EUROPEAN MEDICINES AGENCY
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# Report on PRAC Pilot on Rapid Data Analytics

Time period: November 2019 - January 2021

## Executive Summary

A pilot on rapid data analytics (referred to in this report as RDA) coordinated by the European Medicines Agency (EMA) was performed with the Pharmacovigilance Risk Assessment Committee (PRAC) from November 2019 to January 2021. Its aim was to test the feasibility and usefulness of a process for rapid identification, analysis and reporting of results of epidemiological questions that may arise in the context of regulatory assessments for which Real World Data (RWD) and Real-World Evidence (RWE) can support regulatory decisions by filling knowledge gaps identified during a procedure. The pilot was part of the 2020/2021 PRAC and Big Data Steering Group[1] workplan and it should be seen as a first step towards the promotion of a wider use of RWD/RWE in the development, authorisation and post marketing surveillance of medicines.

EMA committees can obtain RWD/RWE through several mechanism: i) requests or obligations to pharmaceutical companies, ii) analysis of public information including the published scientific literature, iii) analyses and studies conducted or initiated by National Competent Authorities (NCAs), iv) EMA studies on the electronic health databases accessible in-house, v) studies procured through the EMA framework contracts, and, starting from 2022, vi) DARWIN EU. The pilot was performed using the EMA in-house databases, but the processes tested, and experience gained will be beneficial to support PRAC's decision making with independent RWE provided also through other mechanisms.

During the pilot, EMA had access to three databases containing electronic health records from primary care from three different European countries: IMRD UK, IMS France and IMS Germany (the latter also covering some information from specialised health care). A process to provide RDA to PRAC was agreed before the start of the exercise and consisted of three main steps: i) identify topics or questions where RWE could be useful, ii) check whether the current data sources accessible in-house at EMA contains enough and adequate information to conduct the analysis, iii) run the analysis and report the results to PRAC for consideration within its assessment. This process was adapted throughout the conduct of the pilot to better reflect the needs of PRAC or to improve the usefulness of the analyses performed. Three main changes were undertaken. First, on PRAC request, the circulation of the draft analysis plan was extended from the PRAC Rapporteurs of the associated regulatory procedure to all PRAC members in order to increase transparency and to allow a more thorough review. Second, the process was adapted to make the results of the studies publicly available by publishing the report in the EU PAS Register in time for the finalisation of the procedure so PRAC Rapporteurs could include the

[1] Workstream on EU Network processes: https://www.ema.europa.eu/en/documents/work-programme/workplan-hma/ema-joint-big-data-steering-group_en.pdf

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results in their assessment reports shared with the Marketing Authorisation Holders (MAH). Finally, the identification of the topics for RDA, initially limited to PRAC members who expressed interest in the pilot, was extended to all PRAC members and to EMA colleagues who could highlight opportunities for possible analyses to the Rapporteurs by proactively screening confirmed safety signals and the PRAC agenda.

A total of 12 requests for analysis were identified: five requests were directly notified by the PRAC members, and seven requests originated from the screening by EMA of the PRAC meetings' agendas items in particular safety signals (followed by confirmation from the PRAC Rapporteur of the need for the proposed analysis). Eight analyses were considered feasible and four not possible due to insufficient exposure or insufficient number of recorded events. All the feasible analyses were completed and four of them were reflected in the PRAC assessment reports of the associated procedures. They were assessed as part of additional data by Rapporteurs alongside other data including responses provided by MAH. The overall process from request to final report took a median of 84 days, with a range of 26 to 138 days.

During the proactive screening by EMA, 51 confirmed safety signals were reviewed. A suggestion to conduct RDA was proposed to the PRAC Rapporteur in 10 cases. For six cases the PRAC Rapporteurs agreed that further analyses would be helpful to support the evaluation of the procedure. Of the 41 confirmed signals for which an analysis was not proposed to the PRAC, the reasons were a low number of events or limited exposures (23 signals), or insufficient details on events (23 signals) and relevant confounders like concomitant medications, smoking status or obesity (3 signals) recorded in the electronic healthcare databases EMA has access to. One additional topic related to an Article 31 referral was identified during the PRAC pre-meeting briefing with the PRAC Chairs. This later topic as well as the six originating from EMA's proactive screening of confirmed signals consist of the seven requests for analyses referred to in the previous paragraph.

The type of analyses performed in the pilot were mainly descriptive and could be divided into three categories: i) incidence and prevalence of drug use and/or diseases, ii) characterisation of drug use, including indication, amount and duration of exposure, and patients' characteristics such as age and gender, and iii) incidence of specific events in drug users, including the presence of risk factors for the event under discussion (for example prior history of the events or specific co-morbidities) and the time to occurrence of the event. Comparative analyses were only carried out in a descriptive manner, providing crude prevalence or incidence counts. More complex analyses investigating the association between a treatment and a clinical event that also include confounding adjustment usually require more time to agree the details of the protocol and run the analyses. These might be more adequate for procedures with a longer timeline. However, more experience is needed before a clear recommendation can be proposed.

