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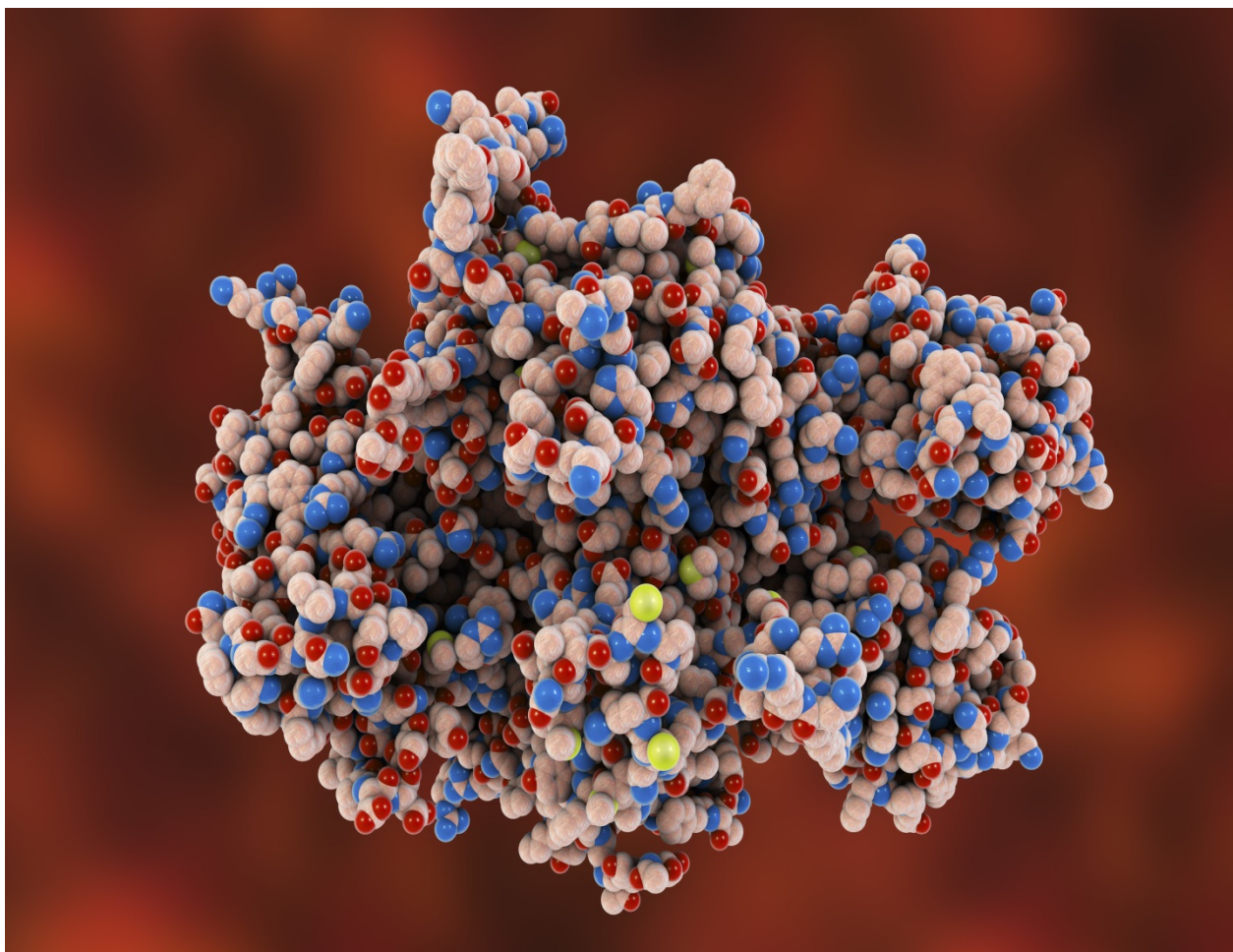
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Pharmacovigilance and Epidemiology and Regulatory and Science Management Departments
Inspections, Human Medicines, Pharmacovigilance and Committees and Evaluation Divisions

Report on Haemophilia Registries

Workshop 8 June 2018

Patient Registries Initiative



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1. Executive summary

The European Medicines Agency's [Initiative for Patient Registries](#) aims to optimise and facilitate the use of patient registries for benefit-risk evaluations of medicinal products. In the case of haemophilia therapies, registries have a crucial role because evaluations are complicated by the relatively small numbers of patients, especially of previously untreated patients, who can be recruited to clinical trials and by the increasing numbers of novel products. Moreover, inhibitor development, associated with a reduction in efficacy of the haemostatic effect of Factor VIII and occurring very commonly during the first fifty days of treatment with Factor VIII products in previously untreated patients, is the most serious complication in the management of haemophilia A. These challenges have contributed to a revision of the 'Guideline on the clinical investigation of recombinant and human plasma-derived Factor VIII products' ([FVIII Guideline](#)) removing the obligation to perform clinical trials in previously untreated patients and requesting post-authorisation studies based on a set of core data elements to be collected in haemophilia registries.

In order to ensure the practical implementation of the requirements related to registries in line with the FVIII Guideline including agreement on the processes for data access, sharing and reporting, and on additional data elements to be collected by registries to support regulatory evaluations of novel products such as monoclonal antibodies, gene therapies and PEGylated products, the European Medicines Agency hosted a multi-stakeholder workshop in June 2018. This explored the opportunities and challenges of using existing registries to support post-authorisation studies of haemophilia products. The expected outcome of the workshop was agreement by stakeholders on implementable recommendations to advance the evaluation and monitoring of haemophilia therapies through the use of patient registries. The factors discussed included registry governance, patient consent, data sharing, data quality, registry interoperability and core common data elements needed by stakeholders.

Workshop participants had clinical, regulatory or development experience with haemophilia products and included representatives of European registries, patient organisations, health care professionals, health technology assessment bodies, the European Commission, marketing authorisation holders and applicants, and national competent authority and European Medicines Agency experts.

