



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Consideration on core requirements for RMPs of COVID-19 vaccines

coreRMP19 guidance v3.1

Introduction/Background

In addition to the EMA guidance on pharmacovigilance and vaccine development, the EMA issued the "[Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines](#)" giving an overview of the monitoring activities to be carried out in the EU for COVID-19 vaccines, including the roles, responsibilities and interactions of the stakeholders involved. Further interactions between EMA, NCAs, and the vaccine manufacturers have identified the need to develop further guidance on RMP requirements for COVID-19 vaccines.

This guidance reflects the EMA recommendations based on current knowledge and experience. As the pandemic situation evolves and further evidence becomes available for the respective vaccine candidates (and new/multiple strain formulations of approved COVID-19 vaccines), the manufacturers should take into account further guidance and experience that EMA communicates, in the form of updated guidance or through the scientific assessment already completed (e.g. EPARs for approved products, RMPs of approved products).

Scope

This coreRMP19 document addresses the planning for post-marketing surveillance for COVID-19 vaccines in the context of marketing authorisation in the EU.

Objective

- providing supplemental section-by-section guidance and requirements for drafting the RMPs of COVID-19 vaccines.

coreRMP19 requirements and guidance

These coreRMP19 requirements should be read in conjunction with existing relevant EMA guidance (including Guideline on (good pharmacovigilance practices) GVP Module V, GVP Module VI, GVP Module IX, Guidance on the format of the risk management plan (RMP) in the EU, Product-or Population-Specific Considerations I (GVP chapter P.I): Vaccines for prophylaxis against infectious diseases, Guideline on Influenza Vaccines - Non-clinical and Clinical Module, Guideline on the exposure to

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medicinal products during pregnancy: need for post-authorisation data, etc. published on the EMA website; the requirements and guidance they provide should be read and applied in the context of pandemic use of COVID-19 vaccines.

EMA publishes¹ the RMP of approved COVID-19 vaccines; these documents should also inform the Applicant's submissions, as they provide precedents in an ever-evolving pandemic situation.

Part I – Overview

If the RMP includes information on both the originally approved product and the product containing different/additional strains, the administrative details need to be presented individually in this section.

Part II – Safety Specification

Module SI - Epidemiology of the indication(s) and target population(s)

This should reflect the up-to-date information on COVID-19, acknowledging the existing uncertainties.

Module SII - Non-clinical part of the safety specification

For RMPs submitted with an initial marketing authorisation application, this part could be available early in the submission plan, so, when available, it should be included in the earlier versions of the RMP (i.e. with earlier rolling reviews).

Module SIII - Clinical trial exposure

It is acknowledged that final exposure and follow-up data will only be available at the finalisation of clinical trial reports. Information from protocols of ongoing trials should be submitted in an earlier round of the rolling review, to keep EMA up to date on the expected size of the safety database and the limitations in safety follow-up.

Additional clinical trial data generated post-approval (including for different/additional strains) should be included, as applicable.

Module SIV - Populations not studied in clinical trials

SIII advice above applies

Module SV - Post-authorisation experience

If there is information available for post-approval of the vaccine in other regions of the world, or from emergency use access in the EU, this should be provided. It is acknowledged that it is likely that this experience will be unavailable at the time of initial submission for an EU approval through the centralised procedure.

RMP updates post-approval should include data on the use with marketed formulations to put the total safety database in perspective.

Module SVI - Additional EU requirements for the safety specification

This section is not expected to be relevant for COVID-19 vaccines.

Module SVII - Identified and potential risks

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https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine/search_api_aggregation_ema_therapeutic_area_name/COVID-19%20virus%20infection?search_api_views_fulltext=

It is acknowledged that only limited information may be available at early stages of regulatory submissions (e.g. first rolling reviews) while clinical trials are ongoing. A more complete safety specification in the RMP will only be available after preliminary clinical trials results are available (i.e. at the time of the efficacy endpoint analysis) with further data being generated from the same trials post-approval. In addition, the Applicants should consider for the generation of the safety specification:

- The vaccine construct and the formulation; this includes risks identified for other approved (COVID-19) vaccines using similar technology;
- The degradation of the active substance / antigen and potential impact on safety related to this; (e.g. for mRNA-based vaccines)
- The presence of an adjuvant;
- Any important potential risks that may be specific to vaccination for COVID-19 (e.g. vaccine associated enhanced respiratory disease²).

