SCOPE Work Package 8
Lifecycle Pharmacovigilance

Practical Guide on Safety-related Referrals

2016

SCOPE

SCOPE Work Package 8
Lifecycle Pharmacovigilance
Practical Guide on Safety-related Referrals

Contents

Acknowledgments

Main authors

Jane Woolley (UK), Alison Shaw (UK), Jelena Ivanovic (IT), Virginia Cuconato (IT), Leonor Chambel (PT), Margarida Guimares (PT)

Co-authors/contributors

Anja Schiel (NO), Ingebjørg Buajordet (NO), Yvette Escudero (ES)

WP8 active participants

This document is developed and adopted with participation of all WP8 contributors:

Ingebjorg Buajordet, Niamh Buckley, Eleanor Carey, Leonor Chambel, Maria Consuelo Cicalese, Virginia Cuconato, Marco Di Girolamo, Yvette Escudero, Rolf Gedeborg, Margarida Guimaraes, Rimul Gunnar, Jelena Ivanovic, Karl Mikael Kälkner, Miguel Ángel Macia, Elena Marotta, Ana Martins, Dolores Montero, Anja Schiel, Eva Segovia, Alison Shaw, Almath Spooner, Annika Wennberg, Jane Woolley, Qun-Ying Yue

1. Introduction

1.1 Purpose of the document

This guide may be useful for any Assessor who is involved in a safety-related referral. It offers practical advice at all stages of the process and should be used in conjunction with other relevant guidance and the EMA templates. It is mostly written from the perspective of the (Co)-rapporteur Assessor, but many aspects may also be of value to the non-rapporteur. This guide is not intended to provide procedural, scientific or benefit/risk (B/R) evaluation guidance.

The document has been drafted as generically as possible but it is acknowledged that different systems for pharmacovigilance (PV) assessment are in place across the MSs and so some aspects may not be relevant to all Assessors or do not apply in every country.

1.2 Relevant guidelines

EMA guidance[1] may be found at:

- www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0
- www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/referral_search.jsp&mid=WC0b01ac05805c516f

Templates for all documents required during a referral procedure may be obtained from the EMA referrals team.

[1] Based on Directive 2001/83/EC, as amended by Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010, without prejudice to the implementation of the changes resulting from Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance.

1.3 Definitions and abbreviations

Terminology	Description
AR	Assessment Report
B/R	Benefit/Risk
CAP	Centrally Authorised Product
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination Group for Mutual Recognition and Decentralised Procedures (Human)
CIOMS	Council for International Organisations of Medical Sciences
DSUR	Development Safety Updated Report
DUS	Drug Utilisation Studies
EC	European Commission
EPITT	European Pharmacovigilance Issues Tracking Tool
EMA	European Medicines Agency
eRMR	Electronic Reaction Monitoring Reports
EU	European Union
HCPs	Healthcare Professionals
HCP WG	Healthcare Professionals' Working Group
LoOI	List of Outstanding Issues
LoQ	List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MS	Member State
NAP	Nationally Authorised Product
NCA	National Competent Authority
NUI	Non-Urgent Information
PA	Procedure Assistant
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Studies
PCWP	Patients' and Consumers' Working Party
PDCO	Paediatric Committee

Terminology	Description
PI	Product Information
PL	Patient Leaflet
PM	Procedure Manager
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PSUSA	Single assessment of Periodic Safety Update Reports
PV	Pharmacovigilance
RMP	Risk Management Plan
SAG	Scientific Advisory Group
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TC	Teleconference
WP	Work Package

2. Background

The main objective of the different types of referral considered by the Pharmacovigilance Risk Assessment Committee (PRAC) (Articles 107i, 31 and 20 – see section 3.1.2 of this document) is to resolve issues over the safety or the balance of benefits and risks of a medicine or class of medicines and, where necessary, to propose measures to minimise harm to patients throughout Europe. While formal guidance on referrals is available (see section 1.2), one of the recommendations that arose from analysis of the results of the SCOPE survey on B/R procedures (topic 4) and internal discussion among contributors to WP8 on 'Lifecycle Pharmacovigilance' was the proposal to develop a practical guide for Assessors involved in referrals.

