ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

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December 30, 2020

Dear EMA:

ISPOR – the professional society for health economics and outcomes research - is pleased to respond on behalf of its membership to the draft Guidelines on Registry-Based Studies. We strongly agree that registry-based studies are an important aspect of real-world evidence and thank the Agency for this opportunity to provide our comments on this draft guidance.

ISPOR is a scientific and educational society with many of its members engaged in evaluation of health technologies, including pharmaceuticals, medical devices, and other interventions. We have a large membership living and working in 110 countries globally, across a range of disciplines, including health economics, epidemiology, public health, pharmaceutical administration, psychology, statistics, medicine, and more, from a variety of stakeholder perspectives, such as the life sciences industry, academia, research organizations, payers, patient groups, government (including some from European regulatory agencies), and health technology assessment bodies. The research and educational offerings presented at our conferences and in our journals are relevant to many of the issues and questions raised in this request for information.

The response to this consultation was led by our most senior advisory body, the Health Science Policy Council (HSPC). To engage our membership, we created a survey where all interested members could provide comments on the draft guidance. These comments were then synthesized by the representatives of HSPC and several other ISPOR Councils and Special Interest Groups. Those comments are found below.

ISPOR would be happy to answer any questions about our response, as well as to participate in any follow-up consultations on the relevant program items mentioned within the report.

Sincerely,

Nancy S. Berg
CEO & Executive Director
ISPOR

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2020

Submission of comments on 'Guideline on registry-based studies' (EMA/484811/2020)

Comments from:

Name of organisation or individual
ISPOR – The professional society for health economics and outcomes research

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

*When completed, this form should be sent to the European Medicines Agency electronically to EMAregistries@ema.europa.eu in **Word format** (not PDF).*

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The guideline would benefit greatly from the addition of specific examples of existing patient registries and examples of registry-based studies. More "real life" examples of both registries and registry-based studies will illustrate the differences between them and will make the guideline more understandable and relevant to end users.	
	There are many useful but vague points made around data quality and collected variables throughout the guideline. In this regard the annex is probably more targeted than the main document. Cancer registries are governed by several international associations (e.g. IACR) which have produced different quality standards against which registries regularly benchmark the quality of their data. This could be used as an example to illustrate some of these points and make them more concrete. Cancer registries also traditionally collect a core set of variables such as date of diagnostic, base of diagnostic, gender, etc., to produce national yearly incidence figures, as well as other variables supporting so-called high-resolution studies for specific research purposes. These could also serve to illustrate some of the points made around core datasets, etc.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
46-47		**Proposed change**: A *registry-based study* is an investigation of a research question using the infrastructure of (a) new or (an) existing registry(-ies) for patient recruitment and data collection that utilises the exposure and outcomes data from (a) registry(-ies).	
53-56		**Proposed change**: A *patient registry* is defined in this Guideline as an organised system that collects data and standardised information – typically for ease and speed of search and retrieval - on a group of people (or participants) defined by a particular disease or condition, and that serves a pre-determined scientific, clinical and/or Health Technology Assessment (HTA) for public health (policy) purpose.	
57-58		Some organizations have moved to the use of the term 'participant'. We should align on terminology and include in the terms **Proposed change**: The terms 'people', 'participants' and 'patients' used in this definition and Guideline are synonyms, independently of the health status of the individual.	
59-61		**Proposed change**:	

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		The EMA Patient Registry Initiative and the Cross-Committee Task Force on Registries (2) have explored ways to improve the use of patient registries for registry-based studies in order to support the benefit-risk evaluation of medicinal products for regulatory decision-making within the European Economic Area.	
59-70		**Comment**: Suggest starting the introduction section with the second paragraph and then continue with the first. The fundamental concepts would be more clearly connected with the objectives and scope of the guideline on registry-based studies **Proposed change**: Swap lines 59-70 with 46-58	
71-101		As healthcare systems differ, examples of data that are in or out of scope for this guideline would be necessary. For example, administrative claims databases appear to be out of scope, but could claims data linked to EHR data be "in scope"? Please provide examples of data that are in or out of scope for this guideline on registry-based studies.	
72-74		**Proposed change**: The objective of this Guideline is to provide recommendations on key methodological aspects that are specific to the use of patient registries by marketing authorisation applicants and holders (MAAs/MAHs) planning to conduct registry-based studies.	
74-75		**Proposed change**:	