It is essential that each decision to classify a (potential) risk of a vaccine is evidence-based and adequately presented and justified in the RMP Module SVII, even if initial considerations are driven by previous clinical and non-clinical experiences with vaccines in general, vaccines using the same construct/platform, or from other COVID-19 vaccines from the same or other manufacturers, as applicable.

When the clinical results do not raise particular safety concerns, it may be acceptable that no **important identified risks** are included in the RMP; this may be expected for a medicine that is to be used for prophylaxis, where risks related to the administration procedure are expected to be adequately managed by vaccinators and have minimal impact on risk/benefit considerations for the product.

The list of **important potential risks** should include risks with potential impact on the risk/benefit balance, for which there is clinical and/or pre-clinical evidence suggesting a causal relationship with the vaccine, but for which the strength of the evidence does not (yet) allow to infer causality.

While some of the important potential risks may be derived from the experience with the vaccine construct/platforms, pre-clinical data, or clinical trials, some will derive from the evolving global knowledge of the COVID-19 and any role vaccines could have, or based on more theoretical considerations, (e.g. vaccine-associated enhanced respiratory disease, immune mediated disorders).

Applicants should include a well justified list of important potential risks for which evidence as described above exists, and not a comprehensive list of all theoretical risks for vaccines in general. Such theoretical risks could be included in the list of AESI to be followed up via routine and additional pharmacovigilance activities. The list of AESI should be described in section SVII.1.1., but not into the sections SVII.1.2 nor SVII.3. Relevant pharmacovigilance activities should be designed to be able to monitor existing and detect new safety concerns. Focused activities should prioritise, in addition to important risks (identified or potential) and missing information, the AESI (see below for further guidance).

If new safety concerns are identified following the change/addition of strains, this should be presented in this section and highlighted in the summary of safety concerns.

It is understood that clinical trials may have exclusion criteria that might result in subpopulations not being included in the clinical investigations; not all these subpopulations will necessarily constitute missing information in the summary of the safety concerns in the RMP. Based on current evidence and

² Including considerations for antibody dependent enhancement

concerns, the following missing information should be considered to be added in the RMP (unless clinical trials data - in these populations - is considered comprehensive):

- Use in pregnancy and while breast-feeding;
- Safety in patients with severe co-morbidities (e.g. Use in immunocompromised subjects; Use in frail subjects with unstable health conditions and co-morbidities (e.g. chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders, autoimmune disorders or inflammatory disorders);
- Safety in children (when part of approved indication);
- Long-term safety;
- Interaction with other vaccines.

Further considerations for Module SVII for COVID-19 vaccines:

- Reactogenicity:
 - If the vaccine in clinical trials shows a higher reactogenicity profile than the control (especially if the control is another vaccine with an already elevated reactogenicity profile), the RMP should include a discussion on this high reactogenicity, its impact on the safety profile and necessary risk minimisation measures;
 - Reactogenicity in subgroups such as frail vaccinees and the risk of flares in patients with chronic inflammatory conditions needs to be discussed;
 - Differences in reactogenicity with a second (or subsequent) dose should be discussed, when applicable;
 - The impact on reactogenicity and the overall tolerability should be discussed if additional strains are added to the vaccine (e.g. the effect of multiple antigens; the increase of the active substance quantity)
- Aspects of the formulation and preparation of the vaccine should be discussed when they may increase the risk of ADRs. e.g. a formulation where a diluent for reconstitution needs to be added may affect sterility, leading to clinical reactions such as increased local reactions, abscesses;
- In case two (or more) doses are recommended, the risk of vaccine drop out e.g. due to reactogenicity should be evaluated as well as the risk of disease enhancement; the discussion should consider the recommendation for administration of a e.g. second dose containing replaced/additional strains instead of the original product, or a of subsequent dose containing replaced/additional strains after a full vaccination course with the original product;
- Any early signal from clinical trials should be adequately documented and discussed in this section;
- The relevance of the long-term follow-up should be discussed, and adequate pharmacovigilance activities should be considered. Challenges of using the ongoing CTs for this should be presented (e.g. maintaining blinding).

