is extremely successful among all the three social media tools it has adopted. The YouTube page consists of hundreds of videos. The organization posts all kinds of healthcare-related videos to help users to live a better life, for both healthy people as well as patients.

Closed/private community social media platforms

Sermo, Discourse, Slack, Facebook Groups can create communities, with the possibility of requiring registration or other screening measures for members. Creators can use private groups to bring members of their community together to bond over shared challenges, help answer each other's questions, and feel a sense of professional belonging. Many groups (especially on Facebook) require members to answer a few questions before joining to screen out spammers. Sermo perhaps is the most popular site for healthcare providers on the web today. Sermo is focused on connecting "verified and credentialed" physicians from around the world in 150 countries, with plans to expand even further globally. Doctors can ask their peers anonymous questions regarding patient care in this "virtual doctors lounge." Currently, the site has over 800,000 users.

Disappearing content formats

Snapchat, Instagram Stories, Facebook Stories, LinkedIn Stories are used for sending ephemeral messages such as announcements, limited edition items, or live events privately and publishing timely, in-the-moment content for all followers to view for up to 24 hours. Snapchat has proven to be a good fit for medical practices who want to tell a story and educate their audience at the same time. One real-world example of this is in plastic surgery. Plastic surgeons are using Snapchat as educational tools about the surgeries themselves (the content of which can be graphic at times). Unlike Instagram, which has a reputation for blocking explicit content, Snapchat users have access to raw surgical content, and they are eating it up. Snapchat also allows medical spas and plastic surgeons to post before and after pictures

(with patient consent, of course), giving those physicians another avenue to connect with current and prospective patients.

3. PV AND DIGITAL MEDIA: REGULATORY FRAMEWORK

An analysis of the current requirements or guidance on Digital Activities enacted by the major Regulatory Agencies worldwide (i.e. EMA, FDA and MHRA) was conducted.
The Pharmacovigilance aspects of Digital Activities are currently described, although not in details, in the following EU requirements:

- REGULATION (EU) No 1235/2010 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products
- DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use
- COMMISSION IMPLEMENTING REGULATION (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council
- Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2) - 28 July 2017 EMA/873138/2011 - VI.B.1.1.4

FDA guidance, not specifically referred to pharmacovigilance, are:

- Guidance for Industry Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics - DRAFT GUIDANCE - January 2014
- Guidance for Industry Internet/Social Media Platforms with Character Space Limitations - Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices - DRAFT GUIDANCE - June 2014
- Guidance for Industry Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices - DRAFT GUIDANCE - June 2014

UK references are:

- The Human Medicines (Amendment etc.) (EU Exit) Regulations 2020
- The Association of the British Pharmaceutical Industry (ABPI) Code of Practice for the Pharmaceutical Industry 2021 by Prescription Medicines Code of Practice Authority (PMCPA) – 1 July 2021
- ABPI Guidance notes on the management of safety information and product complaints from digital activities – 27 Apr 2021 shared with MHRA
- PMCPA - Informal guidance on digital communications – March 2016

Finally, the following international references contain a mention to digital sources of safety data:

- International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) topic E2D: Postapproval safety data management – Step 5 - NOTE FOR GUIDANCE ON DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING (CPMP/ICH/3945/03)
- Council for International Organization of Medical Sciences (CIOMS) 2001 – Report of CIOMS Working Group V - Current challenges in pharmacovigilance: pragmatic approaches - Section IId (p.55)

4. GENERAL ASPECTS

Digital projects are generally complex in nature and require a structured and multifunctional process, in order to guarantee a holistic approach to regulatory and other legal requirements.

In many circumstances, privacy and pharmacovigilance aspects that are linked to direct contact with end users and to enhanced interactive features need to be considered together with legal aspects. This is mainly due to the involvement of vendors or public administration (e.g. hospitals, research institutes or other institutions), but also due to the relevant aspects linked to scientific contents that require medical or regulatory evaluation.

4.1 Governance aspects

Considering the above, a multidisciplinary approach is much more efficient compared to single step approvals of each individual aspect: a cross functional Committee with different functions (PV, Legal, Compliance & Privacy, Regulatory, ad hoc like medical, IT, Procurement, depending on the project) should be in place and clearly foreseen by internal procedures for approval of complex digital projects.