The survey responses highlighted that most NCAs who had participated in referrals do not have a formal internal document to provide structured guidance for Assessors. It also identified a number of challenges faced by MSs and described the strategies that have been adopted to overcome these. This valuable information has been combined within this document to give some useful practical tools and advice for Assessors to consider throughout the referral procedure; it is not intended to guide Assessors to evaluate complex safety data or weigh up benefits and risks though some information on this is provided in section 3.2.1. Some aspects of this paper may not be feasible or relevant for everyone – this does not matter. The intention is that Assessors can dip into this paper and take from it any ideas they think might help them during the referral procedure; anything that is not suitable or relevant can be ignored.

3. Practical guidance

In order to achieve its objectives a referral needs a clearly defined scope that ensures all relevant scenarios are taken into consideration. It also needs a clear focussed list of questions to MAHs to ensure that all relevant (and no irrelevant) information is provided. This will help Assessors to draw appropriate conclusions and make clear recommendations. Expert input at a national and/or European level may be important in ensuring that any recommendations are clinically feasible.

Familiarity with the Legislation and the EMA guidance on procedural aspects of referrals is recommended. Either having previous experience of, or training in critical appraisal of scientific data and B/R evaluation will also make it easier to draft the AR.

It is acknowledged that preferred work patterns and practices vary amongst MSs and Assessors. This is considered to be an advantage for the network; however it is important that in all cases ARs are clearly written and consistent with the available data, and present a comprehensive but concise and critical analysis of all relevant data with clear, justified conclusions and recommendations. To enhance quality, seeking peer review and if possible, expert input, is strongly advised.

This guide is written largely from the perspective of a (Co-) Rapporteur; however, where relevant, reference is also made to the role of a non-Rapporteur Assessor.

3.1 Planning and organisation

3.1.1 Information gathering before triggering a referral

As the MS which is considering triggering a safety referral, make sure you are aware of any relevant previous or parallel procedures for the substance/product. Consulting the EPITT and the information exchanged via the NCAs PV mail network could be of help in collecting information on any discussions on safety issues. Consider also evidence from available scientific literature.

Consider:

- Whether it is a well-known issue that has been previously reviewed. If so, when and what was the regulatory action?
- What is the evidence?
- Are there relevant ongoing procedures?
- Are there other relevant sources of data?

Ensure also that you are aware of all relevant guidelines necessary for appropriate evaluation of the safety issue. In particular, clinical professional bodies and scientific association guidelines could be useful for addressing aspects relative to use of the medicine(s) in real-world clinical practice.

Some issues arising from the evaluation of PV data automatically trigger an urgent union procedure under article 107i. These include a MS or the EC suspending or revoking a MA, prohibiting the supply of a medicine or refusing to renew a MA. In addition an Article 107i procedure is triggered if a company informs a MS or the EC that, on the basis of safety concerns, it has interrupted the placing on the market of a medicinal product or for safety reasons has taken action or intends to take action to have a MA withdrawn, or has not applied for the renewal of a MA.

In situations that do not result in the automatically triggering of an urgent union referral procedure, it is good practice to consider if a referral is the best way to manage the safety concern. Talking to the EMA can help with your decision. Other options that could also be considered include: PSUSAs, safety signals, Article 5(3) referrals ('scientific opinion'), worksharing type 1B/II variations and, for CAPs, PAM-like procedures or urgent safety restrictions.

Key factors to bear in mind when deciding the best way to take forward a safety concern include:

- Urgency/importance of issue and timeframe for completion (are clock-stops possible?)
- Scientific complexity
- Requirement for expert input from other WPs, SAGs etc.
- Possibility for a company oral explanation
- Whether the outcome needs to be legally binding
- Whether the changes can be implemented directly, without the need for another procedure

3.1.2 What type of referral?

If, on consideration of all the above, a safety referral is still considered to be the most appropriate option, the referral procedure that is most appropriate needs to be decided. This will depend on the seriousness of the concern (and therefore its urgency) and the route of authorisation of the products involved. In general, issues that involve NAPs only or a mix of NAPs and CAPs are dealt with through article 107i referrals if they are urgent and through Article 31 referrals if they are non-urgent.