This report summarises observations made by the participants on the use of registry data to support registry-based post-authorisation studies of haemophilia products. It makes recommendations for actions that aim to facilitate and improve registry data use.

The immediate priority action is for stakeholder collaboration to ensure that as many as possible of haemophilia registries (and their affiliated treating centres) can collect the core data elements specified in the FVIII Guideline. To support this, it is also necessary to harmonise data element definitions across registries, establish measures that ensure data are collected systematically with appropriate verification and quality assurance, and confirm that arrangements are in place to permit data sharing. Registry holders, patient representatives, regulators and marketing authorisation holders and applicants need to optimise their communications in order to expedite these actions and ensure that previously untreated patients in particular can be appropriately evaluated when they commence haemophilia treatment.

Table 1 summarises the main recommendations from the workshop and Table 2, the actions required to achieve the objectives.

Table 1: Summary of the main recommendations on utilisation of registry data in supporting regulatory evaluations of haemophilia therapies

| Topic | Workshop Recommendations | Measures Agreed | Contributors |
|---|--|--|--|
| Governance | Registries and haemophilia treating centres to ensure that all patients are offered the opportunity to be included in a registry and that centres collect the FVIII Guideline core data elements | Registries to collaborate to optimise treating centre inclusion, data collection according to FVIII Guideline requirements and patient representativeness | Registries Regulators MAHs/MAAs |
| | MAHs/MAAs to be aware of the Guideline-specified core data elements to be collected in registries and of the additional data elements to be collected for novel products | Improve registry, MAH/MAA and regulator collaboration so that registry holders understand the nature and quality of data needed for regulatory purposes | |
| | Communicate to patients and the public the benefits and uses of patient registry data | Raise patient and public awareness of the value of registry data for monitoring treatment follow-up | Registries Patient representatives |
| Informed consent, data protection and data sharing | Ensure treating centres confirm that registry patients have provided consent in line with European GDPR | Registry holders to ensure confirmation of consent is received from centres | Registries |
| | Review whether current patient consent is broad enough for data sharing following GDPR | Alert treating centres to ensure consent is adequate for sharing of data in line with GDPR Registries to establish a centralised process for stakeholders to request and obtain data Registries and MAHs/MAAs to agree a common protocol for the conduct of post-authorisation studies | MAHs/MAAs |
| Core Common Data elements | All registries to collect the FVIII Guideline-specified core common data elements | Ensure treating centres collect FVIII Guideline-specified core common data elements | Registries Regulators |
| | Harmonise data element definitions across registries | Provide data element definition information to stakeholders | MAHs/MAAs |
| | Agree on additional common data elements to be collected for novel products | 'Crucial' data elements for evaluation of novel products to be included in registries | Patient representatives HTA & payer representatives |
| | Agree on PROs that could feasibly be collected systematically | All stakeholders to collaborate on defining PROs | |
| Data Quality | Implement indicators on registry data consistency, accuracy and completeness | Registries to publish at agreed intervals reports on their data quality & completeness | Registries |
| | | Provide guidance on the EMA qualification procedure | Regulators |

EMA = European Medicines Agency; GDPR = General Data Protection Regulation HTA = health technology assessment; MAH / MAA = marketing authorisation holder / applicant; PRO = patient reported outcome.

The actions required of stakeholders to achieve the objectives are summarised in Table 2.

Table 2: Summary of actions for the main stakeholder groups

| Group | Actions |
|--------------------------------------|---|
| Regulators | <ul style="list-style-type: none"> Facilitate communications between Registries and MAHs/MAAs especially at early stages of product development Provide guidance on the EMA qualification procedure Support registries in developing a policy on sharing aggregate (summary), pseudo-anonymised, and individual patient data and establishing a centralised process for requesting and obtaining data Communicate to relevant stakeholders the potential value of data from patient registries for supporting regulatory decision making Engage with relevant initiatives exploring use of registry data for healthcare evaluations, e.g., the European Network for Health Technology Assessment (EUnetHTA) Joint Action 3 |
| Registries | <ul style="list-style-type: none"> Ensure registries and treating centres collect the FVIII Guideline-specified core common data elements according to harmonised data element definitions For novel products, ensure that data elements prioritised as ‘crucial’ and ‘should have’ are available in the registries according to common definitions of each element Collaborate across registries to ensure that standard processes for quality assurance of data, including source data verification are applied systematically Develop a policy and a process for sharing aggregate (summary), pseudo-anonymised, and individual patient data and establish a centralised process for stakeholders to request and obtain data Inform patients on the benefits and uses of registry data including appropriate data sharing with relevant stakeholders Inform MAHs/MAAs and regulators of the type and detail of data that may feasibly be collected by registries and shared within consent and governance parameters |
| MAHs / MAAs | <ul style="list-style-type: none"> Liaise early in product development with registry holders to consider the post-authorisation data required if marketing authorisation is granted Commence planning for post-authorisation data collection early in product development Develop a preliminary common study protocol for post-authorisation studies and explore with the registry holder/s and regulators if the registry could fulfil the data needs, for example, through a scientific advice procedure |
| Patient Representatives | <ul style="list-style-type: none"> Engage with registries in order to communicate to patients the potential uses and associated benefits and risks of sharing their data to assist in medicines evaluations Advise on appropriate quality of life and patient reported outcomes that might feasibly be collected systematically and included in registries |
| HTAs and Reimbursement Bodies | <ul style="list-style-type: none"> Learn about the nature and purpose of the data collected in patient registries Engage with registries to adapt their data collection where feasible to support information needs, including for quality of life measures and patient reported outcomes Continue stakeholder engagement via current initiatives, e.g., EUnetHTA JA 3 |

It is recommended that, as a next step, an implementation plan should be developed by each of the stakeholder groups facilitated as needed by the European Medicines Agency’s Registries Task Force. The workshop report is without prejudice to any European Medicines Agency committee opinion on any products submitted or authorised in the European Union.

2. Background

The European Medicines Agency (EMA) is exploring the use of real world data in supporting medicines authorisation and supervision once on the market. EMA's [Initiative for Patient Registries](#), launched in September 2015, aims to optimise and facilitate the use of existing patient registries for the benefit-risk evaluation of medicinal products.