An early advice process (e.g. a formal committee, but also less formal approaches can be considered) may be of help to ensure efficacy and agility in approval processes.

Suggested reference to internal Ethic Code of Conduct as principle for the Committee approval (for example, in Ethic Code of Conduct there are principles around Patient Safety as mandatory requirement to be considered when developing activities) is strongly recommended.

A tracking system is a fundamental instrument for audit and inspection readiness: it is strongly recommended to have a registry/tracking system with project approvals/start date/end date and clear ownership for the digital channel; the tracking system is very important to allow traceability of initiatives and retrospective analysis as needed.

The tracking system may be manual or automated, in case of multinational companies, and the tracking can be shared with Headquarter for oversight purposes.

Based on PV risk assessment, digital projects are subject to audit/assessment (this consideration applies to all involved vendors, as applicable).

An issue escalation process to quality should be in place (i.e. for example, in case of deviations or non compliance with the approved project set up). Late AE reporting should be included in the possible escalation topics.

It is strongly recommended to have a SOP describing the governance and approval of digital projects and channels with clear reference of the need of PV risk assessment and early involvement of pharmacovigilance functions.

In the SOP it should be described how the information is captured, how the digital media monitoring is conducted, and the need of periodic reconciliation and checkpoints, based on the specific PV risk assessment of the digital channels.

In the SOP it should be required the assessment of AEs capture and monitoring and the need of PV re-assessment in case of relevant changes to the project, such as additional of new fields for data capture, changes in the intended use, new relevant information available in the area covered (for examples for website), new digital channels covered (for example addition of new social media covered by the digital activity itself…).

Training on this SOP should be provided to all relevant personnel (including marketing/sales/medical/digital functions) in order to allow for proper understanding of PV compliance requirements.

Training for vendor personnel involved in digital projects should be foreseen (see specific paragraph).

A Quality Management System covering PV aspects should be in place: this quality system should cover digital activities with PV impact, allowing analysis of trends and issues and the discussion in the periodic management review.

Quality Assurance should be involved in the above-mentioned activities, structuring the process and the SOP to support the approval of digital projects, and supporting the risk assessment approach.

4.2 Open points and interaction with other departments

A constant alignment with Quality Assurance and the other functions is required to maintain oversight also from a quality perspective, in particular for:

- checking alignment on documentation and training needs, considering also potential vendor needs (see also other points in this guideline)
- preparing documentation, that needs to be ready in a timely manner in case of audit and inspection

Another important point to be considered is the need to keep in mind that sometimes different regulation should be applied at the same time and to the same project (for example, APP as Software as Medical Device: in this case, there is the possibility of applying the medical device regulation, in addition to pharmacovigilance regulation for the risk of collection of AE on the MAH products through the APP).

It is therefore very important to have a holistic approach to complex healthcare projects/solutions and to promote an evaluation in a multifunctional way from the beginning.

For sure, some aspects are still under discussion and will evolve with the technology evolution itself, leading to the need of a constant increase and update of the companies' internal competencies in this matter.

A training/development plan should be internally developed (including not only Safety but also Quality Assurance) to build the new competencies required in the digital area, which is quite new for all functions and also constantly evolving.

5. INTERNAL PV PROCESSES FOR MANAGEMENT OF DIGITAL PROJECTS

5.1 Set up, risk assessment and approval processes

It is really important to have Pharmacovigilance (PV) function involved since the very beginning to identify the right project set up and to guarantee full oversight of PV requirements and the most appropriate way to cover them, in terms of:

- Due Diligence (that leads also to the Vendor selection),
- Contract PV clause and relevant trainings,
- Reconciliation and quality monitoring (when applicable)
- PSMF relevance (when a vendor is involved)

Each project is evaluated according to:

1) National legislation and requirements

2) Company relevant procedures

3) Local Operating company internal process, at least for approval flow with PV evaluation and relevant documentation to prepare and maintain.

The Project owner should provide all the functions and especially PV with at least the following information:

- Classification of the proposed digital project: i.e company websites; social media pages; app(s) for patients with or without wearables; app(s) for physicians, telemedicine pages, webinars;
- Scope of the proposed digital project: disease awareness; Patients Support Program or service; virtual interviews; virtual room for physicians roundtable;
- Company involvement: sponsorship with logo visibility; owner of social media pages for disease awareness; support for increasing company reputation; online service for Q&A (via e-mail or phone calls with consultants on Therapeutic areas of interest)
- Level of interactions with the audience: Listening; Broadcasting; Engaging.