Safety concerns that involve only CAPs are dealt with through an Article 20 procedure under an urgent or a non-urgent timetable, as appropriate.

3.1.3 Triggering the referral

Once the referral type has been decided, it may be necessary to systematically collect further information. If so, NCAs are encouraged to work closely with the EMA to gather this as soon as possible. The requested information should aim to:

- Facilitate identification of concerned products, their availability, indication, use, alternatives etc.
- Provide an overview of the issue in other MSs
- Inform about the scope of the potential referral procedure
- Propose other sources of information relevant to the issue;
- Support the drafting of a referral notification and a LoQ

EPITT could be used to gather some of this information, through a (NUI request. The NUI will be received by all MSs, the EMA and the EC through EPITT via the rapid alert mailbox. As time is short for responses, only information that is considered critical should be sought.

When all relevant information has been received through the NUI the appropriate referral notification[2] should be drafted, taking the following into consideration:

- Background of the safety concern (previous action, supporting evidence, etc.)
- Description of safety concern – frequency, severity, reversibility, sequelae, etc.
- Possible impact on public health
- Supporting evidence
- Scope

All these aspects need to be reflected as concisely as possible in the notification document of the referral.

3.1.4 Scope of the referral

When drafting the referral notification it is essential to consider carefully the proposed scope. This should be focused, relevant and take the following into account:

a) Is it restricted to a drug substance or is it a therapeutic class safety issue?

b) Is it limited to a specific indication, dosage, formulation, route of administration, or legal status?

c) Should combination products be included?

[2] http://ec.europa.eu/health/files/eudralex/vol-2/2014-05_vol2a_chap_3.pdf

d) Is it limited to specific patient(s) population – population at risk?

e) What is the specific clinical context of the safety concern(s)

f) Is there variability in how a therapy is used across member states (based on the responses to the NUI – section 3.1.3).

Bear in mind any relevant clinical and scientific association guidelines as these may allow a better understanding of real-life clinical use/practices of the product(s) in question and take into consideration the impact on different healthcare settings (e.g. unmet clinical need, availability of alternative treatments, innovative characteristics of medicinal product, etc.).

3.1.5 List of questions

The LoQ to the company(s) needs to be focused, relevant and precise. It should also be as short and simple as possible and completely consistent with the scope. As the Assessor evaluating the data, if you get the opportunity to provide input to the LoQ consider very carefully what information is absolutely essential to help make your decision. Just as important, consider if anything in the draft LoQ is not important – do not ask for anything that is a 'nice to know'.

Whenever possible, provide templates for companies (including instructions about data presentation/stratification) in order to make the data easier to assess and compare. Make sure the questions won't be misunderstood – ask others for their opinion on the draft, when possible and/or applicable.

If external expert advice is required from a Scientific Advisory Group (SAG) or other committee during the procedure the same principles should be applied to the LoQ. Similarly, in Article 107i procedures a LoQ for HCPs, patients' organisations and the general public will be needed.

3.1.6 Agreeing the referral timetable

Article 107i referrals have a defined 60 day timetable without clock stop. As the maximum number of days for assessment is defined, flexibility around the timetable can be limited (other than to shorten it). Where the urgency of the issue permits, the PRAC may also decide to hold a public hearing within the 60 day timetable.