A Patient Registries Workshop in October 2016 which included registry holders, patient groups, marketing authorisation holders (MAHs), health technology assessment (HTA) representatives, reimbursement representatives and regulators made [recommendations](#) on optimising the use of registries. The EMA subsequently hosted multi-stakeholder disease specific patient registry workshops on Cystic Fibrosis, Multiple Sclerosis and chimeric antigen receptor T-cell (CAR T-cell) therapies. In each case, participants agreed on implementable recommendations to assure the quality and interoperability of the respective registry data for supporting regulatory evaluations while ensuring also that appropriate governance arrangements are in place. The recommendations are published ([Reports](#)) and have informed ongoing actions by registry groups in all three areas.

Haemophilia is a rare disorder arising from mutations in the genes coding for coagulation Factor VIII (haemophilia A-HA) or Factor IX (haemophilia B-HB) leading to reduced synthesis of the factors. In Europe, around 1:10,000 children are born with haemophilia A and 1:50,000 with haemophilia B. Treatment poses challenges for regulators and healthcare providers not least because of the small numbers of patients, especially previously untreated patients (PUPs), available to be included in trials of rapidly-evolving new treatments including factor concentrates with prolonged half-lives (PEGylated products), monoclonal antibody and gene therapies. The development of factor VIII inhibitors, especially among PUPs during the first 50 treatment exposure days, is a major concern. These challenges are reflected in the revised 'Guideline on the clinical investigation of recombinant and plasma-derived Factor VIII products' ([FVIII Guideline](#)) removing the obligation to perform clinical trials in previously untreated patients and requesting post-authorisation studies based on a set of core data elements to be collected in haemophilia registries.

In order to make recommendations on: 1) how the FVIII Guideline requirements could be operationalised effectively in haemophilia registries; 2) the additional data elements needed for evaluations of novel treatments including PEGylated products, monoclonal antibody and gene therapies, and 3) quality of life measures, the EMA hosted a stakeholder workshop in June 2018.

3. Workshop objectives, participants and methods

3.1. Objectives

The primary objectives of the workshop were to:

- Ensure the practical implementation of the requirements related to registries in line with the revised FVIII Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products
- Agree on processes for data access, data sharing and reporting, and clarify roles of all involved stakeholders
- Agree on the additional data elements to be collected on novel products (PEGylated products, monoclonal antibody therapies, gene therapies) and on quality of life.

3.2. Participants

Most workshop participants had experience with haemophilia products from a scientific, clinical or regulatory perspective. They included representatives from registry groups, representatives of patient organisations and health care professionals, HTAs, the European Commission, MAHs and marketing authorisation applicants (MAAs) for haemophilia products, national competent authority (NCA) experts and EMA experts. The workshop agenda and participant list are available in Appendix 1.

3.3. Methods

Prior to the workshop, three work-group topics were identified that would assist in delivering the primary objectives:

Group 1: Registries' operation to fulfil the guideline requirements

Group 2: Use of registry data for regulatory purposes: legal, ethical and practical considerations

Group 3: Additional data to be collected for novel products (PEGylated products, monoclonal antibody and gene therapies)

Each work-group included participants from all of the stakeholder groups. Prior to the workshop, participants were sent pre-work packages that sought their views, experiences, and needs in relation to their group-work topic. The responses were collated and provided as background information for each group prior to the workshop. The intention was that participants had a good understanding of each other's perspectives in advance of the workshop in order to facilitate productive group work on the day.

The agenda consisted of an outline of the workshop objectives, the regulatory perspective on the efficacy and safety issues relating to haemophilia therapies, the patients' perspective on treatment follow-up needs, an overview on haemophilia registries and information from the European Commission on its European Platform on Rare Diseases Registration (EU RD Platform). During three hours of moderator-facilitated group work based on the pre-work packages, each group agreed its recommendations then reported them to all of the workshop participants for further discussion.

Following the workshop, the work-group observations and recommendations were summarised and circulated to group members for review. They were then collated as eight topics in Section 4. Section 5 provides an outline of the actions arising. The draft report was circulated for review to all workshop participants prior to publication on the EMA website.

4. Workshop observations and recommendations

In this section, participants' detailed observations and recommendations relating to the use of patient registry data to support regulatory evaluations of haemophilia therapies are described.

4.1. Enablers and barriers to the use of patient (disease) registries for post- authorisation studies

Enablers

- Regulatory context: the regulatory guidelines and procedures for post-authorisation safety studies ([PASS](#)) and efficacy studies ([PAES](#)), as well as the guideline on advanced therapy medicinal products ([ATMPs](#)) provided by EMA enable a framework for dialogue between pharmaceutical companies, registry holders/academics and regulators on the design of such studies; parallel scientific advice discussions with HTA and reimbursement agencies provide additional opportunities to collect data in the context of medicines authorisation and reimbursement.
- Common data elements (fields) for haemophilia registries: The [Guideline](#) requirement for a core set of data elements to be collected in haemophilia registries to support post-authorisation follow-up of patients, especially of PUPs, should encourage haemophilia registries to ensure that they can collect the necessary data.
- Qualification process: the opportunity of a [regulatory qualification](#) of registries will foster in-depth understanding by regulators of registry data while endorsement and/or recommendations concerning the proposed use of such data in regulatory decision-making may reassure stakeholders about its suitability.
- Registry integration and collaboration: The need for lifelong treatment of haemophilia coupled with the evolution of treatments supports the integration of patient registries in clinical practice. Many treatment centres already collaborate to provide information to registries. Ideally collaboration needs to advance to establish a Europe-wide network of registries that are harmonized in their core data element collection and capable of providing comprehensive data representative of as many haemophilia patients as possible.
- Some registries already collect data in line with the FVIII guideline requirements on immunogenicity in PUPs (e.g. [PedNet](#), [FranceCoag](#), [UKHDO](#)).