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		To support these recommendations, key considerations and aspects of patient registries that regulators view ~~consider~~ important for their use as good regulatory practice in registry-based studies are included in the Annex.	
87-93		The reference to ATMPs including gene therapy at Line 87 is potentially confusing when the very next paragraph (lines 88-93) indicates that "product registries" are out of scope of this guideline. Also, it is not clear if the studies described in reference to "product registries" can be considered as "patient registries" or "registry-based studies." Please confirm the intent and scope of this guideline around registries defined by product use, e.g. registries which can support studies involving multiple products are in-scope but registries relating only to a single product are out of scope?	
88-101		Product registry is not included in the scope because, as stated at line 91-92: "and does not include specific aspects related to the use of patient registries". This needs to be clarified a bit more by adding some examples; this could be as simple as adding a reference to record 109-110: "Examples where registry-based studies may be useful for evidence generation are presented below"	
102 – 425		Several sub-sections within Section 3 (e.g., study protocol, study population, data quality management, data analysis) address issues that are not specific to registry-based studies but apply to research studies in general. To help future users, the guideline should include specific registry-based	

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		study examples or use cases to illustrate the specificities of registry-based studies compared to other type of studies.	
102 – 425		The potential biases and limitations of registry-based studies could be covered in a new, separate section, possibly between current sections 3.8 (Data analysis) and 3.9 (Data reporting). It is important to identify in study protocols the potential biases and limitations of the study; this can be referenced in section 3.4 (Study protocol). After data analysis and as part of preparing to report a study, when interpreting the study results the potential issues identified in the study protocol as possible sources of bias and limitations should be considered.	
102 - 425		Although the content is well written and comprehensive, it might help future users if some of the text is replaced by tables, figures and/or diagrammatic images. This would allow for less linear reading	
122 - 124		Does this mean that information concerning a comparator group (for a single arm registration trial) can be used for the purpose of primary hypothesis testing or does it just serve to provide benefit and risk assessment? It will be helpful to further clarify.	
141 - 144		The guideline states, "Registry-based PASS can provide data to quantify and characterise risks, to identify risk factors for the occurrence of adverse reactions, to evaluate the safety profile of a medicinal product in long-term use, or to assess patterns of drug utilisation that add to knowledge on the	

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		benefit risk profile of the medicinal product." This is true but can only be accomplished if there is sufficient sample size and an adequate comparison group. The guideline should include a statement noting that this requires sufficient sample size and appropriate study design.	
153 - 160		In addition to studies to evaluate the effects of medications received during pregnancy, the guideline should also cover the use of registries for studying other populations which are usually not enrolled in clinical trials, e.g., children/adolescents, frail/elderly patients.	
165 – 166		The guideline would benefit from new sections and/or additional discussion on these topics presented in the table -- When to start or stop a registry-based study, including a discussion on determining criteria for terminating or discontinuing a study (e.g., futility). This will be context-specific but general principles will apply. -- Raising registry awareness and recruitment of relevant patient groups. Efforts to raise awareness are particularly important if recruitment is slow. Traditional recruitment efforts have included distributing leaflets via physicians, but what other means would be acceptable in an increasingly online environment? -- The most appropriate uses of registry data. -- Expectations for patients' participation compliance	

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		and retention/drop-out in a registry and/or registry-based study with long time follow-up. Moreover, tables should ideally be labelled to facilitate cross-referencing.	
165 – 166		In the registry-based study column of the table, the retrieval of historical-control derived from registries and also potential use of these data to derive informative priors that can be used to inform new trials (for instance for conditional power calculations) should be mentioned.	
165-166 (table)		Given differences within and between countries, it would be helpful for future users if the guideline could provide case studies or published examples.	
165-6 (table, row 6, Data quality control)		For registry-based studies, row 6 states: "Additional quality assurance to be performed for the study data; quality control to be prospectively defined and assessed with a risk-based approach; for RRCTs, data quality control involves central adjudication of events and treatment complications." EMA should clarify whether monitoring and adjudication are required outside of RRCTs within non-interventional studies.	
166 – 223		It should be specified that possible across-country/registry differences in standards of care (definitions and practices) might exist. These should be considered and analysed in terms of the potential impact on the study inputs and the interpretation of the results.	

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166 – 223		Feasibility planning should also include consideration of clear definition and discussion of thresholds for acceptable discontinuation and/or termination of a registry-based study.	
187 – 216		It would be helpful to add, where appropriate, references to other sections in the guideline where relevant topics are discussed in more detail – for example, in the bullet point mentioning risks of bias, a reference to the detailed discussion of bias in section 3.8.	
187 – 216		In addition to the factors suggested, it should be noted that feasibility analysis should also include counts of disease/events and exposure predictions within the registry or registry source population. In general, a discussion of internal validation would be helpful.	
187 – 216		A detailed presentation of the epidemiological context in which the registry is based is essential. Although there is discussion about the registry population in an Annex, it is important to introduce this concept in the main body of the guideline. The registry may meet all the feasibility criteria, but if there is insufficient uptake or coverage of the drug / agent of interest and the study is proposed based on future projections, this should be discussed. The guidelines should include specific elements of epidemiological context and define the expected contents of a 'background' section of the study protocol. This could precede the section on	