Non-urgent referral procedures work to an initial 60 day timetable which can be extended to 150 days, with clock stops for LoOI, public hearings, oral explanations or expert input, and so have slightly more flexibility. When the timetable is first proposed by the EMA, together with your PRAC delegates you should therefore consider the following:

- The volume of data you expect to receive (based on the LoQ and the number of MAHs), and how long it will realistically take to review
- If the issue has been reviewed previously, the amount of data previously reviewed and whether there are major new data

- Whether you need to have your AR ready for a national expert committee prior to the PRAC Rapporteur AR due date
- The possible need to consult an ad-hoc or existing external group of experts (SAG) or committees (e.g. PDCO)
- The need for a public hearing (e.g. depending on the urgency of the issue and in relation to providing insight into the way a medicine is used in practice, its therapeutic effects, the availability of therapeutic alternatives, or the feasibility and acceptability of risk minimisation measures)

Based on the answers to the above, it may be possible to predict whether the bulk of the assessment work will be done at the first or subsequent rounds and this can help inform negotiations around the timetable. It may also be possible to shift the timetable slightly in order to avoid significant holiday periods by giving the companies slightly longer to respond to the LoQ.

If, having considered the above, you think that the initial timetable proposed by the EMA/PRAC will not give you sufficient time to do the assessment let your manager/PRAC delegate know together with your reasons why. It is important that any concerns about the timetable are flagged with your PRAC delegate as early as possible so they can negotiate with the EMA before it is adopted by PRAC. Late identification of a problem will seriously impact on any remedial action that can be taken.

If you are the non-rapporteur for a referral but your Agency decides that the issue is of sufficient national public health importance that a parallel assessment of the submitted data is required, much of the guidance below will also be relevant for you.

3.1.7 Pre-work

To ensure that your conclusions are fully informed it is valuable to familiarise yourself with previous important signals that have been evaluated for that medicine(s), any relevant evidence from other products in the class and any other recent or ongoing procedures. Discussions with other Assessors, including Inspectors, within your Agency may provide you with valuable information.

If you have the time it is also worth familiarising yourself with the key studies/data before the responses come in and ordering any references that you have identified. Although companies should provide all references cited in full, if you have the time before the clock starts you could consider doing your own search of the scientific literature to ensure that you are aware of all relevant information on the subject and give you time to order any important papers that are not available on line. This will allow you to identify any gaps in the company responses. If there is any part of the assessment you can start it will save you valuable time once the clock has started.

As well as the published literature it may be worth considering whether useful data e.g. usage data, may be available elsewhere to support your assessment. A list of useful alternative data sources has been identified through SCOPE WP8 Topic 1 and is available to Assessors.

3.1.8 Data management

Although you can never anticipate exactly how much data you will receive, because MAHs are under no legal obligation to respond to the LoQ and different MAHs will provide substantially different volumes of data, it is a good idea to check in advance Annex 1 of the relevant referral on the EMA website to see how many MAHs have been contacted. At this time you may want to identify the brand leader(s) of your product(s).

In situations when a large amount of data is likely to be submitted (e.g. referrals involving high numbers of products and MAHs or responses from HCPs, patients' organisations and the general public) particular attention should be paid to planning and deciding how the work can most pragmatically be organised. If the referral assessment involves more than one Assessor, good coordination and communication through planning meetings (see section 3.1.10) is essential to avoid duplication of effort and ensure deadlines are met.

Make sure you know the contact details for the relevant referrals team at the EMA. To ensure you have received all the data make a list of MAHs from whom you have had a response once the due date has passed and check this against the list of responses that the EMA has received.

3.1.9 Team working

Working on a referral can easily take up a significant proportion (if not all) of your working time, especially if many companies and/or products are involved. If that is likely to be the case, it is important that you discuss with your manager whether other assessment work can be reallocated or postponed during that time to allow you to focus on the referral assessment. Alternatively explore whether a team of Assessors could be created in order to split the work between you and whether additional input is needed in light of the expertise required to assess the data.

If a team of Assessors is established it will be important to clearly define responsibilities for each part of the assessment work and agree a Lead Assessor – this may depend on other priorities/workload, specialist knowledge, experience etc. Defining clear timelines for delivery of each part of the assessment and identifying any common data in different MAHs' responses is also important. The Lead Assessor should ensure that the whole team is aware of the assessment timelines and the need to meet them. Team members should keep in touch with each other throughout to ascertain whether any changes to the original plan need to be made in order for everyone to meet the agreed deadlines.

