RAPPORT RSNN EXPERT MEETING

25 October 2022

REGULATOR-INITIATED STUDIES FOR REGULATORY DECISION-MAKING: SCENARIOS AND LEARNINGS

On the 25th of October 2022, an RSNN expert meeting took place to discuss the topic "Regulator-initiated studies for regulatory decision-making: scenarios and learnings". For several years, regulators have requested Marketing Authorisation Holders (MAHs) to conduct post marketing studies, which made use of real world data (RWD). These studies have been mostly related to pharmacovigilance. However, over the past years, drug developers have displayed a growing interest to use RWD in the pre-marketing phase as well, for example when experimental study designs such as randomized controlled trials are deemed impossible or unethical. On a European level, the European Medicines Agency (EMA) is exploring the use of high quality RWD in decision-making for instance through the Data Analysis and Real-World Interrogation Network (DARWIN EU®). DARWIN EU® includes a coordination center that is

Category of observational analyses and studies	Description
Routine repeated analyses	Routine analyses based on a generic study protocol • Periodical estimation of drug utilisation • Safety monitoring of a medicinal product • Estimation of the incidence of a series of adverse events
Off-the-shelf studies	Studies for which a generic protocol is adapted to a research question • Estimate the prevalence, incidence or characteristics of exposures • Health outcomes • Describe population characteristics
Complex Studies	Studies requiring development or customisation of specific study designs, protocols and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data • Etiological study measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome considering sources of bias, potential confounding factors and effect modifiers
Very Complex Studies	Studies which cannot rely only on electronic health care databases, or which would require complex methodological work • Studies where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations, or studies requiring additional data collection

Figure 1: The four categories of studies initiated in DARWIN EU® (source: EMA).

responsible for generating timely and trustworthy evidence from observational data sources containing high-quality RWD on usage, safety and efficacy of medicines, with the aim to support regulatory decision making within the EU by the end of 2024. The observational studies executed in DARWIN EU® will be categorized into four categories depending on the research question (Figure 1).

The studies conducted within DARWIN EU® can vary from routinely repeated analyses to very complex studies. Studies on incidence and prevalence may follow a predefined protocol and could be categorized as "off-the-shelf" studies, while for more complex research questions a

case-by-case protocol would need to be developed. Examples of more complex regulator-initiated studies that have been conducted by the EMA can be found here.
The question arises what the role of various stakeholders, such as academia and industry, should be within these regulator-initiated studies, that make use of RWD. When and how will these stakeholders be included and which role each stakeholder has (informed, consulted, review, etc.): from the formulation of the study hypothesis to reviewing the study outcomes? To answer these questions, various international experts from academia, industry and governmental bodies were invited to share their current knowledge and personal views under the Chatham House Rules. This report provides a summary of the discussion, separated in four main themes: 1) Initiation of research questions, 2) Study design & analyses, 3) Regulatory model and 4) Regulatory outcomes.

1) INITIATION OF REGULATOR-INITIATED STUDIES

Criteria and motivation of study requests. Method of developing research questions.

Origin of research questions

There are different motives for regulators to request a study. The questions can address both pre- and post-marketing authorisation related topics. Pre-marketing authorisation questions often emerge from EMA's Paediatric Committee (PDCO) or Committee for Orphan Medicinal Products (COMP) and are related to paediatric investigation plans and waiver applications (resp. PDCO) or related to incidence and prevalence (resp. COMP) and form the basis for Off-the-Shelf studies (Fig. 1). However, product-related RWD is mostly non-existent during the pre-marketing phase and research questions related to usage, safety and effectiveness therefore occur more often in the post-marketing phase. Post-marketing questions often form the basis for (very) complex studies (Fig. 1) and could be related to safety concerns, or product efficacy. In the example of DARWIN EU®, questions come from the different operating committees within the EMA, such as the Committee for Medicinal Products for Human Use (CHMP), Committee for Advanced Therapies (CAT), and the Pharmacovigilance Risk Assessment Committee (PRAC), though national competent authorities (NCAs) also have the opportunity to ask research questions. The intention from DARWIN EU® is to extend subsequently to other stakeholders, such as health technology assessment (HTA) bodies.

Feasibility to conduct a regulator-initiated study

Recently, the EMA has initiated the launch of the first three studies that will be conducted within DARWIN EU®. By 2025, the EMA aims to extend the number of studies conducted in DARWIN EU® to 150 studies annually. Conducting 150 studies annually requires sufficient capacity from the regulators, the coordination center and the data holders. The required capacity is thereby directly related to the study complexity: routinely repeated and off-the-

shelf studies will follow generic study protocols that require few to no adaptations, while more complex studies may require customization of specific study designs (Fig .1).
By the end of 2025, DARWIN EU® will provide an estimation of the required capacity to conduct 150 regulator-initiated studies. If capacity becomes a limiting factor in the ability to conduct regulator-initiated studies, e.g. when a substantial amount of the 150 studies is categorized as (very) complex and therefore require customized and case-by-case protocols, regulators will have to clarify how research questions are selected and prioritized for further development into detailed study protocols for regulator-initiated studies.