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		sample size estimate but warrants explanation independent of the sample size estimate.	
201		It is unclear from the draft guideline if SUSAR collection is relevant only to RRCTs and not also to non-interventional studies. A confirmation that SUSAR collection is relevant only to RRCTs is required.	
217 – 218		**Proposed changes:** "The final report of the feasibility analysis should ideally be published in the EU PAS Register, and may be submitted either separately or as part of the proposed protocol for a registry-based study. ~~and should be published in the EU PAS Register".~~	
224 – 271		Where more than one registry is suitable, yet not all of them are intended to be involved in the registry-based study, the study protocol should provide the justification of the choice, i.e. inclusion and exclusion criteria, and discuss the potential impact on dataset and findings.	
266 – 269		**Proposed changes:** *If a registry-based study is to be conducted across multiple registries, a common study protocol should specify inclusion and exclusion criteria for registries to be incorporated as well as ~~be developed based on~~ core data elements and a common design, even if some aspects of the study may vary according to the characteristics of each registry and not all outcomes may be combined across all registries*	

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262 – 265		The guideline should include discussion of criteria for registry-based study termination/discontinuation, if applicable. The aim of the registry-based study could affect the rationale behind data collection beyond planned or resulted from study size calculation. As it is important and potentially ethical issue separate paragraph is needed or at least short communications like the one proposed below: Registry based study, especially interventional clinical trial, might need to provide rationale and criteria for termination (stopping rule) if prolonged duration is not justified.	
271		The guideline should include a reference for the statement "Additional legal requirements apply if the registry-based study is a clinical trial" so that interested readers know where to locate these additional legal requirements. For example: Clinical Trial Regulation - Regulation EU No 536/2014.	
290 – 306		The guideline should note (perhaps after line 299, for example) that registries that have the ability to link to medical records are preferable to those that are not able to link to medical records.	
292 - 295		However, by limiting the data extracted, unknown or unidentified confounders may be missed.	
296		A better description of what is meant by "initially" missing data would be helpful. How can data that is not in the registry be collected post-hoc?	

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307 – 325		If a registry is designed as a general registry, it may not capture the information needed for a specific research question. If we implement stringent data cleaning, we may lose the ability to establish internal and external validity of the data.	
326 - 398		This section of the guideline should: • Include discussion of methods that allow examination of risk over time (e.g., time to event analysis) as risk may not be constant over time and may be anticipated to vary over time. • Highlight the need to consider analysis methods that adjust for events that are competing risks, exposure ascertainment approaches and analysis methods for time varying exposure over time. • Include a high-level discussion of the use of matching methods (e.g. propensity scores/scoring/weighting) that attempt to eliminate/reduce the extent of differences between groups of patients being compared (e.g., defined by medications taken).	
330		It says "all changes". If the changes have been reflected in the amendment of the study protocol or SAP, are they still necessary to be explained and discussed in the study report?	
365 – 377		This section focuses only on prevalent and new user designs. There are newer and alternative designs that could be considered that overcome the challenges and trade-offs discussed, e.g., prevalent new user designs and self-	

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		controlled case series. The guideline should acknowledge the existence of alternative design approaches.	
378 – 381		Is this a common situation? An example to further explain this situation can be helpful, e.g. in what scenario the initiation of treatment under study occurs after the follow up period.	
405 – 408 & 429 – 430		Several mentions relate to transparency and listing studies on the EU PAS Register. Recommend that this is double-checked to ensure that the requirement remains consistent with Chapter 8 of the ENCePP Good Practice Guidelines.	
411 – 412		"all study results" should be modified to refer to the prespecified analyses. Accordingly, it can be replaced by "all study results from the analyses prespecified in the protocol and/or statistical analysis plan"	
429 – 430		Table section of Record Keeping. For imposed PASS and PAES: the MAH shall ensure that all pharmacovigilance information as well as the analytical dataset and statistical programmes used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection. If the analytical dataset is purely secondary data, the retention policy of the data custodian may prevent the MAH from holding an electronic copy as part of their data licensing agreement. Please also provide guidance on the length of the specific retention period.	

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527		Pregnancy status and pregnancy outcomes would be sufficient only for registries not explicitly designed to study pregnancy. The guideline should clarify that much more information than just status and outcomes would be needed for pregnancy-specific registries and studies.	
653 – 690		The guideline should note that a registry-based study should have a flowchart in place explaining which stakeholders have access to which information. For example, in a patient registry, a hospital providing basic characteristics about a patient should not necessarily have access to, e.g., biomarkers of the same patient if these are provided by an independent source.	

Please add more rows if needed.