It may be useful to create a shared folder where you can store all referral-related documents, including timetables, literature and ARs. It may also be helpful to create your own mailing list that ensures all relevant people are copied into emails.

Working on a referral can be quite isolating and so if you are having doubts about anything during your assessment it can help to talk to another Assessor in the team or someone with experience in referrals.

3.1.10 Planning meetings

It is recommended to have at least one planning meeting with PRAC delegates and relevant managers for their early input into the most appropriate composition of the assessment team (if needed), the structure of the assessment report, the need for national expert advice and agreement of approximate timelines.

Planning meetings are particularly important if you are working as part of a team because you will need to agree at an early stage what approach you intend to take with assessing the different questions – this will be especially important for referrals with very large volumes of data. The benefits of planning meetings for the Assessor, and the quality of the AR are outlined in Table 1.

Table 1 – Benefits of planning meetings as identified in the SCOPE survey

Benefit for the process	Benefit for the quality of AR	Benefit for Assessor
• Better work-sharing • Better definition of the roles in assessment process • Better adherence to timelines and achievement of intermediate steps • Earlier identification of the need for engagement of additional/national experts • Prevention of duplication in work process • Improvements in efficiency	• Builds in time for peer review • Provides additional timely contribution of expertise	• Clarifies vision, expectations and responsibilities • Enables better management of the timeframes • Provides support

For complex referrals with tight deadlines (especially Article 107i referrals) it may be helpful for Assessors to be actively involved in meetings and/or teleconferences (TCs) with the EMA contact points (PM and PA and/or the referrals contact). This may help to keep the assessment on track, on time and to highlight any potential problems or suggest solutions.

3.1.11 Setting assessment timelines

Once the data has been submitted and you know if you will be seeking national expert advice, it is helpful to create a more precise assessment timetable that takes into account the time needed for internal review, the deadline for any national expert committees and the time for updating the report accordingly, before circulating it to MSs (referring to the due date for the PRAC Co(rapp)'s assessment report published on EMA's website). Since the report will likely be relatively extensive and have potentially important consequences for public health, sufficient time should be allowed for internal review and sign-off wherever possible. You may find it helpful to set up automatic reminders at key points throughout the process.

Once you have determined your deadline for internal review or sending the assessment report to national experts, and you know how much data needs to be assessed it is helpful (if not essential) to write yourself a personal assessment plan that gives yourself milestones for what you will need to have assessed and by when.

Upon agreement of the timetable with co-Assessors or your managers/PRAC delegate, it is essential to stick to it. Any delay in circulation of your assessment report to PRAC can have serious implications as it can result in a MAH choosing to challenge procedurally the referral and could mean all your hard work will be wasted. This is something to be avoided at all costs. If you do have concerns about meeting a deadline discuss this with your manager and the PRAC delegate at an early stage.

3.2 Support during evaluation of risks/risk characterisation or for benefit/risk decision making

3.2.1 Consult the available guidance

The template AR gives useful guidance when drafting your report. You may also have other forms of internal guidance such as a checklist, SOP or Q&A document within your agency to help ensure consistency and quality of the report. Alternatively if you want more information on the B/R evaluation process itself you could refer to the guidance on the EMA's website or in Council for International Organisations of Medical Sciences (CIOMS) IV.

3.2.2 Assessing company responses

For referrals that include a number of companies the volume of data can be daunting and an early decision (preferably at the planning stage) should be made on how you plan to tackle the responses. Whether you choose to assess the data from all MAHs on one question, or all questions from each MAH sequentially may differ according to a number of factors including the type of question or your own personal preference. There are advantages and disadvantages to both methods and it really comes down to your own personal preferred way of working, though the SCOPE survey has shown that the first option "one question, all MAHs" is more common. Comparing the answers submitted by the different MAHs to a single question may also be more pragmatic and help you to form a conclusion on it, especially when assessing a large amount of data (see Table 2).

