20 April 2022
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European Medicines Agency

# Minutes - Fifth DARWIN EU® Advisory Board meeting

Wednesday 20 April 2022 10:00 – 12:00 CET, virtual meeting

| Role | Name |
|---|---|
| Co-Chairs | Emer Cooke (EMA) |
| Present | Almath Spooner (EFPIA, EuropaBio, EUCOPE); Claudia Furtado (INFARMED); Jesper Kjaer (DKMA); Katharina Schneider (BfArM); Aldo Maggioni (ESC); Markus Kalliola (SITRA); Niklas Hedberg (TLV); Sara Rafael Almeida (EC); Sari Palojoki (ECDC); Aurora Di Filippo (AIFA); Peter Arlett (EMA); Xavier Kurz (EMA); Juan Jose Abellan (EMA); Sophie Groeneveld (EMA) |
| Apologies | Karl Broich (HMA, BfArM); Wim Goettsch (ZINL), Malek Bentayeb (HDH); Elizabeth Vroom (UPPMD) |
| Minutes | Andrej Segec (EMA) |

| Item | Preliminary draft agenda | Name | Action | Mins |
|---|---|---|---|---|
| 1. | Adoption of draft agenda and minutes from the last meeting | All | For adoption | 5’ |
| 2. | DARWIN EU® project update | Andrej Segec (EMA) | For information | 20’ |
| 3. | NCA use cases for RWE: initial discussion | Claudia Furtado (INFARMED, PT) | For discussion | 30’ |
| 4. | Criteria for selection of data partners (principles and priorities) | Xavier Kurz (EMA) | For discussion | 30’ |
| 5. | Classification of RWE studies | Juan Jose Abellan (EMA) | For discussion | 20’ |
| 6. | Tour de Table | All | | |
| 7. | AOB<br>• Information items | All | | |

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Emer Cooke (EMA) opened the meeting and welcomed the participants to the Fifth DARWIN EU® Advisory Board (AB) meeting and chaired the meeting. Karl Broich (BfArM) was unable to attend and sent apologies.

# 1. Adoption of draft agenda and minutes from the last meeting

The draft agenda was adopted without amendments. Minutes from the last meeting on 16 February 2022 were adopted and will be published on the EMA website.

# 2. DARWIN EU® project update

Andrej Segec (EMA) presented the update. The AB was informed on the activities since the selection of the DARWIN EU® Coordination Centre (CC) and the last update at the February 2022 AB meeting. A public multi-stakeholder information webinar was held on 24 February 2022 with approx. 700 attendees from pharmaceutical industry, academia, healthcare professional and patient organisations, media and other stakeholder groups. The EMA thanked members of the AB for their participation in the panel and for the lively Q&A session. The presentation and recording is available on the EMA website. Further completed activities include the development of a Communication plan for 2022, a round of presentations to EMA's scientific committees to inform of the launch of the network and ongoing or soon-to-be-initiated pilots on RWE use and change management activities.

The EMA and the CC have a twice-weekly meeting frequency and have progressed on a number of topics, including the conduct of a Data Protection Impact Assessment (DPIA), onboarding of **data partners**, **classification of studies** (see further below agenda point 4 and 5), prioritisation of studies, governance, conflict of interest policy and the Coordination Centre website content. The receipt and review of deliverables from the Coordination Centre is on schedule, with the first deliverable – Initiation of the project/Executive summary – already accepted.

Lastly, an update was given on the progress of the adoption of the List of metadata for real world data sources for regulatory purposes, which is being reviewed following the conclusion of consultation via a survey in February 2022 and will be adopted by the BDSG in May 2022. The work on establishing the Catalogue of data sources (building on the ENCePP Resource database) and a Catalogue of observational studies (building on the EU PAS register) based on the list of metadata is ongoing and expected to deliver both catalogues in Q4 2022 or Q1 2023.

In discussion, it was noted that it will be useful to share the templates approved in DARWIN EU®, and this can help inform and leverage existing work on sharing and legal agreements and templates via the Clusters of Excellence, developed via the BDSG.

# 3. NCA use cases for RWE: initial discussion

Claudia Furtado (Infarmed, PT) presented on the NCA use cases. The Portuguese NCA has several areas of action in a lifecycle approach, including regulation, HTA and payer functions and monitoring. The applicable use cases include characterising use and prescribing, identify areas of improvement, monitoring impact of policy and regulatory actions, describe the standards of care and treatment patterns, monitor Managed Entry Agreements and reimbursements restrictions as well as monitor effectiveness in support of reassessment of decisions.

Several data sources are available to Infarmed, including: hospital data, prescribing and claims data, disease registries (developed either by Infarmed including for hepatitis C or SMA, and those operated by other entities, such as the National Cancer Registry). For example, the data from the National Cancer Registry allowed the monitoring of real-life utilisation and effectiveness of pembrolizumab in advanced

melanoma patients[1], observing that effectiveness is slightly lower than in clinical trials and with a comparable safety profile.

Among challenges for RWE, it was noted that it is necessary to identify the medicines for which evidence generation will be required post-marketing (e.g. oncology agnostic treatments, treatments with conditional authorisation, etc.) earlier to allow for planning of RWE generation. Data quality is important for robust conclusions, as is the use of well-established methodology and availability of qualified researchers.

In discussion, it was noted that linkage between prescription and healthcare database and registries is important. Universal collection of data in registries (both for reimbursed and non-reimbursed products) was noted.

As next steps, the EMA will discuss further the particular use cases which could be addressed by DARWIN EU®, including with an outlook at international collaboration and rare diseases and rare outcomes. NCA representatives at the DARWIN EU® AB were invited to present further on use cases at the next AB meeting in July 2022.