Topics that require further considerations from the Applicants, but are not required to be discussed in the RMP by default:

- Risks of vaccination errors in a context of mass vaccination campaigns, including errors arising from the use of multi-dose vials – to be followed up post-marketing and reported in the summary safety reports (SSRs), proportionate to the risk. Summary reviews are expected to be presented immediately, when new safety concerns related to medication errors arise during vaccine use, and in any case in PSURs;
- Safety effects of mixed schedule (following a heterologous booster vaccination strategy or when using formulations with different strains) – to be followed up in post-marketing and reported in the PSURs;
- Antibody waning, the need for a booster dose or revaccination – should be included in the efficacy discussion with the MA application, and with the PSURs rather than in the RMP.

Part III - Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

This section should include the planning in the context of the pandemic, even for activities not routinely included in the RMP: signal detection and ICSR reporting. Challenges related to restrictions during the pandemic (e.g. due to social distancing or limited medical resources) or to the high volume of ADR reports to be processed (e.g. associated with a mass vaccination campaign) should be considered and reflected into the planning document.

Signal detection and management; methodological considerations and requirements are described in GVP Module IX, which should be read in conjunction with GVP chapter P.I.

Further considerations related to the description in the RMP include:

- Data sources for signal detection should be specified; MAHs should perform signal detection using every means available to them. This would include MAHs' own databases and EudraVigilance (EV), other publicly available or private databases, screening of literature etc. While there is currently no obligation for MAHs to continuously monitor EudraVigilance data outside the context of the ongoing pilot³, MAHs are expected to use the database to strengthen their signal management activities, for instance to further investigate signals detected in their own database. The use of a single data source for signal detection and evaluation is not considered appropriate;
- Routine signal detection methods and practices may be insufficient to efficiently screen the expected high volumes of ADR reports, also taking into consideration the situation of a mass vaccination campaign. Limitations when performing and interpreting signal detection methods of disproportionality of reporting on the entire safety database (e.g. EudraVigilance) should be taken into account in any situation where health care professionals and the public are actively encouraged to report defined adverse reactions for defined medicinal products, due to the weights given to these adverse reactions and products in comparison to the background information available in the database. The reporting pattern for a vaccination campaign during a pandemic is likely to differ qualitatively from other reporting, which need to be taken into account when performing the analysis;
- Leveraging the infrastructure and results of global efforts to define lists of AESI and background rates (e.g. ACCESS, CONSIGN, ConcePTION), observed versus expected (O/E) analyses should be part of MAHs' signal detection activities. These are expected to be

³ <https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/signal-management#transitional-arrangements-for-mahs-section>

described in the RMP and reported in the summary safety reports (SSRs). Coverage data sources, periodicity for frequent analyses and periodic reporting to EMA should also be defined and submitted for assessment;

- The list of AESI proposed should also consider the following sources:
 - Brighton Collaboration SPEAC list⁴
 - ACCESS Project List of Adverse events of special interest and case definitions⁵
 - CBER Surveillance Program - List of Adverse Events of Special Interest⁶
- The signal detection activities should be able to detect, differences in the safety profile of the vaccine containing replaced/added strains, as compared with the original formulation approved.

Methods that should be considered by the MAHs for signal detection activities include, but are not limited to:

- Time-to-onset (TTO) analysis;
- Time series analyses and algorithms that may be useful to help detecting batch issues and spurious reports;
- Cluster analyses to help identify groups of ICSRs that may point to syndromes (e.g. narcolepsy and A/H1N1 pandemic vaccines).

