28 June 2019

Submission of comments on 'Discussion paper: Use of patient disease registries for regulatory purposes – methodological and operational considerations' (EMA/763513/2018)

Comments from:

Name of organisation or individual
Alliance for Regenerative Medicine Contact person: Annie Hubert (ahubert@alliancerm.org) The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment and commercialization of transformational treatments and cures for patients worldwide. By leveraging the expertise of its membership, ARM empowers multiple stakeholders to promote legislative, regulatory and public understanding of, and support for, this expanding field. ARM convenes all stakeholders with an interest in regenerative and advanced therapies to provide a unified voice for our 320+ member organizations, including companies – especially small- to medium-sized enterprises (SMEs); academic/research institutions; non-profit organizations; patients, and other members of the advanced therapies community. Our aim is to connect all parts of the innovation lifecycle to address the unmet needs of patients, particularly through supporting commercialization objectives via legislative and policy frameworks that enable next generation therapies to reach those who need them. To learn more about ARM, visit http://www.alliancerm.org. Transparency register number ID: 244710319190-73

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, in Word format (not PDF).

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1. General comments

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	<u>Welcoming and supporting the discussion paper:</u> The Alliance for Regenerative Medicine (ARM) warmly welcomes the discussion paper on the use of patient disease registries for regulatory purposes. The discussion paper is well structured, comprehensive and, for the first time, defines good registry practices which ARM had earlier advocated for. We believe this initiative can be instrumental in the adoption of standards for Real World Evidence (RWE) and we encourage all stakeholders (HTA bodies, payers, patients organization, healthcare professionals), including from other regions, to work together to contribute to the development of registries that meet the needs of all. ARM Members understand that the scope of this discussion paper is broader than good registry practice (GRP) and encourage the EMA to develop a guideline focusing on GRP in more detail in collaboration with the Heads of Medicines Agencies and Member States to avoid fragmented approaches. Additionally, as registries are referred in different ICH chapters including safety and efficacy, on the long-term, an ICH guideline on good registry practices may facilitate harmonization and better acceptance of RWE. A collaborative approach could be followed by building on existing good practices in epidemiology or/and the expertise of other stakeholder groups (e.g. the joint ISPOR-ISPE Special Task Force on Real-World Evidence). It is proposed that this GRP would define principles (in the same way as GCP, GMP) without strictly promoting a specific standard or a fixed process. Flexibility would be needed to allow national specificities to coexist with those principles. <u>Registries are highly relevant to ATMPs:</u> Advanced Therapy Medicinal Products (ATMPs) include living cells and genes and have unique attributes which differentiate them from standard pharmaceuticals and biologics. Some of the specific characteristics of ATMPs include the facts that they are often administered just once or a handful of times within a short period, with long-term, potentially life-long effect. Possible complications include long-term immunogenicity (e.g. for donor-derived cell therapies) or insertional mutagenesis (e.g. for some gene therapies). For these reasons, rigorous monitoring and long-term follow-up constitute critical components for the approval and	

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	commercialization of ATMPs. Registries represent one of the main tools to document long-term safety and efficacy effects and generate real-world evidence (RWE). Therefore, they are particularly important for ATMPs. In addition, registries may be instrumental to provide robust data on natural history of disease which are essential to better characterize meaningful endpoints and provide a benchmark for interventional studies, particularly when double-blind, placebo-controlled studies cannot be carried out for ethical or practical reasons. For many ATMPs, the safety and efficacy data available prior to approval may be limited and non-comparative. Close patient follow-up and disease registries are therefore vital in order to build up evidence on long-term effects. <u>Qualification process:</u> Two registries, the ECFPSR and EBMT, have been qualified by the EMA to date. Although EMA recently published on its website the process for qualification, additional clarification on the qualification process by the CHMP and the process to maintain it would be welcome. Such additional clarification will facilitate interactions between MAH and registry holders. In light of the process, resources and timelines used in the previous qualification procedures, it may be advisable to develop a guide for qualification describing the minimum quality standards expected for a qualified registry, the definition of quality data, the cleaning of "old" secondary data, and audit requirements. <u>Need for collaboration with stakeholders to define registry requirements</u> As RWE is used for other purposes than regulatory, namely is used in HTA and funding decisions, including in requirements for market entry agreements, there is a need to develop robust methods to meet the needs of all. In order to avoid duplication of efforts and lack of sustainability for any registry, considerations to include HTA/QoL related core elements would be helpful.	