Table 2 – The advantages of two assessment methods as identified in the SCOPE survey

Advantages of simultaneously assessing responses to the same question from all companies	Advantages of assessing all responses from each company in turn
Can provide clearer, more complete view on an issue	Can be quicker
Ensures all relevant data taken into consideration in the conclusion	Not affected by late company submissions
Enables easy comparison of the different responses	May be less resource-intensive
May make it easier to meet deadline if have different Assessors reviewing different questions	
Can help reach conclusions and propose recommendations at an earlier stage	

It is useful to remember that each discrete piece of data only needs to be evaluated once – if the same evidence is described multiple times by different MAHs it is sufficient to focus on the most comprehensive, well-considered response. If other MAHs have also provided the same evidence with the same conclusion it is sufficient to simply describe what has been submitted without having to repeat any form of evaluation. If the same evidence is provided but with a different conclusion, this will need to be highlighted.

Comparison of SmPCs for products across all MSs has been identified as being a particular challenge time-wise. This can be helped by asking the MAH to populate a template table with only the information that is relevant to the issue under consideration (it is important to remember that the aim of the referral is to improve information on the issue under consideration and not to harmonise the complete PI between MAHs and across MSs).

It is worth bearing in mind that the content included in the SmPC comparison table could be particularly useful when considering the best form of words to use for any updates to the PI as it may be that one of the SmPCs contains some helpful text that can be used.

MAHs have the right to request an oral explanation to the PRAC – in some cases more than one request may be made. The MAH presentations should be provided in advance to the (Co-) Rapporteur teams and generally focus on specific issues developed by the (Co-)Rapporteurs.

3.2.3 Ensuring internal consistency of the assessment

Referral assessment reports are often very long, which can make it difficult to ensure the final report remains internally consistent. If a small team of Assessors is working together on a referral, it is always helpful for one Lead Assessor to have oversight of the project and pull all the contributions together. This helps with internal consistency and makes sure that appropriate conclusions and recommendations are made based on all the evidence.

3.2.4 Drafting conclusions and recommendations

It is essential to keep in mind that your conclusions need to be evidence-based (all recommendations need to be supported by robust data and based on information provided in the MAHs' responses to the LoQ and your own information search). You need to remain focused on the scope of the referral during your assessment and to restrict the assessment only to the substances, products, indications, populations, formulations, routes of administration, areas of concern etc. that have been included in the referral procedure notification. Although time may be tight, it is worth having regular contact with your co-Assessors, managers and/or the PRAC delegate to ensure you are on the right track with your preliminary conclusions and recommendations.

If there is a large volume of data it may be helpful to define a series of steps that need to be taken to reach your final conclusion, for example, by breaking it down into subsidiary analyses/decisions.

When drafting your recommendations and conclusions highlight clearly the limitations of the data and your analysis. A number of potential conclusions may be reached based on your assessment of the evidence, ranging from no action taken, to the implementation of a range of measures designed to minimise the risk (e.g. adding a warning to the product information, removing an indication/strength from the licence, updating the RMP, or suspending/withdrawing a medicine from the market.

It is extremely useful, as an exercise for yourself and for the reader, to describe the "pros" and "cons" of all the regulatory options including your final position, bearing in mind the feasibility of both the proposed measure and how to assess the effectiveness of it in reducing harm. Your final recommendation should fully reflect the totality of the available data, be proportionate to the risk and be in full alignment with the original scope of the referral. Consideration should be given to differences in healthcare systems across the EU and allow enough flexibility in the proposals to facilitate implementation in the different MSs.

Keep in mind that substantial changes in PI, such as deletion of an indication, strength, pharmaceutical form or route of administration needs to be based on sound evidence and may trigger the suspension or the revocation of some of the MAs concerned by the procedure. It is therefore important to consider the possible impact of your recommendation and any unintentional consequences (e.g. is the product filling an unmet clinical need, are suitable alternatives available, what risks are associated with the alternatives?).

If one of the drivers for the proposed action is a lack of robust efficacy data (e.g. for an old product), first consider whether new data could be gathered. Similarly, if a key safety concern needs better characterisation, consider what type of activity or study may be necessary (and feasible) in order to gather this information.