Barriers

- Most European countries have their own national registries but treatment centres collaborate with the registries on a voluntary basis and there is no registry network that ensures haemophilia patients Europe-wide are offered the opportunity to be included in a registry. While there are examples of co-operation, for example PedNet is a collaboration of over 30 treating centres in 18 countries, and [EUHASS](#), part of EUHANET, has 80 centres from 26 countries contributing pharmacovigilance data, there is considerable heterogeneity in the landscape and some countries have multiple registries.
- Common data elements (fields) for haemophilia registries: while the FVIII Guideline lists the core set of data elements required in a registry, the element definitions remain to be established. An important next step is for stakeholders to implement common data element definitions across treating centres and the associated registries in order to be able to conduct reliable studies that combine equivalent data from multiple registries.
- Quality standards of many haemophilia registries may not fully meet the expectations of regulators, MAHs / MAAs and HTA bodies. Depending on the numbers of treating centres

contributing to the registries, setting-up new procedures for data quality control may have large resource implications.

- Unless registries are integrated into clinical care with data entered directly and/or able to be imported electronically from other datasets at the time of a clinical encounter, any need for duplicate entry of data from clinical records to the registry is likely to be associated with considerable time and resource implications.
- Real time data compilation is rarely possible currently and timelines for routine data collection, pooling and analysis and for adverse event (AE) data collection and reporting may not meet the regulatory requirements. A distinction needs to be made between secondary use of registry data collected routinely, allowing aggregated analyses on the incidence of AEs, and primary collection of data for a specific study, e.g. analysis of AEs occurring in individuals.
- Sustainable funding is necessary to ensure registry viability and quality standards. Some registries receive project-based funding from MAHs/MAAs for specific studies while others have an annual fee for data access and for some, limited government funding is available. Registries may need structural funding to strengthen routine operations such as monitoring and auditing activities and maintenance of a quality system. This situation explains why quality assurance may be stronger for specific studies than for routine activities (e.g. data entry at centre level).
- Patient-reported outcomes (PROs), including quality of life, are not routinely collected by treating centres or by registries; certain PROs are of particular relevance for HTA and reimbursement bodies as well as for patients.

Recommendations

- While registries were acknowledged by the workshop stakeholders as the way forward for collection of data on haemophilia patients, products, and treatment outcomes, collaboration between registries needs to be strengthened to optimise treatment centre inclusion and patient representativeness.
- Registries should work with haemophilia treating centres to ensure that all patients are offered the opportunity to be included in a registry, and that all treating centres collect the core set of data elements outlined in the FVIII Guideline.
- Agreement by stakeholders on definitions for the core common data elements described in the Guideline will support the standardisation of data collected in all treating centres (based on a single database for each registry) and consequently in the associated registries, facilitate the mapping of data elements and the conduct of registry-based studies.
- Sustainable funding is a prerequisite to support staff training and to develop and maintain adequate data and process standards; registries should work with relevant stakeholders to improve their sustainability.
- Regulators and HTA bodies should provide guidance on the expected quality assurance approaches that support the use of registry data in regulatory evaluations.
- All stakeholders should collaborate to agree relevant PROs for regulatory, HTA and reimbursement evaluations that are feasible to be collected systematically.

4.2. Informed consents

Observations

- Patient consent is critical for the reporting and sharing of data. Under the general data protection regulation (GDPR) of May 2018, patients own their personal data and can ask the treating centre and/or associated collaborators to delete their data at any time (<http://www.eugdpr.org/>).

- Haemophilia centres are responsible for obtaining patient consents but consents vary according to centre and national legislation as well as on the nature of data sharing leading to complications at many levels when attempting to share data.
- Consent renewal requirements vary between countries and centres.
- Depending on the nature of individual studies, study-specific consent may be needed.
- There is a risk that children reaching the age of consent are 'lost' for future study unless registries and treating centres are vigilant to the necessity of obtaining their consent as adults for collecting and sharing their data.
- Some patients are registered at more than one treating centre leading to risks that their data could be duplicated in several registries if they have consented at both centres to registry participation.

Recommendations

- Treating centres should remain accountable for ensuring patient consent and updating childhood consents; affiliated registries should receive from each centre a confirmation that patients have consented to share their data.
- Registries need to work actively with treating centres to communicate to patients and the public the benefits of data sharing for public health and the potential uses of the data arising from patient participation in registries.
- Patients should be provided with clear information on why data are collected, the benefits and risks of participation, the uses for the data, and with whom it will be shared and at what level of detail. They should be aware that they can withdraw consent at any time and that they can provide consent for some activities but not others.
- Registries should take a central role in working with their affiliated treating centres to harmonise patient consents ensuring they are aligned with the GDPR as well as with national requirements allowing sharing of aggregated and anonymised patient-level data for research or regulatory purposes.
- Registries need to have a system in place to minimise the risk of patient / data duplication. While a unique patient identifier for registry participation is attractive, it would be a major administrative task to implement this notwithstanding identifiers already in use in different countries.

4.3. Governance, data sharing and study protocols

Observations

- Currently, haemophilia registries provide anonymised pooled data in their reports to industry and could follow the same practice for providing data to regulators.
- Registries do not provide patient level data to regulators or MAHs / MAAs, but they can provide anonymised patient level data if required and justified.
- Registry concerns about sharing data for analysis with regulators are related to patient consents, losing data control and data protection. Individual registry mandates may also affect data sharing, for example, the FranceCoag registry can provide data to other parties through the French Public Health Agency which provides it with funding.
- In studies of investigational new products, the MAH/MAA concerned may not wish to share data, or confidentiality agreements may prevent sharing, especially of pre-authorisation data. Owing to the limited numbers of patients available for study, this may lead to missing information on large proportions of particular patient groups. The gap may be important, for example, in the case of Factor VIII inhibitor development.

- Registries generally prefer to perform data analyses within the registry but analyses through a third-party (e.g. academic institution) could be acceptable.
- Protocols agreed by relevant stakeholders who could include MAHs / MAAs, registries and the EMA are used for answering research questions or for providing the information requested in risk management plans (RMP).