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	ARM believes that there should be a pre-approval coordination between the EMA and HTA agencies to define the registry data requirements and address issues such as registries fragmentation, leading to fragmented access to data, and potential duplication of data entry in different registries. This is needed to avoid that each individual HTA agency comes with additional variables to collect, making the data collection very complex and difficult to start in some countries or centres, at the expense of the quantity and quality of the data collected. Such difficulties have been reported in the case of CAR-T products for example, despite the qualification of EBMT registry for regulatory purposes. It would be beneficial that any mandatory study (PASS/PAES) that could also serve to collect necessary data to support EUnetHTA is agreed between EMA and EUnetHTA to ensure consensus on variables that need collection. In addition, as registry filing is burdensome for the treatment centers, the expectations of the regulatory and HTA bodies should remain realistic and too detailed CRF should be avoided. The data collection should match the usual, standard medical record content and any additional requirement kept to the minimum. Including too complex data requirements will make it difficult for treatment centres, jeopardizing the data collection and quality of the resulting analysis. Therefore, the EMA and HTA bodies should drive a wide consultation with future treatment centers, and not be based on disease expert opinion only, to define the scope of the registry and the required data collection. <u>Need for international collaboration and linkage between registries:</u> International collaboration is important to avoid fragmentation of RWE collection, preventing pooling and analysis of data. The concept of 'Good Registry Practice' could be expanded internationally, with development of international standards and could be proposed as part of an ICH initiative. The discussion paper encourages linkage of existing databases/registries, however understanding options for how to best link these databases, e.g. either into a consolidated/umbrella registry or a registry study combining data from multiple registries, is unclear. Pooling/combining of data from multiple distinct registries, the linkage of registry data with other data sources (e.g. administrative claims, EHRs), or when a registry is	

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	being actively designed can potentially allow for a richer and more complete source of patient data. Further discussion and recommendations on this topic, and in particular, methodological and operational considerations for data pooling/linkage, would be very beneficial. At least two levels of harmonization may be needed to ensure interoperability and linkage between registries, one relating to the database structure, the other relating to the information collected: - Data structure: the alignment on common rules as those exposed for interoperability by the EUnethHTA PARENT project are welcome. Technical solutions may exist to remove obstacles and a new database format may emerge in the future to become a new standard, facilitating harmonisation. - Harmonization of the content (data collected): initiatives such as the International Consortium for Health Outcomes Measurement (ICHOM) project could be leveraged, with enlargement to information relating to product assessment. Implications of registries linkage with respect to GDPR requirements would also have to be considered and addressed. Need to develop pan-European Real-World Evidence infrastructure Real-World Evidence (RWE) development is instrumental in addressing uncertainties on long-term effect, safety, health-related quality of life and use of healthcare resources for ATMPs. To address these uncertainties, there is a need to develop RWE infrastructure at European level to support long-term evidence generation and procedures to enhance quality of the collected evidence. The development of such infrastructure would require strong collaboration between regulatory and HTA bodies and other stakeholders. ARM advocates for investment in the development of pan-European infrastructure to generate long-term evidence on ATMPs, develop harmonized standards and robust methods to analyze long-term evidence development plans and data, enhance the quality of evidence, as well as to generate and strengthen the evidence on natural history datasets in key indications and disease areas.	

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	<u>Funding and incentives:</u> Successful registries are the outcome of a shared effort of treatment centers, patients, medical societies and MAH. Unlike in clinical trials where the sponsors usually deal with a dedicated clinical trial team in treatment centers, a registry may have to be placed in centers without the infrastructure, capabilities, or resources needed for adequate data collection and registry management. Funding needs to address the maintenance of the registry, storage and administrative structure in addition to its core business. Some stable funding mechanism is needed to keep registry running per good quality and good registry practices (e.g. "official registries"). Where new registries need to be set up as part of post-approval commitments, the financial incentive provided by the MAH may not be enough to ensure data collection and data quality in some centers where limited resources are available. This means that the good quality of a registry cannot be guaranteed by the MAH in the absence of adequate funding. Furthermore, the principle that the MAH is the only financial sponsor for a registry to be set up, qualified and maintained is questionable. ARM calls for incentives to be established for the set-up, qualification and maintenance of registries at pan-European level (such as with the development of pan-European RWE infrastructure as discussed above), and/or at national or regional level. Such incentive should not be limited to meet the need of one specific stakeholder (e.g. payers) but should, overall, be sufficient to meet the needs of all stakeholders. Where existing registries are used for registry studies, the registry infrastructure and maintenance should not become dependent on the funding from registry studies with a limited number of sponsors. For example, a MAH may need to provide adequate funding to carry out post-authorisation commitments such as a non-interventional post-authorisation safety study (PASS) – as stated in section 6 of the paper – but how to ensure that the funding is limited to the registry study and does not serve to fund the registry? Here too, alternative funding sources need to be secured to make sure registries meet quality standards and remain sustainable over time. Additional principles around funding and incentives, including the need for transparency, should be considered	