2) STUDY DESIGN & ANALYSIS

Validation and acceptability of research methodology. Data quality and accessibility.

Validation of study design

Acceptability and validation of the developed research methodology plays a large role when converting research questions and formulated hypotheses into study plans with detailed methodology. For the methodology, the regulators have to comply with predefined standards, such as the methodologies described in the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, to assure high-quality regulator-initiated studies. Validation is also stimulated by the ability to replicate studies as other stakeholders will have the ability to execute the same study protocol to try to reproduce results. The registry for post-authorisation studies (EU-PAS) will be used for the publication of the study protocols, prior to study initiation, and study reports, after finalisation. Currently, in the EU-PAS registry, protocols and study reports of non-interventional post-authorisation studies are published, which preferably adhere to the ENCePP code of conduct.

Establishing high-quality data

The study design itself should adhere to predefined standards to ensure high-quality evidence generated from regulator-initiated studies. In addition, data quality and accessibility are important factors to be considered. Feasibility testing will be applied to search for data sources that could contribute in answering the research question. For certain research questions (e.g. prevalence), the data sources may require population-based representation. For other questions, subgroups represented in a single data source may be enough to provide the answer (e.g. a specific disease registry). For DARWIN EU®, fitness-for-purpose testing criteria should be applied to select the best data sources for the proposed study design. Moreover, to ensure sufficient data quality within the selected data sources, database partners on-boarded in DARWIN EU® are assessed for quality and completeness. These databases have their data mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). The OMOP CDM is a community-based data standard to standardize and unify the structure and content of observational data. The central

components are the OHDSI standardized vocabularies which standardize medical terms used across various clinical domains.

Accessibility of study data

To continue with the example of DARWIN EU®, only aggregated data are provided by the database partners to the DARWIN EU® coordination center. The data is thereby locally accessed and one "master" script containing the analyses is applied to all selected data sources. Access to the same data sources by other stakeholders in this case is therefore limited and depends on the specific agreements made with the database holder. During the expert meeting, participants working in the pharmaceutical industry expressed their concerns with the limited accessibility to the full datasets within the DARWIN EU® network, as this puts limitations on the reproducibility of regulator-initiated studies. Regulators may therefore consider notifying (industry) stakeholders of study plans and which data sources will be used prior to conducting the study, i.e. before it is publicly disclosed, to provide a possibility to reproduce the evidence generated from regulator-initiated studies.

3) REGULATORY MODEL

Involvement of stakeholders (how and when)

Transparency & independency

During the expert meeting, regulators, academia and industry showed willingness to collaborate to embrace regulator-initiated studies. The involvement of stakeholders in regulator-initiated studies requires a sophisticated regulatory dialogue model, such as EMA's signal procedure. However, several potential points of friction within this stakeholder-interaction model can be anticipated, as described further in detail below. Based on these points, the regulatory dialogue model should be engineered.

From the regulators' perspective, both transparency and independence are of great value within this dialogue model. However, in the particular case of stakeholder-involvement in regulator-initiated studies, this dialogue model creates a thin line between collaboration and transparency, which may lead to conflicts of interest. On one hand, there is the need for transparency and collaboration, where everything in the process – from formulation of the research question to reporting the study outcomes – is openly communicated and reported. On the other hand, this may affect the independent and autonomous status of the regulatory authorities, as other stakeholders, i.e. pharmaceutical industry, are open to explain, question and influence the study process and can provide critical feedback to the methods applied by the regulator. At first sight, this is a welcoming scenario as

1) the industry may provide additional information that is required
2) (industry) stakeholders may improve study design, methodology, and analysis.

However, safeguarding the independent decision-making position of the regulatory authorities and their reputation should be considered when it comes to a transparent dialogue model that facilitates interaction between stakeholders, as to avoid conflict of interest. Learnings can be made from the European Ombudsman decision on inquiry OI/7/2017/KR, where the ombudsman questioned the objectivity of the EMA when it came to the industry being involved in pre-market activities and especially scientific advice. While the EMA explained that the involvement of industry in scientific advice does not cause a conflict of interest, safeguarding measurements were put in place by the EMA. The Ombudsman example emphasizes the concerns for regulators to operate independently and transparently.

Stakeholder-interaction

One could therefore think of establishing a peer-reviewing process, similar to submitting scientific articles to renowned scientific journals, with involvement of all stakeholders, such as academia and pharmaceutical industry. While not discussed, appropriate measures safeguarding confidentiality would need to be put in place. However, the short reaction timelines often seen in regulatory procedures, such as EMA's signal procedure, would limit the - often time-consuming - peer-reviewing process. Hence, peer-reviewing could be interesting, but is not the final solution in this discussion.