Recommendations

- As a general principle, registry based studies should adhere to the recommendations of the [Good Pharmacovigilance Practice \(GVP\) Module VIII](#) (post-authorisation safety studies) and of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct ([ENCePP Code of Conduct](#)) for data management. While the patient owns her/his data, the registry holder should be in charge of the control, use and sharing of the registry data.
- For specific studies fully or partially funded by MAHs/MAAs, and including regulator-imposed studies, the research contract and the study protocol should include the plans for the submission of progress reports and final reports to regulators, including milestones. The research contract should describe intellectual property rights arising from the study, access to study data and dissemination of results, allowing sharing of unpublished results with regulators and with MAHs/MAAs initiating the study.
- For regulatory studies to be conducted across multiple registries, a common protocol needs to be developed based on the core common data elements in the FVIII Guideline. This should be agreed by the registries, the EMA and the MAHs/MAAs. Depending on the study question, a comparison group should be included.
- Specific protocols may be needed to answer a regulatory or research question that requires additional data and these may need to include a request for anonymised individual patient data if appropriate.
- Specific protocols need to be sufficiently detailed as to allow registries to assess whether they can participate (in terms of data availability and quality).
- Data analysis should preferably be performed by the registry owner or by a third-party (e.g. academic centre, contract research organisation or EMA) rather than by MAHs/MAAs. If data analysis is conducted by the registry holder or a third party, results of product-specific data analysis should be shared with regulators and the concerned MAHs/MAAs in line with provisions of the study protocol.

Regulatory agencies and HTA bodies should be able to receive from registries aggregated data, fully anonymised or pseudo-anonymised patient data upon request, in line with governance procedures.

Recommendations for novel products

- A three-way communication between MAAs, registries and regulators may be established before or at an early stage of a product authorisation application with the following objectives:
 - To be aware of the data that are collected or can be collected by registries when information or studies are requested from MAAs, and to agree on the data to be collected for a specific product.
 - To support harmonisation of datasets across registries to allow for pooled analysis by the registry, the MAAs and /or the regulators.

Such communication should be initiated by MAAs and supported by regulators at an early stage during the development process or authorisation procedure, using opportunities such as the EMA's

business pipeline meetings, [PRIME](#)-related discussions, [scientific advice procedure](#), pre-submission meetings or interactions with Rapporteurs and Scientific Committees.

4.4. Data entry, format and frequency of analysis

Observations

- The core data set described in the FVIII Guideline is a positive first step in harmonising data collection across haemophilia registries.
- Registries providing information on their procedures have electronic data collection through haemophilia centres or patients via device applications, for example, at [France Coag](#), there is an electronic form (eCRF) for data entry from the clinic; at [AICE](#) (Italy), data are entered by treating centre staff using an electronic form with data imported from patient records and an electronic App is shortly due for patient data entry; for [PedNet](#), data are collected from 32 treating centres in 18 countries using a web-based system and are entered to the registry from patient records according to a protocol; at [HemoNED](#) (NL), data are entered by the treating physician/team and patients provide data using an electronic App.
- The capacity for electronic linkages to patient source data included in the registry as well as other potentially relevant data, for example, data from electronic health records, laboratory / radiology records, prescription databases, education or employment records, is desirable in order to support data verification and registry quality processes and to provide comprehensive evaluations based on registry data. This may depend on systems capacity as well as on patient consents and data protection requirements.
- A centralised common data warehouse and the Central Meta Data Repository within the European Platform on Rare Diseases ([EU RD Platform](#)) being developed by the European Commission's Joint Research Centre (JRC) and presented at the workshop, could provide a means to share data from multiple registries but there are many hurdles to achieving this currently including matters relating to data sharing. The EU RD Platform of the JRC also offers a pseudonymisation tool service for registries participating in the EU RD Platform.
- The frequency of registry data analyses is related to the study question and may be limited by the fact that analyses are performed on routinely collected registry data; there may be a time-lag between data collection by a treating centre and upload to a registry.
- Timelines for reporting of adverse events (AEs) and suspected adverse drug reactions (ADRs) depend on the context (routine reporting versus reporting for specific studies and complexity of the report) and may be adapted if necessary, e.g. to be aligned with reporting timelines for PSURs periodic safety update reports (PSURs). Some registries actively prompt treating centres to report ADRs, for example, UKHDO asks affiliated treating centres to report ADRs and deaths monthly.

Recommendations

- Registries need to agree on a common data collection format that meets technical specifications that support data quality in terms of consistency, accuracy and completeness (Section 4.5)
- Registries need to agree on the timelines for data upload from treating centres to registries. For example, if the registry platform is embedded in the clinical care record, then data availability in the registry is immediate but if data need to be extracted from clinical records for upload to the registry, then delays arise. In the latter case, agreement between treating centres and the registries is needed on the frequency of data upload.
- Timelines for data collection and reporting should be proposed in the study protocol by MAHs/MAAs (e.g. in the context of a scientific advice procedure or a risk management plan) or by registries (e.g. in the context of a scientific advice procedure) aligning where appropriate with existing

registry reporting timelines and agreed with regulators. The following frequencies of data analyses by registries are proposed:

- Immunogenicity: at least annually
 - Thromboembolism: early detection is possible therefore more frequent data analysis is desirable
 - New products: the PSUR cycle and the Risk management plan could be used to establish the frequency of analyses
- Registry data are currently not suited for causality assessment of AEs in individual cases based on expedited reporting requirements, but a system should be in place in the registry to ensure that physicians are aware that suspected ADRs should be routinely reported according to the normal practice of the national pharmacovigilance system, even if they are also reported to the registry and even if an additional system for the reporting of AEs to the MAH has been established for a specific study.
 - Registries are currently best suited for secondary data collection ([GVP Module VI C1.2.1.2](#)) and periodic reporting of aggregated or summarised data based on an agreed protocol; acceptable levels of data quality for regulatory evaluation purposes should be agreed between MAHs and regulators; funding mechanisms for reporting procedures should be agreed between MAHs and registries.