  Listening: performed mainly on non-company-sponsored sites, may be described as a process of learning from public conversation, blog entries, virtual communities, just to provide some examples. The relevant pages of the site should be monitored for AEs for the period of the listening only (the company should declare its presence by registering on the site with the company name where possible). The monitoring could be done manually or electronically (i.e via e-learning machines for instance with established keywords to be reviewed periodically to ensure an appropriate level of sensitivity). Both methods have pros and cons and need to be evaluated case by case

  Broadcasting: digital activities may allow sharing messages/information with the audience in only one way, usually from the company to the audience. It is important to verify the site doesn't allow for interactive dialogue or the creation/uploading of user-generated content.

  Engaging: this action is performed to interactively communicate with the audience. Bloggers, influencers and celebrities can be contracted for certain activities that require a dedicated contract to cover PV responsibility when the activities are conducted on their digital sites. When engaging is conducted via company digital sites, the monitoring should be performed on an ongoing basis when the audience may leave a message or request information (for instance, on a daily basis)

- Data collection: the project has high/low probability to collect data, including AEs, SSI, PQCs (audience comments are allowed; there is a direct contact between consultants and the audience; the digital sites is on a therapeutic area where the company has/is developing treatments)
- Company access to data collected and stored, also via vendors with access for technical reasons: this implies not only PV responsibilities and monitoring for AEs, but also compliance with privacy laws and discussion with the legal department should be carried on
- Project duration: to establish reconciliation schedule (on a monthly basis, on a yearly basis or just at the end of the activity) and training assignment schedule (just before the project starts or to be repeated after one year)

Program Risk assessment

This is applicable before starting the Digital Program: administering the Program Risk Assessment for the assessment of risk of AE reporting associated with program activities is key and it is based on the above described information.
Program risk assessment is important to understand the level of control that MAH needs to apply for PV processes: PV function may increase the frequency of any of the AE reporting associated activities if required by local processes or to address compliance issues.
Based on the information collected, a risk -assessment can evaluate the project to take the most appropriate approach to cover PV requirements when needed:

- If low risk, no or low oversight required.
- If moderate/high risk: PV Clause in Agreement, Training, Reconciliation (Quantitative mandatory, and Qualitative if feasible), Audit (risk based, may not be required if the site is not generating safety data and qualitative reconciliation has been performed to confirm this).

Level of acceptable risk should be described in a Company document/procedure, to allow objective evaluation from PV function.

An implemented tool would be useful to have the same parameters to evaluate all the company projects in the same, consistent way.

It would be useful to perform a regular review of the project to check if the original evaluation was correct and PV requirements are still duly covered. Otherwise, some corrective measures may be required, also in alignment with other company departments.

5.2 Vendor due diligence/assessment

This activity is recommended if a vendor is involved in the digital activity.(*De Carli G.2015. "QUALITY ASSURANCE E FARMACOVIGILANZA. PARTE II - Quality Assurance in Pharmacovigilance (ii)" Giornale Italiano di Farmacoeconomia e Farmacoutilizzazione. 7 (1): 27-35)*

It is an activity to be planned before the Vendor has been selected to conduct a Digital Program, before the starting of the program and with a periodic re-assessment, in order to evaluate the risk associated with the PV Vendor.

It is suggested to administer the Vendor due diligence questionnaires for AEs Identification and Collection in order to evaluate the Quality Management System and PV procedures for managing of AEs/Training of the Vendor. The vendor selection could be facilitated for instance using a customized checklist including the main characteristics a vendor should have.

The checklist should be available and applicable to all the vendors to guarantee consistency in the evaluation and approval process.

The local PV function can use an algorithm for Vendor Risk Assessment, based on the answers received and other available information (meetings done with the vendor during the selection/available information from other programs/experiences…)

The vendor evaluation may involve at least the activity owner, Business quality and PV.