ICSR reporting requirements are described in GVP Module VI, which should be read in conjunction with GVP chapter P.I and Detailed guidance on ICSRs in the context of COVID-19⁷.

Specific follow-up questionnaire(s) should also be considered by applicants to obtain additional structured information for reports of selected safety concerns in the RMP and suspected AESI, in consultation and with pre-submission agreement of the EMA; the forms should be provided in RMP Annex 4 for evaluation. Applicants are strongly encouraged to reuse the content of already approved forms, as published on EMA website as part of the EPAR documents (published RMPs, including Annex 4⁸). The questionnaire should use the language of the reporter and, where feasible, ask only for information missing in the initial report. When specific follow-up questionnaire(s) are implemented, the MAH should provide with the PSURs process data (e.g. response rate, the need for corrective actions), and reassess the need for continuing this routine pharmacovigilance activity. The MAHs are encouraged to contact the NCAs in the individual MS to agree on the language to be used, the additional national reporting contact points to be included, the practical use, and distribution path.

To facilitate prompt review of safety profile of COVID-19 vaccines, and detect safety changes that can point to new signals, during the pandemic, the MAHs of COVID-19 vaccines are expected to submit **Summary Safety Reports** (SSRs) to the EMA; the submission of such reports does not replace, but complements the submission of PSURs. Given the current COVID-19 vaccination patterns, the initiation of SSR submission requirement for new vaccines should only be triggered by the start of mass

⁴ https://brightoncollaboration.us/wp-content/uploads/2020/06/SPEAC_D2.3_V2.0_COVID-19_20200525_public.pdf

⁵ <http://www.encepp.eu/encepp/viewResource.htm?id=40361>

⁶ <https://www.bestinitiative.org/wp-content/uploads/2021/02/C19-Vaccine-Safety-AESI-Background-Rate-Protocol-FINAL-2020.pdf>

⁷ https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/detailed-guidance-icsrs-context-covid-19-validity-coding-icsrs_en.pdf

⁸ Questionnaires for Anaphylaxis and Vaccine enhanced disease have been included at the data lock point for this version of the guidance

vaccination using the product in any EU Member State. The SSRs should initially have reporting periods of one month and be submitted to the EMA according to an agreed schedule (typically the DLP is at the last day of the month, with submission on the 15th of the following month).

The length of the reporting period, DLP, and the submission date would normally be adjusted once the submission frequency changes e.g. for a bi-monthly submission: reporting period covering 2 months, DLP on 15th of the previous month, submission on 10th of the month. The need and periodicity of continuing the submission of the SSRs will be initiated by the Rapporteur and re-evaluated based on the available post-marketing evidence for each vaccine, and at the request of the MAH, as soon as the safety and usage data enables a decision to be made. Considerations for SSR frequency changes or removing the requirement to submit an SSR include: change in exposure in a mass-vaccination campaign; change in formulations that present new safety concerns; addition to the indication of new population with limited safety profile characterisation; addition of a booster ; conclusive safety data from observational research or from spontaneous reporting in the context of usage the product in a large number of vaccinees; the evolution of the pandemic and the strategy for vaccination in EU; safety evidence with other vaccines that might be relevant for the product; a significantly lower use in EU than anticipated, in which case safety monitoring with PSURs and from observational research could be considered sufficient; end of the COVID-19 pandemic, as declared by World Health Organization.

The table of contents for the first SSR should be agreed with the regulators and should include as a minimum:

- Interval and cumulative number of reports, overall and by age groups and in special populations (e.g. pregnant women);
- Interval and cumulative number of reports per HLT and SOC;
- Reports per EU country;
- Exposure data based on administered doses rather than distributed doses whenever possible⁹, stratified by region by age groups, gender, and by dose number (when applicable);
- Changes to reference safety information and actions taken in the interval for safety reasons;
- List of ongoing and closed signals in the interval, including a summary of their evaluation; Reviews of signals identified during the period or of safety topics identified by EMA and requested to be addressed in the SSR;
- Summaries of reported cases of selected AESI considered relevant for periodically review with the SSR submissions (see Appendix for an illustrative example of content – including AESI – to be considered for the SSR preparation), and RMP safety concerns: report numbers and relevant cases, including O/E analyses. Any O/E analyses should be performed cumulatively, using appropriate background rates, e.g. background rates provided by ACCESS available from: http://www.encepp.eu/phact_links.shtml, an appropriate risk window and when appropriate, should be stratified by age groups, or presented per region (e.g. if background rates vary), and complemented with a sensitivity analysis. If an increased O/E ratio is detected, a further evaluation of the concern should be presented;
- For first few SSR submissions a discussion if any unusual pattern of fatal reports is observed during initial post-marketing use. Data on medication errors should be included only if a pattern of errors leading to harm is identified and/or risk minimisation activities are considered

⁹ including publicly available sources, e.g. <https://gap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab>, <https://covid19-vaccine-report.ecdc.europa.eu/>

warranted (e.g. changes to the PI; DHCP); otherwise, this data should be included with the (six-monthly) PSURs;

- Details of the MAH's search strategy, case definitions etc. for all provided reviews and methodology for O/E analyses including source of background rates, risk windows, etc.;
- Risk/benefit considerations.

Subsequent SSR content requirements are defined by previous SSR assessment(s), for each individual product.

In case of a change in indication (e.g. new populations to be vaccinated) and when the safety profile in the initial indication warrants only a safety monitoring using pre-pandemic pharmacovigilance tools e.g. signal detection, PSURs, etc., the SSR (if required by EMA) content should focus on the new populations.

Once the marketing authorisation of the vaccines will be varied to include replaced/additional strains, when data points towards a different safety profile, the data presentation in the SSR should be structured by "product" (i.e. original formulation and new formulation) and cumulatively for the vaccine. This concerns O/E analyses, if exposure data is available by "product". No design of an **enhanced passive surveillance** (EPS) was considered robust in the evaluation of the first four approved COVID-19 vaccines, PRAC discourages the use of such surveillance methods and advises the Applicants/MAHs to focus efforts and resources on other types of pharmacovigilance activities.

Traceability using the provision of vaccination cards (one for each vaccinee) and of stickers 2D-barcoded and human readable with brand name and batch numbers to the vaccinators (two for each dose) are considered useful for pharmacovigilance needs, acknowledging that the circumstances in each Member State for vaccination might not allow their optimal use in all cases. The use of such tools for traceability should be described in this section of the RMP.

The vaccination card would typically contain:

- Placeholder space for name of vaccinee;
- Vaccine brand name and manufacturer name;
- Placeholder space for due date and actual date of first and subsequent doses, and associated batch/lot number (if vaccine requires two or more doses);
- Reminder to retain the card and bring to the appointment for the second and subsequent doses of the vaccine (if vaccine requires two or more doses);
- Optional QR code that links to the MAH website with additional information on product use;
- Adverse event reporting information. The importance of including brand name and batch numbers with every ADR report is even higher if formulations including additional strains are approved for use; this information should be highlighted if applicable.

Recording of brand name and batch numbers information using electronic tools should be facilitated by the inclusion of a 2D bar code on the traceability stickers containing both printed and a 2D-code encoding brand name, expiry date, and batch number¹⁰.

¹⁰ preferably in accordance with the international standard format GS1 Datamatrix: https://www.gs1.org/docs/barcodes/GS1_DataMatrix_Guideline.pdf (see Annex A.6) and using GTIN for brand identification

Updated traceability tools are considered paramount for the post-approval monitoring and should be in place at the launch of a new formulation including changed/additional strains, to ensure that ADRs received can be traced to the original formulation vs the updated ones.

The safety clinical data on the changes/multi-strain formulation may be limited at the time of the variation application, so a robust signal detection and observational research plan is required post-approval with the MA variation.

III.2 - Additional pharmacovigilance activities

Continuation of safety surveillance from **ongoing clinical trials** should be a priority and included as additional pharmacovigilance activities. Protocol review of long-term follow-up should be performed early in the RMP assessment, before the Opinion, acknowledging that changes at that stage might be limited in scope. The final safety results from pivotal trials are expected to be submitted for assessment.