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	and addressed in the discussion paper, for instance as an additional item under the governance section. <u>Governance:</u> Establishing good governance principles is critical; the roles and responsibilities for all stakeholders should be clear before using the registry, the impact of potential national fragmentation should be addressed and a change management system, sufficiently flexible to meet the needs of all should be foreseen. The qualification process should not be seen as a means to fix potential issues. It would be helpful if these aspects could be added and reinforced in the beginning of the governance section. Section 5.8. on governance could also be supplemented with consideration on the following situations: • Where a single study protocol using one registry could be leveraged to support PASS or PAES for different products with different MAHs, the role and responsibilities of each MAH remain unclear. Further guidance on the governance, obligations and sponsor responsibilities would be beneficial. • How to approach closure of registries and how the information collected need to be archived? In case a registry would end, a mechanism of transfer of data to another, preferably qualified, registry should exist. The GDPR obligations in such a situation should be addressed, i.e. to retain personalized information only for as long as it is required for a fair and legitimate purpose. A transfer of archive to preserve data and the investment of patients and others for research would need to be done in line with the GDPR obligation. • How can a MAH enact changes needed in the registry in order to fulfil its obligations? As a sponsor of a registry-based study, a MAH is bound by critical regulatory and legal obligations. A mandatory requirement made by the regulator to use a dedicated / qualified registry owner would require a correct balance of responsibilities between the registry owner, the MAH and regulatory authorities, with a true trialogue (as initially proposed in previous EMA workshops) so that MAH has a role in the governance and decision-making process for the registry. • Funding and incentives: How funding should be approached to ensure sustainability of registries and how to avoid that registry infrastructure is too dependent on the funding from MAHs or registry studies with a	

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	limited number of sponsors? The discussion paper only contains very brief information on the need to have principles for receiving funding from private and public sources, with no details. ARM would like to see further guidance on this as explained on the comment above. • How to approach auditing? Good registry practices and quality management are important to provide confidence in the quality of the data that can be generated. A system of independent audit could be envisaged. Finally, as a general principle, ARM would like to avoid monopolistic situations where specific medical societies would be appointed for registry coordination in some diseases. Data ownership, intellectual properties and data publication on large series of patients are of high scientific interest and may be sensitive topics for the medical community with possible divergent interest between medical societies, cooperative groups or other formal and informal national or European networks. ARM believes that the MAHs should have the freedom to choose between the different groups to optimize their good adhesion, the data quality and best costs management. <u>Reporting of safety information:</u> Safety reporting requirements should be clearly described and fully aligned with Good Pharmacovigilance Practice (GVP) Modules 6 and 8, or alternatively should refer to the relevant GVP Modules. For disease registries, safety reporting according to national requirements is proposed. For registry studies, GVP will apply. With respect to GVP requirements around all AE reporting, this may be logistically challenging as registries are not designed to accommodate this. <u>Terminology & definitions:</u> Terminology could be clarified, or definitions added for some aspects in the discussion paper: - "Quality" and "high quality": quality management is a key theme in the discussion paper, but it is unclear what a 'high quality' registry would be. More details to qualify quality, with measurable criteria would be welcome. For instance, in section 5.6.2. Requirements of data quality, the percentage of completeness or	