4.5. Common data elements required for regulatory evaluations

Observations: Core common data elements to be collected in registries

- The common data elements outlined in the FVIII Guideline as 'essential allowing for potential data merging and analysis' are presented in the Table 3 below.
- The core data elements are already implemented in PedNet, UKHCDO and FranceCoag and will be implemented in the Italian registry, AICE, by 2019.

Table 3. Factor VIII Guideline: Core data elements required in haemophilia registries

| Core Data Element Category | Core Data Elements Required |
|---|---|
| Administrative information | <ul style="list-style-type: none"> • Registry • Center |
| Demographic information | <ul style="list-style-type: none"> • Patient Identifier • Date of birth • Gender |
| Anamnestic information | <ul style="list-style-type: none"> • Type of haemophilia • Severity of haemophilia (% Factor activity) • Date of diagnosis of haemophilia • Family history of haemophilia/inhibitor (yes/no) • Risk factors (e.g. FVIII gene mutation) |
| Haemophilia treatment information (each treatment) | <ul style="list-style-type: none"> • Date of treatment • Number of exposure days since start of treatment • Weight • Product • Treatment regimen/modality (on demand/prophylaxis) • Dose • Treatment reason (e.g. surgery, trauma, pain) • Bleeding (yes/no), if yes • Reason • Location • Severity • Follow-up treatment |
| Inhibitor information (each measurement) | <ul style="list-style-type: none"> • Date of measurement • Titre (BU/mL) • Assay description (e.g. Nijmegen, Bethesda, ELISA) |
| Relevant information on concomitant events (e.g. infections, allergic reactions) | <ul style="list-style-type: none"> • Date of event onset • Event description • Date event resolved |

Recommendation

- Definitions for the data elements required by the FVIII Guideline need to be agreed and applied across treating centres and registries; the associated data dictionaries need to be established and maintained.

Observations: Additional common data elements needed for novel products

- Prior to the workshop, participants suggested additional common data elements that should be collected for novel products (i.e. PEGylated products, monoclonal antibody and gene therapies).
- During the workshop, participants then evaluated the proposed elements, refining details as necessary, specifying which data elements are already captured in registries, adding overlooked elements, and coming to an agreement on whether, in a haemophilia registry, each element listed was “crucial” or “nice to have”. Where appropriate, a frequency for data collection was also proposed.

Working definitions

- **Crucial:** Participants agreed that this data element is core and must be included in the registry; if it is not currently available in the registry, then measures must be taken in the short term to include it in order to support regulatory decision-making.
- **Nice to have:** Participants agreed that this data element is of interest and if already available in the registry, it may be useful for some stakeholders but they did not consider that measures should be taken to include it

Recommendation

- Definitions also need to be agreed for the additional data elements and applied across treating centres and registries; the associated data dictionaries need to be established and maintained.

Following the workshop, the outline recommendations were collated by the EMA Patient Registries Initiative team and were reviewed by group participants. This step allowed for collection of missing information and clarifications where needed. Table 4 sets out participants' recommendations on the data elements needed for novel products.

Table 4. Proposed core data elements needed for novel products

| Category | Data | Already captured in at least one registry? | Priority | Frequency where applicable |
|---|--|--|--------------|----------------------------------|
| Medical history | • Immune tolerance induction (ITI, yes/no) | Yes | Crucial | NA |
| | • Annual Bleeding Rates and subfields (traumatic/ non-traumatic) | Yes | Crucial | NA |
| | • Patient product preference | No | Nice to have | NA |
| | • Product name; Dose; Frequency of administration (only for PEGylated products) | Yes | Crucial | Annually |
| | • Treatment: batch and lot number for gene therapy | No, but can be retrieved if required | Crucial | NA |
| Immunogenicity | • Binding and Neutralising antibodies (rFVIII and rFIX including extended half-life products, PEGylated, gene therapy) | Yes | Crucial | Defined by 2 tests when detected |
| | • Other antibodies (anti-Mab) (only for Mab products)/ aPTT anti-PEG antibodies | No | Crucial | NA |
| | • Association with adverse event | | | |
| Safety monitoring (organ function, biochemistry) | • Hepatic function (including alternative causes for enzymes elevation) (PEGylated products, gene therapy) | Yes | Crucial | Annually |
| | • Renal function (PEGylated) | Yes | Crucial | Annually |

| Category | Data | Already captured in at least one registry? | Priority | Frequency where applicable |
|--|---|--|--------------|--|
| | products) | | | |
| Safety reporting | • Fatalities | Yes | Crucial | NA |
| | • Transmission of infectious agents (plasma-derived products) | Yes | Crucial | NA |
| | • Viral vector-associated disease (gene therapies) | Yes | Crucial | NA |
| | • Nephrotic syndrome (PEGylated products) | Yes | Crucial | NA |
| | • Neurological events (PEGylated products) | Yes | Crucial | NA |
| | • Thromboembolic events (including thrombotic micro-angiopathy) | Yes | Crucial | NA |
| | • Malignancies and other potential late events | Yes | Crucial | NA |
| | • All serious adverse events (AEs) | Yes | Crucial | NA |
| | • New onset autoimmune events | No | Nice to have | NA |
| Concomitant medications | • Concomitant coagulation factors administered | Planned | Crucial | NA |
| | • Concomitant bypassing agents administered (Mab) | Yes | Crucial | NA |
| | • All other concomitant medications (only on trigger and to be collected while reporting AEs) | Partially | Crucial | NA |
| | • Dose and timing (only on trigger) | Planned | Crucial | NA |
| | • Drug interactions | No | Crucial | NA |
| Other data elements proposed | • Perioperative management, especially for emergency surgical procedures | Partially | Crucial | NA |
| | • PEG-levels | No | Nice to have | Annually |
| Quality of Life data | • EQ-5D-5L | No | Crucial* | Annually |
| | • SF-36 | No | Nice to have | Annually |
| | • Brief Pain Inventory Short Form | No | Nice to have | Annually |
| Specific data for gene therapy | | | | |
| Medical history and efficacy monitoring | • Factor VIII activity (%) | No | Crucial | Quarterly for first year then annually long term |
| | • Factor IX activity (%) | No | Crucial | |

* This element is considered crucial for Health Technology Assessment but the practical difficulties of collection in a registry setting were highlighted by stakeholders. NA: not applicable; Mab: monoclonal antibody; SF-36: Short Form (36) Health Survey; EQ-5D-5L: EuroQoL 5-dimension 5-level health-related quality of life instrument.