An alternative and less time-consuming solution is establishing novel communication frameworks, without overwriting the already existing frameworks that address the interaction between regulators and other stakeholders. Learnings could be made from the interaction model in place when it comes to pharmacovigilance and safety procedures (EMA's signal procedure), as this model of interaction is comfortable for all stakeholders.

Transparency within these interaction models is not a case of 'all or nothing', but should be fine-tuned according to the questions addressed by the committees. "Off-the-shelf" and "routine repeated" study protocols may be published without consultation of stakeholders due to their limited complexity. In the case of regulator-initiated drug utilization studies for example, it should not be required to consult all potential stakeholders due to (generally) following the "off-the-shelf" principle. More complex studies, as seen in Figure 1, however, may require more extensive interaction with potential stakeholders. During the expert meeting this was described as complexity-based consultation, where stakeholders, such as the applicant or MAH, would like to become involved in the protocol design of (very) complex studies.

Trust

Furthermore, openly questioning the processes of the regulator may cause confusion to the broader public, damaging the reputation of all involved stakeholders. A similar example could be observed during the COVID-19 pandemic, where different authorities and important

stakeholders openly questioned findings from other stakeholders. For example when it came to the efficacy of face masks in preventing COVID-19 infection (Hyland-Wood et al., 2021). These public debates may lead to loss of trust in stakeholder(s) by the public. Another recent example of dissonant interaction between stakeholders is the debate caused by public communication of preliminary results from an university-sponsored observational study. This particular study even received media-attention, since it contradicted earlier results on reductions in hospitalizations and mortality communicated by the marketing authorisation holder (MAH). To avoid loss of trust, unambiguous communication should be endeavored, while remaining transparent and independent as described earlier in this report.

4) REGULATORY OUTCOMES

How and where are outcomes published

Publication of study results

As stated, transparency is considered important in regulator-initiated studies and during the expert meeting the industry participants expressed the desire for regulators to make publicly available protocols and evidence obtained from regulator-initiated studies. Study protocols should become available, accessible, and understandable for all involved stakeholders. (Aggregated) outcomes will be incorporated in the European Public Assessment Reports (EPARs), though regulators should aim to publish the results of their studies in scientific journals if deemed relevant (e.g. answering novel research questions or using complex and/or novel study designs). Full study reports should become available for all regulator-initiated studies in the designated archives. During the expert meeting, EU PAS register was mentioned several times as an example where both protocols and study reports of PASSs are published publicly, without affecting possible scientific publication. Publication of study results in the EU PAS register could allow industry and other stakeholders to access the outcomes of regulator-initiated studies.

The evidence generated by these regulator-initiated studies could end up in regulatory procedures and can become part of the decision-making process. In these cases, regulator-initiated studies must adhere to the timelines of the procedure and therefore face the same consequences as anyone else involved in the procedure not adhering to said timelines. In any other non-procedural case, timely reporting the evidence is based upon the need for an urgent answer to the underlying research question.

Consistent reporting of outcomes

To ensure consistent reporting within the global regulatory network, continuous meetings and discussions with non-EU authorities, such as the FDA and Health Canada, are required to establish high quality international reporting of protocols and evidence obtained from regulator-initiated studies.

CONCLUSION AND FOLLOW-UP

Many of the themes addressed during this meeting will be explored and developed during the initiation of EMA's DARWIN EU®. Regulators, academia and industry have shown willingness to collaborate to embrace regulator-initiated studies within the European regulatory framework. Industry and academia would be involved where needed in a timely and transparent manner through (novel) stakeholder-interaction models (like EMA's signal procedure), especially when it comes to complexity-based consultation. Future meetings, discussions and workshops within, but not limited to, the European regulatory network are recommended to establish dialogue models to facilitate interaction between stakeholders, which address all the perspectives and concerns of involved stakeholders. These frameworks cover the whole process for regulator-initiated studies, from the formulation of research questions to the publication of study outcomes, as described in chapters 1-4. Anticipating friction points and engineering the design, execution, interaction and publication process of regulator-initiated studies accordingly, could facilitate acceptability and incorporation of the outcomes from regulator initiated studies into the regulatory decision making process.

During this RSNN expert meeting, the experts indicated that a follow-up meeting on this topic is welcomed due to the rapid evolving European landscape regarding regulator-initiated studies. The aim of this follow-up meeting is to discuss relevant use-cases related to complexity-based consultation, as regulator-initiated studies will be carried out as part of the development of the DARWIN EU® project.

REFERENCES

Hyland-Wood, B., Gardner, J., Leask, J., & Ecker, U. K. (2021). Toward effective government communication strategies in the era of COVID-19. *Humanities and Social Sciences Communications*, *8*(1), 1-11.