Referring to previous referral decisions may be useful for considering options for recommendations: http://ec.europa.eu/health/documents/community-register/html/index_en.htm.

3.2.5 Updates to product information

If you conclude that PI needs updating it may help to see if any useful information already exists in the current EU SmPC wording provided by the MAHs. In addition you could:

1. Consult the SmPCs for other products within the same class
2. Consult the SmPC guideline
3. Consult the QRD guidance and reference documents
4. Consult prescribing information for the product from a non-EU country

Proposed changes should:

- Be clear, concise and consistent: SmPC changes should also be applied to the patient leaflet (PL) in lay-terms and vice-versa
- Be related to the referral scope, supported by data and justified in the AR
- Take into account, as far as possible, the information, terminology and structure of the existing PI (mainly English version) to avoid introducing conflicting or inconsistent information, or "gaps"
- Serve a purpose

The impact of proposed changes to the existing PI should be assessed. Consider the possibility of asking the MAH(s) for a proposal of the wording that can be changed and/or integrated into the existing PI so that it can be assessed in context. Any necessary changes to the PI should be considered at an early stage so that PRAC can discuss and agree on a proposal, whilst allowing the MAH(s) sufficient time to comment. Finally it is important to consider whether implementation of the proposed changes is feasible in practice at a national level.

3.3 Support for drafting the list of outstanding issues

Further data may be needed from the companies before final conclusions can be drawn. As with the LoQ, the LoOI needs to be clear, relevant and precise. It should avoid wording that is open to misinterpretation. It is useful to seek peer review and/or expert advice on your proposed draft questions before they are finalised.

It is key that the LoOI is restricted to the issues that are essential to address, in order to help make an informed decision – there should be no 'nice to know' questions. When asking the MAH for supplementary data or analyses, include in your request clear instructions on how the data need to be presented and/or stratified (e.g. define the age groups, particular populations, important cofounders, or any other factor that seems to be relevant for assessment of the safety issue). This approach can facilitate your assessment and decision making. Bear in mind how much time you will have to assess the company responses.

3.4 Support for better delivery of high quality recommendations and final outcomes

3.4.1 Consulting others

It is important throughout the referral procedure to build in quality at all stages. Although each NCA will have its own ways of assuring quality, for the (Co-) Rapporteur Assessors it is generally useful to have someone else (preferably your manager and/or the PRAC delegate) peer review your report. Seeking advice from national experts adds another layer of reassurance.

Non-rapporteur Assessors should be prepared to critically assess the (Co-) Rapporteurs' assessment reports – in some cases you may also wish to seek national expert input.

For the network in general it is beneficial to receive as many views from other MSs as possible to make the final outcome as robust as possible; as non-rapporteur sending comments prior to PRAC is strongly encouraged.

If you consider that additional risk minimisation measures and/or communications are needed it is best to start working with the companies on a communication plan and materials as early as possible in the procedure so that the final product is of high quality. The feasibility and utility of these measures in practice should be an important consideration and, if possible, expert/lay input should be sought on their practicality or appropriateness in real life.

3.4.2 EU expert input

In addition to seeking national expert advice, also consider as early in the procedure as possible whether a SAG or ad hoc Expert Group of the EMA is likely to be needed to discuss some of the more clinical aspects of the referral. Similarly consider whether the PRAC will need to consult with any of the other committees, such as PDCO, the PCWP, or the HCP WG. This may be particularly important if the preliminary conclusion is to restrict availability of the medicinal product to patients in any way. In this situation expert input should be sought on the practicalities of the restriction as well as the clinical consequences for both healthcare professionals and patients. Sometimes a decision on this may not be possible until after the first round of assessment.

A useful perspective could also be obtained from consulting patient support groups/associations. PRAC may consider that a public hearing should be convened, in which case a pre-defined set of questions will be required. The decision to hold a public hearing is taken on a case-by-case basis, depending on a number of considerations including the urgency and seriousness of the safety concern and the level of public interest.