Given the potential challenges, both logistic and ethical, on continuing the clinical trials as initially designed once sufficient efficacy and safety data to support approval have been collected, the manufacturers should plan of pharmacovigilance activities early. Considerations should be given whether routine activities will be sufficient to provide adequate data to further characterise important identified and potential risks and investigate missing information or if, in addition to ongoing or planned clinical trials, an observational **post-authorisation safety study (PASS)** is required. The RMP assessment will specify what safety concerns should be the focus of a PASS; additionally, it may be suitable to add secondary safety endpoints based on the list of AESI. Protocols should take into account the recommendations from ENCePP Guide on Methodological Standards in Pharmacoepidemiology (http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml), and ACCESS and CONSIGN projects results, once available.

If an observational PASS is considered needed, the following considerations apply:

- As the date of marketing in different regions of the world might differ considerably, the PASS should include an EU cohort, and not rely solely on non-EU databases. Studies already planned in Member States (e.g. by public health authorities) or by consortia or cross-EU initiative (e.g. Vac4EU, CONSIGN) could be used if the MAH can obtain access to the safety data in a way that brand-specific analyses can be used for risk/benefit monitoring.
- Key elements for a desirable suitable PASS design would be the ability to start data collection shortly after the vaccine's approval and distribution, the ability to perform rapid analyses of safety and deliver frequent reporting to EMA for regulatory purposes (i.e. interim results).
- The change or inclusion of additional strains in the vaccine formulation should prompt the MAH to evaluate the suitability of ongoing and planned PASS to investigate the safety concerns for both formulations and consider an enlarged sample size recruitment and an update of the study protocol.

While recognising that depending on vaccination policies, the enrolment of pregnancies in the early phases of the vaccination and recruitment of women who may become pregnant shortly after vaccination will be challenging, a study to further investigate the safety in pregnant women and pregnancy outcomes may be warranted e.g. using existing **pregnancy registries** such as INOSS and

Covi-PREG. CONSIGN¹¹ project recommendations should be taken into consideration. Ensuring pregnant women are adequately followed in the PASS is considered useful.

Effectiveness studies should be included in this section of the RMP. It is recommended that the MAHs make use of the established EU efforts that can provide brand-specific, reliably and timely data (e.g. from public health institutes networks, real-time risk/benefit monitoring network initiatives using databases, etc.). Effectiveness data generated should be brand specific. Effectiveness should also be measured for vaccine formulations developed to address variants.

Part IV: Plans for post-authorisation efficacy studies

No specific/additional requirements related to RMP presentation.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

It is agreed that in principle routine risk minimisation in the form of the product information could be sufficient to minimise the risks of the product. MAHs should consider facilitating the dissemination of the product information via publicly available on-line communication channels.

Given the EMA review role in time-constrained procedures, it is considered useful that EMA and the MAHs agree on "key messages to the public health authorities that may be used for inclusion in national educational material" to facilitate national efforts for communication and risk management.

The MAH should discuss the transitional plans for new formulations including additional strains, the period of overlap, and the risk minimisation measures needed to reduce the potential for confusion of different products and schedule administration errors.

Part VI: Summary of the risk management plan

The entire RMP (main body and Annex 4) will be published on EMA website at the time of the authorisation, as part of the EPAR.

No additional requirements for the Summary of the RMP.

Annexes

Where applicable, no additional requirements.

¹¹ Further updates expected at <https://www.ema.europa.eu/en/news/covid-19-ema-sets-infrastructure-real-world-monitoring-treatments-vaccines>

Appendix 1 for the coreRMP19 guidance - Example of a topics list to be considered when building the SSR submission

Note that the example below is a starting point for the SSR requirements at initial Marketing Authorisation evaluation; individual product data (clinical and epidemiological), as well as experience with other similar vaccines, will determine the specific requirements for each authorised product.