4.6. Factors affecting data quality

Observations

- Factors affecting data quality include the systematic collection of core common data elements, common definitions, a common coding terminology, e.g. the Medical Dictionary for Regulatory Activities ([MedDRA](#)), a regular reporting process and the availability of an audit system allowing verification of the accuracy and completeness of the registry data.
- For information beyond the core data set described in the FVIII Guideline and proposed for novel products (above), for example, medications for other disorders, a harmonised dataset across different registries is also desirable but multiple registry datasets could be used if data are mapped and standard queries are applied.
- The potential for data entry errors can be minimised by introducing automated checks in the data entry software (conditional on funding availability).
- Compliance of centres with accurate data entry and robust data management must be assured. This can be achieved by continuous training and feedback from the registries to the treating centres (conditional on funding availability).

Recommendations

- Key components of data quality should include:
 - Uniformity: use of a minimum set of common core data elements, common definitions, a common coding system and common data entry procedures; as nomenclature systems evolve over time, a mechanism should be in place to take account of changes.
 - Completeness: registration of complete information on all eligible patients, absence of / minimal missing data.
 - Accuracy: data available in the registry are a correct representation of patient data, e.g. data available in medical charts / records.
 - Timeliness: there is timely recording and reporting of data based on the intended use of the data and an agreed procedure.
- The highest level of data quality should be pursued, and all quality assurance approaches justified given the anticipated use of the data.

4.7. Quality verification processes

Observations

- Individual registries have measures to support and verify the quality of data in routine practice. For example, PedNet has external monitors who undertake site visits and perform source verification of 100% of the baseline data from treating centres.
- There is no external audit system applying to haemophilia registries. Data monitoring is undertaken when registries participate in clinical trials and can also be done in post-authorisation studies (PASS and PAES).
- Registries would benefit from improved capability to implement quality control measures in routine operations, including the monitoring of the completeness and quality of data through automated quality control systems (e.g. edit checks with alerts).
- Completeness of data could be improved with linkage between registries and electronic healthcare records.

Recommendations

- Established quality standards should be in place and adequate for routine activities and for all registry studies; a dedicated data control and follow-up system should be introduced only for very specific studies or where the existing system is not (yet) adequate.
- A critical aspect of quality control is the definition and implementation of key indicators measuring e.g. the extent of missing data, the timeliness of data entry or the fraction of data that undergoes source data verification, and their acceptance by regulators (see also Section 4.8)
- Timelines for monitoring and periodic reporting of aggregated data should be defined between participating registries, regulators and MAHs/MAAs, as applicable, to allow data availability at important milestones, e.g. for PSURs.
- External (and/or internal) audits (routine or *ad-hoc*) may be agreed between registries and MAHs/MAAs or regulators to provide confidence in quality control systems, for example to verify that all eligible patients are registered.
- Software solutions for data entry, transfer and verification from electronic medical records should be pursued.
- European registry holders may submit an application for a [regulatory qualification](#) through a scientific advice procedure of the EMA.
- In relation to harmonisation of data elements across registries:
 - The use of common definitions for data elements is critical to support comparative studies and /or studies potentially combining data from several registries and should be finalised as soon as possible.
 - The definitions in use by the registries or the system used should be available to stakeholders including regulators, MAHs/MAAs, and HTA and reimbursement bodies.

4.8. Data quality indicators

Workshop participants considered three components of data quality - consistency, accuracy and completeness of the data. The table below summarises potential indicators of quality and the registry systems or solutions that would be needed to facilitate these.

Table 5. Potential indicators of data quality

| Data Quality Component | Definition | Proposed indicators of quality | Quality Solutions to facilitate data quality |
|------------------------|--|--|---|
| Consistency | Uniformity of the data overtime (e.g. lab data routinely entered) | Number of fields changed over time | Manual checks at centres level, audits |
| | | % of fields missing over time | Standard terminology, coding |
| | | % of forms reported per scheduled follow-up | Standard operating procedures, user guides Campaigns, dashboards for clinicians |
| Accuracy | Accuracy of data entry: no errors, no contradictions or impossibilities in data, absence of duplicates | Change in value of data filed by x% creates alerts | Drop down menus, alerts, text prompts, flags |
| | | Variability across fields | Validate against source data (eg, 10%), cross form validation |
| | | | Staff training, software checks. Help screens/desks, training, newsletter |
| | | | Funding for data managers |
| Completeness | How much data is missing? | Agreed % of fields completed in audit procedures (e.g. >90%) | Audits |
| | | Lost to follow up % | Mandatory fields Engagement with patients and/or health care providers (HCPs) |
| | Absence of core variables | Minimum agreed core common data elements reported | Agreed list of data elements and definitions |
| | | All treated patients reported, not selected patients only | Cross check patient numbers with numbers of products used at treating centres during a defined period |

5. Next steps and Actions

5.1. Role of the EMA Patient Registries Task Force in guiding implementation of recommendations

The EMA Patient Registries Task Force will work with stakeholders as needed to facilitate implementation of the workshop recommendations. Where possible, the Task Force will advise stakeholder groups in completing the actions outlined (Sections 5.2 – 5.6).

5.2. Actions for Regulators

Regulators need to support other stakeholders by:

- Facilitating communications between registries and MAHs/MAAs through existing EMA platforms;
- Agreeing a timeline with registries for harmonisation of data element definitions;
- Ensuring that post-authorisation study outcomes are based, as far as possible, on the core data collected in the registries reflecting the Factor VIII Guideline and the stakeholder recommendations on crucial additional data elements to be collected for novel products;
- Supporting registry efforts to optimise measures for assuring the quality of registry data;
- Providing guidance on the EMA qualification procedure with HTA/reimbursement body involvement;
- Collaborating with relevant initiatives that are also exploring the potential of registry data to contribute to healthcare evaluations, for example, the work of EUnetHTA in its Joint Action 3 ([Work Package 5B](#)) and the European Platform on [Rare Diseases](#) Registration.