Each company may have a different approach and different SOPs and processes, but generally speaking a vendor has to be evaluated and approved considering for instance:

- the activity and the expertise and experience in the required area
- the Business Continuity Plan
- the Quality Management Systems (including Non-conformance / Deviations, CAPA, Change Control)
- SOPs in place: vendor's ones or company's ones
- Quality system : quantitative KPI and qualitative KPI : Risk based approach
- Vendor's audit and involvement in company's audits
- the results of previous audits (if any).
- the records management
- the computer system validation, if applicable
- use of subcontractor.

N.B.: In case there is an option for the vendor to use subcontractors, this has to be covered in the main or PV Agreement.

A proper documentation should be prepared and maintained, also in view of future audits or inspections.

5.3 Vendor management

Once the vendor is selected and approved, the company prepares a contract to be signed by the relevant functions for both the company and the vendor.

PV has to be consulted for potential PV language to be included in the contract depending on the vendor activities. Each company may have global template including at least:

- training and training record retention
- collection and reporting of AEs/SSI and other safety information
- timeframes for reporting
- responsibilities for FU activities
- reconciliation and reconciliation frequency (based on the project duration/chance to collect AEs)
- record retention
- audit rights
- list if contacts at both parties
- termination activities

During the agreement discussion consider:

- Discussion and alignment on vendor's tasks and obligations, agreement on reconciliation timeline and modality (secure e-mail? Fax? …) Who starts the reconciliation? Who is involved? LSO? Activity Owner
- the level of interaction with the audience and the chance to collect AEs/safety information

- Who is in charge of the training? Content administration, test execution, proof maintenance
- How to describe roles and responsibilities of potential subcontractors

If the same vendor is already working for the company, the training could have been already completed and being still valid (accordingly to the company requirements)

The AO and PV should establish a way to maintain training records and the reconciliation schedule oversight, for compliance with the company requirements.

Contractual agreements and relevant PV clauses needs to be available, duly signed before the start of the activity and inspection ready

A periodic check of the vendor activities should be performed as routine review and appropriate assessment confirmation.

5. 4 Maintenance activities during the program

Reconciliation

Reconciliation is aimed to ensure that all appropriate information has been correctly identified from the dataset and transferred to Pharmacovigilance (PV) and is performed with internal functions/external parties required to record and file incoming information which may also contain safety-related information that is forwarded to PV.

Reconciliation process is well described into a dedicated section of Pharmacovigilance Agreement (PVA) with the service provider.

Reconciliation might be:

- Case-by-case: This type of reconciliation is required usually if smaller numbers of source documents are involved. PV function of MAH and service provide should archive acknowledgment of ICSR receipt
- Periodic reconciliation: it is required usually if larger numbers of source documents are involved and is performed using a reconciliation form, which is attached to the PVA. Reconciliation is performed considering the number of cases, which have been exchanged in the reference period and the reconciliation process might be started both from vendor and from PV function of MAH. Reconciliation form must contain unique ICSR(s) identifier(s) and should be archived by PV function of MAH.

Quality check

Quality check has to be performed regularly, at a defined periodicity, and is aimed to verify if ICSRs have been properly identified by service provider during carrying out the activities. Quality check process, as well as periodicity, are well described into a dedicated section of Pharmacovigilance Agreement (PVA) with the service provider.

The sample to be involved in quality checks might be defined at the beginning of the activity or each time the quality check is conducted according to the amount of the activities conducted by the service provider (i.e. published post on Facebook/ Instagram, screened comments for AOL, ...). In both scenarios, an acceptance number of not identified ICSR must be defined at the beginning of the project

and will support the PV function of MAH to evaluate if quality check should be tightened or not during the next quality check.

Quality check activity must be documented, preferably in a dedicated form.

Based on the number of not identified ICSR and on frequency of when it occurs, preventive actions might be requested to service provider

In case the service provider has established quality measures to ensure complete ICSR identification, quality check activity is not deemed necessary and might not be performed.

In addition to above described periodic quality checks, PV function of MAH might perform random checks aimed to verify if service providers properly identify and forward ICSR, as per PVA. Random checks are performed generating a fake ICSR.

Compliance with reporting timeline (KPI)

The Agreement with the service provider must have a PV section. In this section monitoring requirements, monitoring frequency and monitoring duration should be described. In addition, the reporting timeline for AE and other special situations should be described. KPI can ensure the safety profile of the products and comply with regulatory/HA requirements. Quantitative indicators are used for measuring both timeline reporting and service provider quality. In case of non compliance with the requirement of the agreement, the service provider should communicate these findings to the company and discuss corrective and preventive action.