The pilot showed that in many cases, analyses were not feasible due to insufficient exposure and/or insufficient number of recorded events, especially for signals related to antineoplastic or immunosuppressive medicines, which represented half of the screened signals and were further identified to be used in specialised or hospital settings[2]. Availability of data from healthcare settings going beyond routine ambulatory care such as hospital data and data from oncology care is therefore needed to support the regulatory procedures discussed by the PRAC. Another reason for non-feasibility was the lack of recorded details in the electronic healthcare databases available. Many signals concerned reactions of skin disorders, which like for rare diseases, require a very specific terminology to precisely identify the events. This may not be available in the databases at EMA's disposal, and

[2] Flynn R, Hedenmalm K, Murray-Thomas T, Pacurariu A, Arlett P, Shepherd H, Myles P, Kurz X. Ability of primary care health databases to assess medicinal products discussed by the European Union Pharmacovigilance Risk Assessment Committee. Clin Pharmacol Ther. 2020 Jan 18. doi: 10.1002/cpt.1775

existing ICD codes were not sufficiently granular in the absence of further clinical documentation needed for an assessment of the precise nature of the reactions. To address such issues, access to registries, e.g. of skin disorders, could be considered, as well as increased availability of data from imaging or laboratory testing in electronic databases.

Experience gained from the pilot has revealed several important aspects to consider for future roll out of the process. For example, having access to pre-calculated exposure information for rapid feasibility analyses, like number of patients treated or with specific conditions per year, may be helpful to facilitate this initial step and to decrease the workload for the data analysts. In addition, the use of a dedicated software for the analysis of this type of data, with pre-specified queries that can be easily adapted for the specific question of interest, would also be useful for this purpose and to expand the base of analysts. Finally, a formal process, including quality management, documentation of the analyses and publication in the EU PAS register is needed in order to manage the different steps and actors involved in conducting in-house analyses for Committees.

The pilot for RDA was presented at the PRAC Assessors Training 2020. Overall, there is a need to create more awareness across the EU regulatory network about the existence of the RDA process, its added value and capability to assist assessors at national level, and the steps to follow to request such analyses. The network should also be better informed on the other ways, existing (procured studies through the EMA framework contract) and in development (DARWIN EU), to request RWE from EMA.

The following table summarises the main recommendations drawn as an outcome of the pilot that will help optimise usage of RWD and RWE by the PRAC and will facilitate its integration within core business regulatory processes to support the committee's decision making on medicinal products.

| Area | Recommendations |
|---|---|
| Type of analyses | • Rapid analyses are most appropriate to provide descriptive information to investigate patterns of drug utilisation, progression of clinical events and their incidence with the prescribed treatment<br>• More complex analyses investigating associations between prescribed treatments and clinical events, including confounding adjustment, might be more adequate for procedures with a longer timeline. More experience is needed before a clear recommendation can be proposed |
| Type of data | • A wider spectrum of data sources is needed to meet the requirements of the regulatory procedures discussed by PRAC<br>– Access to data beyond routine ambulatory care such as hospital data, data from oncology care, registries of skin disorders as well as data sources comprising laboratory data. Ideally these sources should be linked to primary care data<br>– Access to data from a larger number of EU Member States to increase the representativeness of the analyses<br>– Access to region-nationwide data to increase the external validity and the size of the analyses |
| Scope of collaboration | • Building interactions between EMA and NCAs analysts could facilitate collaborative analyses using EMA in-house databases and other data sources available at national level |
| Communication, awareness and change management | • Presentations and awareness sessions addressed to the EU regulatory network (e.g. EMA, committees and assessors) are needed to increase knowledge on the possibilities to request RWE to EMA to support regulatory assessments (via studies on in-house databases |

| Area | Recommendations |
|---|---|
| | but also procured studies and later DARWIN EU). Tailored presentations at national level and e-learnings should be considered<br>• A short guidance document made easily accessible to assessors (e.g. in MMD) is needed to clearly outline the scope of analyses (type of data sources, type of epidemiology questions than can be addressed) so assessors can identify where requests for additional data could be of added value for their daily work<br>• Assessors could be systematically prompted to consider the possibility to request additional RWE analyses via a specific field in the relevant PRAC AR templates depending on the regulatory procedure. For signals, consideration could be made at validation stage via a tick box in EPITT, as well as at confirmation stage by adding a dedicated section in the signal confirmation assessment report template |
| Process management – Collaboration with Committee | • Conducting analyses to support Committee decision-making requires a formal process encompassing appropriate documentation, quality management and requests for approval for publications in the EU PAS Register<br>• Proactive early dialogues (e.g. via TC) to clarify the details of the analyses' needs and timelines will contribute to ensure the results are provided in time for the procedure's finalisation. RDA timetables could be tailored based on analyses characteristics (e.g. type, urgency), including the possibility to reduce the length and number of stakeholders consulted on key steps of the analyses<br>• For time optimisation, clear and better structured EMA templates should facilitate rapporteurs' review on feasibility feedback, analysis plan and report |
| Process management – Performing analyses | • Having quick access to pre-calculated exposure information like the number of patients treated or with specific conditions per year would facilitate the initial steps of the feasibility analyses and decrease the workload<br>• Using a dedicated software that facilitates rapid data analytics, with pre-specified queries that can be adapted, would make the analyses faster and expand the base of analysts<br>• Training of additional analysts for the conduct of analyses as part of routine processes would increase the availability of senior analysts for more complex tasks |
| Process scope | • Considerations should be given as to the possibility and the best way to extend the EMA proactive screening to other PRAC regulatory procedures than safety signals only, e.g. safety referrals, PSUSA, safety variations and RMP. As a starting point, focus could be made on topics tabled for discussion during the PRAC preliminary meetings with the (co)Chairs |