EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 December 2020

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

Comments from:

Name of organisation or individual
Jan Hillert, representing Karolinska Institutet, the Swedish MS registry and the Big MS Data Network

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)*
	I write these comments from my viewpoint as a neurology professor and long-term register holder, i.e. of the Swedish Multiple Sclerosis registry (SMSreg), which I started more than 20 years ago and which has become one of the leading MS registries. The SMSreg has since 10 years expanded into a Neurology Register as we have developed similar registries for 9 other disease groups within clinical neurology, including Parkinson's disease, epilepsy, migraine and neuromuscular diseases. In addition, I also speak as the chairman of the Big MS Data Network (BMSD) which consists of 6 national and international MS registries (the Czech, Danish, French, Italian and Swedish national MS registries as well as MSBase, an international registry with partners in 37 countries. Participation in PASS is an important activity of both SMSreg and BMSD, and BMSD is in the process of applying for a qualification opinion of BMSD and its contributing registries to participate in and potentially run PASS projects in multiple sclerosis (MS). The points of view expressed here are meant to be of general relevance and not confined to my own field of clinical and research expertise. I am personally very positive towards EMA's Patient	

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	Registry Initiative as well as to the initiative to define guidelines on registry-based studies. I expect such guidelines to become important given the increased use of patient registries not only in clinical research in general but evidently in studies intended for regulatory decisions. The guidelines are generally well organised and cover the relevant topics, and the design and specification of general criteria in specific annexes is appropriate and gives room for more detailed definitions and explanations. In general, I have only one principal concern, which is that the ambition of assuring stringency of data has led to the expression of expectations on design, structure and quality measures that will be very difficult to live up to, specifically for pre-existing, patient registries. In case of a registry set up for the purpose of a specific study, naturally this is much less of a concern. As I understand it, the existence of mature quality registries in several disease areas and their potential usefulness as data sources for regulatory decisions was one of the triggers of the Patient Registry Initiative. Such registers typically each has a long history and often go back several decades. As a consequence, their	

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	variable, design, technical platforms and governance structures have developed stepwise and are the result of consensus efforts within the responsible clinical or scientific communities. Naturally, you cannot expect such registries to live up to the same ideal criteria as a contemporary registry set up de novo. Another property of existing patient registries, is that few have the option of providing primary data and will be confined to secondary data use. The reasons are existing governance models in which the individual physician is providing data to the registry but is not a participant in the project. Data are simply not collected for the purpose of the specific study and thus secondary. In other words, it seems, which is indeed not surprising, that the current version of the guidelines is highly influenced by standards gradually developed by EMA, FDA and other regulatory bodies and meant to allow robust conclusions to be drawn from RCTs. With the risk of over-simplifying - in RCTs, sample sizes are typically chosen with narrow margins resulting in low tolerance to errors introducing noise potentially hiding the sought-after signal. Thus, high accuracy is the currency. When real world evidence is generated by patient	

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	registry data, sample size and precision are still critical, but not the prime issue. Instead the currencies are representativity of the target population, also expressed as generalizability or validity, and sometimes time span, allowing analysis of events over many years. Thus demands on quality criteria and measures should be allowed to differ depending on the nature of the study, e.g. between an RCT, a treatment registry and a patient registry. In conclusion, I'm concerned that too ambitious guidelines may result in the exclusion of many data sources that could not only give robust results but also offer qualities not available by other means, most importantly validity of conclusions for the target population. Such qualities are evidently also of importance in regulatory decisions. Some specific points raised below exemplify the concerns raised above. Finally, I would like to suggest, that either the text of the Guidelines would be adapted to give room to some more flexibility. Alternatively, it could be stated that the Guidelines should be applied variably strictly depending on the nature of studies and data sources to be used.	

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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)*
454-461		Comment: It should be explained, that when using an existing patient registry, individual are typically not individually enrolled, but have consented in general for their data to be used in an IRB-approved research project. Proposed change (if any):	
492-550		Comment: The description of core data expected to be available shows clearly lack of understanding how the dynamics of data collection differ between patient registries and RCTs. I state this with a vast experience of what is possible to collect broadly in a clinical situation, which is sharply different from what you take as granted in an RCT. The experience is: the more you ask for, the less you get. I have failed many times to get quality of data for such items as co-morbidities, concomitant treatment and life-style. For many registries such data are either collected in special efforts or obtained by linkage to other data sources. On the other hand, administrative information, Patient data, disease variables, disease-related treatment, safety and pregnancies are true core elements that every registry should provide. Patient-reported outcomes is by experience also a challenge to some but a core elements of others.	

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		Lines 551-563: Comment: Standardization of data elements is key but is developed gradually by international collaboration and should be used when available and stimulated. Proposed change (if any)	
564		Comment: The Quality management paragraphs contain descriptions of an ideal situation which most sensible registry custodians strive for but few have reached. I hope those principles can be used with somewhat less stringency than now expressed, or few existing patient registries may be able to comply and thereby to contribute their data. Proposed change (if any):	

Please add more rows if needed.