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	the range of acceptability for completeness could be mentioned. - There is no definition of "Registry study", such addition would be beneficial. In addition, the scope of registry studies should be clarified, with a definition (e.g. "Detailed investigation and analysis of a research question or hypothesis using a registry as a source population") - Differentiation between primary data collection and secondary use of existing registry data. A clear understanding of primary data collection and secondary use of existing data should be made in the context of a registry study or a newly initiated registry. In the guidance, it is unclear what the conditions to use one versus the other are. In some sections (e.g. Data quality page 8), this is not sufficiently clearly differentiated. Such differentiation is very important and additional clarification in chapter 3 (core concepts) and in elsewhere in the document, with illustrative examples would be helpful. - Differentiation between primary data collection and active data collection: would active data collection only refer to primary data collections, meaning the collection of prospective data, or would this include "secondary data collection" even though only retrospective data is utilized? The overlaps and/or the differences between active data collection and primary data collection should be clarified. <u>Conclusion and next steps</u> ARM would appreciate understanding EMA's overall vision of stronger collaboration between registries, their sustainability and EMA's willingness to support interactions with other stakeholders and to align internationally through appropriate forum (e.g. ICH). A definition of next steps would be helpful in that regard. In its conclusion, the EMA states it is "*willing to support interactions and provide tools to facilitate recognition of disease registries as data sources to conduct studies for registries*", however minimum requirements for registries to be qualified for regulatory purposes are not entirely clear. If a company wants to leverage an existing registry to satisfy a post-approval requirement for safety and/or efficacy, the requirements, i.e. acceptability levels for the different quality indicators, would need to be clear. To address some of the comments above, ARM would like to propose a multi-stakeholder meeting with regulators, experts in GDPR, not for profit organizations, registry holders, patient associations, industry,	

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	member state representatives, and relevant authorities to collectively discuss important governance questions such as funding, sustainability, closure and transfer of registry data and reach balanced decisions that preserve scientific independence and registry participants' rights.	

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)*
P.7 – Lines 11-12		**Comment**: "*Reporting of suspected adverse reactions through the national or regional pharmacovigilance system should be encouraged*". "Encouraged" is vague and not strong enough to ensure adequate reporting.	
P.16 – Line 17		**Comment**: Missing word **Proposed change :** "*The registry can be used as a source of patients <u>data</u>, based on either primary data collection…*".	
P.16 – lines 15-22		**Comment**: A differentiation should be made between primary data collection and secondary use of existing registry data in the context of existing registry or initiated registry.	
P.23-26 (Section 5.6.)		**Comment**: In the context of post-authorisation registries study imposed to MAHs by regulators as a condition of the marketing authorisation, the legal responsibility to conduct the study and provide valid and reliable results lies with the MAHs as stated on lines 32-35 on page 23. However, the paper does not clarify the responsibility for data quality assessment and who should be conducting the data source verification and periodic auditing in such situation.	
P.28 Lines 2-22 (Section 5.7.1)		**Comment**: Further clarify on the requirement for collection and reporting of ICSRs from registries and from registry studies would be helpful to ensure the viability of any proposal and compliance with safety reporting obligations.	
P.29 (Section		**Comment**: The discussion paper only contains very brief information on	

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5.8.1.)		the need for registry coordinators to have principles for receiving funding from private and public sources, with no details. General principles on funding and incentives would need to be further elaborated (see under 'General Comments' above).	
P.35 –36 (section 6.1.)		**Comment**: Due to varying national requirements and differences in routine clinical practice, a same registry study protocol can be classified as a non-interventional study in some countries and as an interventional study in others. Additional guidance is sought on how to deal with multi-national registry studies considered non-interventional in some countries and interventional in others.	
P. 35-36 (section 6.1.)		**Comment**: It would be helpful to provide some examples on how data from registries have served, for example in product label updates or when assessing study results with an orphan drug compared to natural disease history data. This would help clarify situations where registries can be used to support regulatory evaluations.	
P.35 – Lines 26-27		**Comment**: It would be helpful to define further what should be covered in contracts with independent third parties in a registry study so that the MAH can fulfil its obligations. Presently it is not entirely clear how this would work and who is liable in case of failure by the independent third party to fulfil its contractual agreements.	
P.41 – Lines 5-7		**Comment**: The requirement to report all non-serious and serious AE can be a significant barrier to participation to the registry study and would make it increasingly non-naturalistic. It is proposed to consider adopting safety reporting obligations that are 'fit for purpose' and ideally limited to the potential AEs that are of greatest concern to maximize recruitment and retention.	

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P.42 – Lines 5-25 (Section 6.9)		**Comment**: It would be helpful to clarify the scope of the reporting requirements, whether this cover registry studies required by the EU regulators (PASS/PAES) or also other registry studies not part of regulatory commitments.	

Please add more rows if needed.