5.3. Actions for Registries

Registries must ensure that treating centres contributing data can collect the Factor VIII Guideline-specified core common data elements according to a harmonised format and common definitions. This is especially important given removal of the obligation to perform clinical trials in PUPs and should be implemented rapidly. For novel products, registries need to ensure data elements prioritised as 'crucial' and 'should have' are available according to a common definition for each element. Element definitions (or the definition system used) need to be known by stakeholders.

Registries need to prioritise measures to assure the quality of registry data and its reliability by:

- Developing or reinforcing data quality control for routine operations in each registry.
- Ensuring that processes for quality assurance of registry data, including source data verification, are harmonised and applied systematically across registries.
- Considering opportunities such as a registry regulatory qualification that may provide reassurance on the suitability of the data to support regulatory decision making.

Registries should optimise communications with patients, MAHs/MAAs, HTA and reimbursement bodies and regulators by:

- Informing patients on the benefits and uses of patient registry data including appropriate sharing of patient data with relevant stakeholders in line with the [GDPR](#).

- Informing MAHs/MAAs and regulators of the type and detail of registry data that may feasibly be shared within routine consent and governance parameters and of additional data that could be collected with additional informed consent.

5.4. Actions for MAHs/MAAs

Both MAHs and MAAs need to:

- Have an in-depth understanding of the extent and detail of data available in patient registries when planning registry-based post-authorisation studies;
- Develop a preliminary study protocol for post-authorisation studies of any new product and explore with the registry / registries and the regulator how the registry could fulfil the data needs, for example through the Scientific Advice procedure.
- As applicable and needed, liaise with registry holders to discuss means to increase data quality control to comply with their regulatory obligations.

MAAs for novel products need to:

- Understand the regulatory data requirements that are likely to arise during the application process especially in planning for post marketing surveillance given the prolonged duration of follow-up that is required for some products;
- Initiate discussions with registries and regulators before or at an early stage of a marketing authorisation application on the relevance and adequacy of one or several existing disease registries for the long-term monitoring of their specific product.

5.5. Actions for patient groups

Patient representatives are encouraged to engage pro-actively with registries in order to:

- Ensure they can communicate to patients the potential uses and associated benefits and risks of using patient registry data to assist evaluations of novel products, especially in long-term follow up and including appropriate data sharing with relevant stakeholders;
- Provide insight for other stakeholders on patient reported outcomes that might feasibly be collected in registries.

5.6. Actions for HTAs and reimbursement bodies

HTAs and reimbursement bodies should develop their understanding of the possible roles for patient registries in supporting HTA and informing reimbursement decisions by:

- Learning about the nature and purpose of the data collected in patient registries for novel products;
- Engaging with registries to adapt or optimise data collection in order to support their information needs where feasible, taking into account the challenges of collecting some measures such as EQ-5D-5L in a clinic setting;
- Engaging with patient groups to understand relevant PROs that can feasibly be collected.

Ongoing work by the European Network for Health Technology Assessment in its Joint Action 3 ([Work Package 5B](#)) is highly relevant in this respect bringing together multiple groups to focus on registries in health technology assessment.

6. Conclusions

There is clear recognition by stakeholders of the opportunities and challenges of using registries in post-authorisation studies based on a set of core data elements to be collected in the registries in line with the FVIII Guideline.

Agreement on harmonised definitions for all registry data elements and on 'crucial' data elements to be collected for novel products, along with systematic processes to verify source data and assure registry quality will help ensure that data from as many patients as possible will be available to contribute to these activities. It is important for all stakeholders, most especially for patients and previously untreated patients in particular, that haemophilia registries widely ensure they can collect the appropriate data.

[Regulatory qualification](#) of registries would help ensure regulators understand the data while regulators' endorsement and/or recommendations concerning the proposed use of such data would provide reassurance to users regarding its suitability.

The immediate priority action is for stakeholder collaboration on registry collection of the core data elements specified in the FVIII Guideline in order to ensure that previously untreated patients in particular can be appropriately evaluated when they commence haemophilia treatment. Early priorities are to improve communications between registry holders, regulators and MAHs/MAAs and to create a centralised process for requesting and obtaining data. The ultimate objective is that relevant data from patient registries will be incorporated in benefit-risk evaluations throughout medicinal product lifecycles.

7. Glossary

- Aggregate data: numerical or non-numerical information collected from multiple sources and/or on multiple measures, variables, or individuals and compiled into summary reports
- Anonymised Data: Data 'rendered anonymous in such a way that the data subject is not or no longer identifiable' (Recital 26, GDPR)
- EUnetHTA: European Network for Health Technology Assessment
- GDPR: Generalised Data Protection Regulation <http://www.eugdpr.org/>
- [GVP](#): Good pharmacovigilance practices
- HTA: Health Technology Assessment
- Individual patient data - Data separately recorded for each participant in a clinical study http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf
- Informed consent: The process by which a patient learns about and understands the purpose, benefits, and potential risks of a medical or surgical intervention, including clinical trials, and then agrees to receive the treatment or participate in the trial (medicinenet.com)
- MAA: Marketing authorisation applicant
- MAH: Marketing authorisation holder
- NCA: National competent authority
- PAES: Post authorisation efficacy study
- PAS: Post authorisation study
- PASS: Post authorisation safety study

- Patient Registry: An organised system that uses observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000658.jsp
- PRO: Patient reported outcome
- Pseudo-anonymised Data: data processed 'in such a way that the data can no longer be attributed to a specific data subject without the use of additional information.' (Appendix 3; GDPR Article 4 (5))
- PSUR: Periodic safety update report
- QoL: Quality of life

8. Appendices

Appendix 1: [Workshop agenda and participants list](#)