# 4. Criteria for selection of data partners (principles and priorities)

Xavier Kurz (EMA) presented the update to inform and consult the AB on the criteria for selecting the data partners for onboarding in DARWIN EU® in phase I, and a draft list of data partners for phase I. The criteria follow the requirements included in the Technical specifications of the procurement procedure for selecting the DARWIN EU® Coordination Centre.

In the establishment phases I and II, it is proposed that the network onboards data sources converted to the OMOP common data model (CDM) and in the operation phase(s), additionally onboard data partners who have not (fully) converted to a CDM. This will allow a quick establishment in order to start delivering the benefits of DARWIN EU®.

Among the prioritisation criteria, sources should have continuous data collection with an at least annual update and a lag time in data made available for analysis of less than 6 months. Health outcomes and prescribing data should be captured and linked to individual but unidentifiable patients. The underlying population of patients should be well defined and conversion into the CDM with appropriate validation/testing is beneficial. Both ambulatory care and inpatient hospital care (incl. use of medicines and capture of outcomes), to allow for a variety of medicines use studies, as well as a geographical spread for a good representation of the EU population were proposed.

Additionally, non-EU data partners could be considered for inclusion if this facilitates achieving the objectives of DARWIN EU®. Databases which allow linkage between primary/secondary care or mother/child linkage as well as large databases, further to the data quality and geographical spread criteria, would be beneficial.

From the proposal received from the DARWIN EU® Coordination Centre, EMA is considering 16 data sources, including primary and secondary care data (including sources which span both settings) and health claims data. An initial look at possible data partners for phase II was also included. The DARWIN EU® Coordination Centre will in parallel run an open call for expression of interest for DARWIN EU® to available data sources, based on a value proposition which is being developed.

[1] Borges FC, Ramos C, Ramos A et al. Monitoring real-life utilization of pembrolizumab in advanced melanoma using the Portuguese National Cancer Registry. Pharmacoepidemiol Drug Saf. 2021 Mar;30(3):342-349. doi: 10.1002/pds.5163.

In discussion, track record in research and collaboration including in cross-border projects, as well as legal aspects with established governance were viewed as important. The AB was supportive of including non-EU data sources (e.g. UK data sources), considering they could be valuable for RWE analyses and enriching the results (size of sources and breadth of data, enlarging the sample size for rare diseases/outcomes, etc.). The same governance and data quality requirements would apply, as for EU data sources would need to apply.

The final criteria for selection of data partners for DARWIN EU® are therefore as follows:

**First order**

- Continuous data collection with at least yearly update and an ideal lag time between the data capture and the data made available for analyses of 6 months or less.
- Health outcomes and medicines prescribed or dispensed must be identifiable and linked to individual but unidentifiable patients; estimation of indication, dose and duration
- Well-defined underlying population consisting of patients with enrollment and migration dates; resources in which patients can be enrolled on multiple occasions using different identifiers should be avoided.
- Conversion into common data model with appropriate validation/testing
- Different care settings appropriate for study topics known to be frequently requested, both ambulatory care and inpatient hospital care (incl. use of medicines and capture of outcomes).
- Geographical spread: good representation of the EU population, especially in the context of descriptive studies (e.g. drug utilisation, disease epidemiology, standards of care)

**Second order**

- Non-EU data partners may be included depending on their contribution to the objectives of DARWIN EU® (e.g. response to research questions raised by EMA Committees)
- Databases which provide linkage and continuous follow up between primary and secondary care and databases that can provide mother/child linkage
- Large sample size (i.e. number of active patients) - secondary to data quality and geographical spread
- *Amount of information on governance*
- *Track record in research.*

# 5. Classification of RWE studies

Juan Jose Abellan (EMA) presented the update to inform and consult the AB regarding the classification of RWE studies to be performed via DARWIN EU®. Drug utilisation studies, disease epidemiology studies, safety monitoring and aetiological studies are common RWE study types to support decision making. It is the goal of DARWIN EU® to increase both the number of data sources that can be analysed as well as the capacity for studies that can be performed annually, while delivering efficiency gains in standardised analytics, time and cost savings.

In line with the Technical specifications of the procurement procedure for selecting the CC, studies are classified as either off-the-shelf, complex or very complex and can be also performed as a routine repeated analysis (of an off-the-shelf or complex study).

Discussions are ongoing with the CC on defining each study type with the use cases in mind, its outputs and typical focus (e.g. a therapeutic class, selection of substances or disease areas). Examples of study designs and outputs were presented. The aim is to maximise the volume of delivered analyses to support decision making of the EU Medicines Regulatory Network. In later years of establishment/operation of DARWIN EU®, pre-computation of analyses can be considered, e.g. periodic drug utilisation analysis or ADR monitoring.

In discussion, it was noted that the data source selection per study should be driven by its utility, with the view of robust results with internal and external validity. The network's results will deliver evidence for decision making, and these should be leveraged to deliver the maximum benefits for patients. The AB will be informed at a later meeting in 2022 of benefits analysis and monitoring.

# 6. Tour de Table

None.

# 7. AOB, Information items

None.

Emer Cooke (EMA) thanked the AB members and the presenters and closed the meeting.

**Topics for future meetings:** Benefits analysis, repurposing of medicines, EC initiatives and legal proposals (e.g. EHDS, Pharmaceutical strategy, Health Union proposal, European Health Emergency Preparedness and Response Authority (HERA)), and ECDC presentation on use cases

**Next meeting:** 6 July 2022