Please bear in mind that the LoQ for the experts needs to be focused and that the advice needs to be based on their expert clinical opinion. For example, if restricting the use of a medicine in a specific patient population is proposed, questions such as: "In your clinical practice do you use this product in population X?" would be better rephrased as: "In your opinion, should this product be used in this population?". Depending on your conclusions and recommendations, questions around alternative therapies and possible consequences of restrictive risk minimisation measures would also be important.

3.4.3 Keeping everyone informed

A proactive approach that ensures prompt and effective communication and coordination with all stakeholders involved in the procedure (e.g. Rapporteur and Co-Rapporteur, EMA PM/PA, PRAC delegates, MAHs, experts etc.) is particularly important for successful management of referral procedures.

If the procedure is in the phase of drafting a Joint Assessment between more than one member state, proactive communication and close coordination between Rapporteurs and Co-Rapporteurs is warranted, using TCs if necessary to agree on important matters. This will ensure circulation of a draft report to the (Co-)Rapp(s) in a timely manner, to allow adequate time for commenting and circulation of the final report in line with proposed timeframes.

Make sure everyone who needs to be, is copied into all relevant emails and kept abreast of any developments. It is particularly important to work closely with your PRAC delegate and, depending on the products included in the referral, you will also need to work closely with either your CHMP delegate (if all products are CAPs) or CMD(h) delegate (if any NAPs are included).

Many referrals will be followed with interest by the professional and lay media. If you are aware of media interest it is good practice to work with EMA to circulate some lines to take to the network for use by MSs. This is particularly important where the outcome will result in a restriction in use or suspension of a product.

3.4.4 Presenting your Assessment Report at PRAC

As PRAC (Co-) Rapporteur for the referral you will most likely need to help prepare for the EU meetings, by providing power point slides and briefing for the PRAC delegates. You may also be asked to attend the discussion (and present the issue) at PRAC.

Any presentation to PRAC should be concise and focus on the key issues. It should include, but not necessarily be limited to:

- Background to the referral, safety concern and scope
- Overview of the key benefits and risks
- Summary of evidence relating to the safety concern under consideration
- Conclusion on the evidence

- Options and rationale for regulatory action - advantages and disadvantages
- Need for risk minimisation measures
- Expert opinion; MAH(s) position; (Co-)Rapporteur opinion; MS comments – areas of harmony/contention
- Final conclusions and recommendations including current PI wording (if any) and proposed updates and/or any RMP amendments
- List of outstanding issues including the need for further studies (e.g. PASS/PAES/DUS)
- Communication plan (in the final round)
- Key areas for discussion by PRAC

If a SAG has been consulted as part of the procedure, the SAG chair will usually be invited to provide feedback to PRAC.

When deciding on the most important points to express in the presentation you will need to consider the (Co-)Rapporteur's position – especially where you have a difference in opinion. It may be helpful to contact the EMA contact for advice on procedural aspects and to involve them if there needs to be any agreement with the other Rapporteur over coordinating any joint presentations. It is also essential to engage with your PRAC delegate(s) as they may have helpful advice based on previous experience.

During the period of the PRAC meeting you will likely be required to input into the drafting of any reports/communications that are required.

If the referral includes a centralised product the issue will go for discussion at CHMP, if not, it will be considered by CMD(h). For Committee discussions you will need to provide a Reader's Guidance and a set of slides that are updated to include the PRAC advice.

For Article 31 referrals MAHs have a 15-day window to notify the EMA of their intention to request a re-examination after the PRAC recommendation. Finalisation of a referral at CHMP/CMD(h) will therefore routinely be postponed to the following month (i.e. 6 weeks later) for those where a re-examination is possible. When a re-examination is requested the MAH has 60 days to send PRAC the scientific grounds for the re-examination. (Co)-rapporteurs from two different member states are then appointed to evaluate the points of the PRAC recommendation (or 'opinion') that have been identified by the MAH; no new data can be assessed at this point. After a further 60 days PRAC adopts its final recommendation. Companies do not have an opportunity to request a re-examination in the case of an Article 107i urgent union procedure or an Article 20 procedure.