Program closure

The service provider agrees to cooperate with the MAH for record retention as detailed in the Main Agreement or in the Pharmacovigilance Agreement . During the agreement and for other years (to be established by the company) following the expiration an appropriate confidentiality agreement should be in place. For audit/inspection processes/ document retention with respect of safety information.

6. REPORTS MANAGEMENT

The MAH or third party working on behalf of the MAH, should regularly screen the internet or digital media under their management or responsibility, for potential reports of suspected adverse reactions (*Brosch S, de Ferran AM, Newbould V, Farkas D, Lengsavath M, Tregunno P. 2019. "Establishing a Framework for the Use of Social Media in Pharmacovigilance in Europe." Drug Saf 921-930*).

The frequency of the screening should allow for potential valid ICSRs to be submitted to the Competent Authorities within the appropriate regulatory submission time frames.

Unsolicited reports of suspected adverse reactions from the internet or digital media should be handled as spontaneous reports. The same submission time frames as for spontaneous reports should be applied.

6.1 Collection of reports (considering also set-up of IT tools)

Safety information can come from various digital sources:

- sites of the Medical-Scientific Societies where exchanges of views between patient and medical specialist take place

- newspapers column

- open sites for exchanging information among patients

- app, web site, web page, blog, vlog, social network, internet forum, chat room, health portal

- 'listening', 'broadcasting' and 'engaging' activities - artificial intelligence (AI) system

If the AI is operated by a third party, there would need to be assurances that the third party doesn't renege on any of the responsibilities of the sponsor and that the tool could be inspected by regulators.

The AE screening of all incoming information should be performed for all websites and Social Media channels and accounts controlled or sponsored by MAH.

It is also essential that the responsible person captures the date the information was posted on the site and the date that anyone from the company or working on behalf of the company first becomes aware of the information.

All SI/PC identified by company employees or any individual representing or acting on the company's behalf need to be captured and reported to the company's PV department. It is recommended that this is within one business day of receipt. A confirmation of receipt may be issued.

The following information should be collected, if possible:

- an identifiable patient
- a suspect drug
- an adverse event
- an identifiable reporter

The MAH is not required to routinely monitor a non-company sponsored web site and digital medium, but if a report of suspected adverse reaction described in any non-company sponsored digital medium is identified by the MAH or third party working on behalf of the MAH, it should be assessed to determine whether it qualifies for submission as ICSR. As there is no legal requirement to monitor non-company sponsored digital activities, Day 0 is the day the MAH first becomes aware of the SI/PCs.

The screen shot of the page containing the potential ICSR, together with the link to the page, will be the source document.

The transcription of the report received through tools that capture the voice, such as Artificial Intelligence, is used as a source document.

MAH may also consider the use of their websites to facilitate the collection of reports and follow-up management of suspected adverse reactions by providing adverse reaction forms for reporting or appropriate contact details for direct communication.

If the country of the primary source is missing, the country where the information was received, or where the review took place, should be used as the primary source country.

6.2 Identification of the reporter

The identifiability of the reporter refers to the possibility of verification of the existence of a real person based on the information available e.g. an e-mail address under a valid format has been provided.

A reporter who has registered through an app is considered valid if an email address under a valid format has been provided during registration.

6.3 Follow up and privacy

After the MAH has identified the suspected adverse reaction, and managed the report, MAH can request further follow-up information.

The owner of the website or digital platform should identify and provide the MAH with an internal contact point that can manage follow-up requests in compliance with privacy in line with the applicable law.

Notice should be given on company- sponsored sites that user-generated information deemed to be a safety information (SI) or product complaint (PC) will be collected by the company in order to meet legal obligations.

It is advisable to explain why such information is beneficial for the protection of public health.
It should also be noted that the company may follow-up directly with the individual who generated the SI/PC information in order to gain more information. Please consider the General Data Protection Regulation (GDPR) approved by the EU Parliament on 27th April 2016 and enforced on 25th May 2018, the PIPA guidance notes on UK data protection in post-marketing pharmacovigilance, and the applicable national data protection legislation.