Topic	Requirement	Observations
Authorisation status	To be included from first SSR submission	
Actions taken in the reporting interval for safety	To be included from first SSR submission	
Exposure	To be included from first SSR submission	Focused on estimate of interval and cumulative use; stratified by dose, age, gender
Responses to previous requests	In next SSR, unless otherwise specified	
Medication errors	Expected with PSURs submissions only	Unless specific concerns with a new vaccine arise
Summary tabulation of number of reports	No recommendation given	Cannot anticipate situation with a new vaccine use; decision to be taken at Opinion
Literature review	To be included from first SSR submission	Considered useful, if focused on topics included in SSR
Overview of signals	To be included from first SSR submission	
RMP safety concerns		
Anaphylaxis	Expected with PSURs submissions only	
Myocarditis/pericarditis	To be included from first SSR submission if applicable to the product	
VAED/VAERD	Expected with PSURs submissions only	
Use in pregnancy and during breastfeeding	Expected with PSURs submissions only	
Use in Immunocompromised Patients	Expected with PSURs submissions only	
Use in patients with autoimmune or inflammatory disorders	No recommendation given	Cannot anticipate situation with a new vaccine use; decision on how to monitor and report will be taken at Opinion
Use in frail patients with co-morbidities	Expected with PSURs submissions only	
Interaction with other vaccines	Expected with PSURs submissions only	
Long-term safety data	Expected with PSURs submissions only	

Use in children	No recommendation given	Decision on how to monitor and report will be taken at Opinion depending on indication approved and level of concern
TTS	To be included from first SSR submission if applicable to the product	
Thrombosis	To be included from first SSR submission if applicable to the product	
GBS	To be included from first SSR submission if applicable to the product	
Thrombocytopenia, including immune TCP	To be included from first SSR submission if applicable to the product	
Immune mediated neurological conditions	To be included from first SSR submission if applicable to the product	
AESI		
Anaphylactic reactions	Expected with PSURs submissions only	
Cardiovascular AESIs	No recommendation given	Cannot anticipate situation with a new vaccine use; decision on how to monitor and report will be taken at Opinion
COVID-19 AESIs	Expected with PSURs submissions only	
Dermatological AESIs	Expected with PSURs submissions only	
Facial paralysis	Expected with PSURs submissions only	
Haematological AESIs	No recommendation given	Cannot anticipate situation with a new vaccine use; decision on how to monitor and report will be taken at Opinion
Hepatic AESIs	Expected with PSURs submissions only	
Immune-mediated/Autoimmune AESIs	To be included from first SSR submission if applicable to the product	
Musculoskeletal AESIs	No recommendation given	Cannot anticipate situation with a new vaccine use; decision to be taken at Opinion
Neurological AESIs (including demyelination)	No recommendation given	Cannot anticipate situation with a new vaccine use; decision to be taken at Opinion
Other AESIs (e.g., pyrexia, herpes zoster, etc)	Expected with PSURs submissions only	

Pregnancy Related AESIs	Expected with PSURs submissions only	
Renal AESIs	No recommendation given	Cannot anticipate situation with a new vaccine use; decision to be taken at Opinion
Respiratory AESIs	Expected with PSURs submissions only	
Stroke	To be included from first SSR submission if applicable to the product	
Sudden death	Expected with PSURs submissions only	Fatal cases are discussed for each safety concern included in the SSR
Thromboembolic AESIs	To be included from first SSR submission if applicable to the product	
Vasculitic events	To be included from first SSR submission if applicable to the product	
Eye disorders	To be included from first SSR submission if applicable to the product	
Gastro-intestinal disorders	Expected with PSURs submissions only	
Special situations/populations		
Death	Discussion on an unusual pattern of fatal cases, if observed, with first few SSRs; expected only with PSURs submissions afterwards	Fatal cases are discussed for each safety concern included in the SSR
Lack of efficacy	Expected with PSURs submissions only	Not a requirement for SSR
Vaccine interactions	Expected with PSURs submissions only	Not a requirement for SSR
Risk-benefit evaluation and conclusion	To be included from first SSR submission	Product Information update proposals to be included when warranted