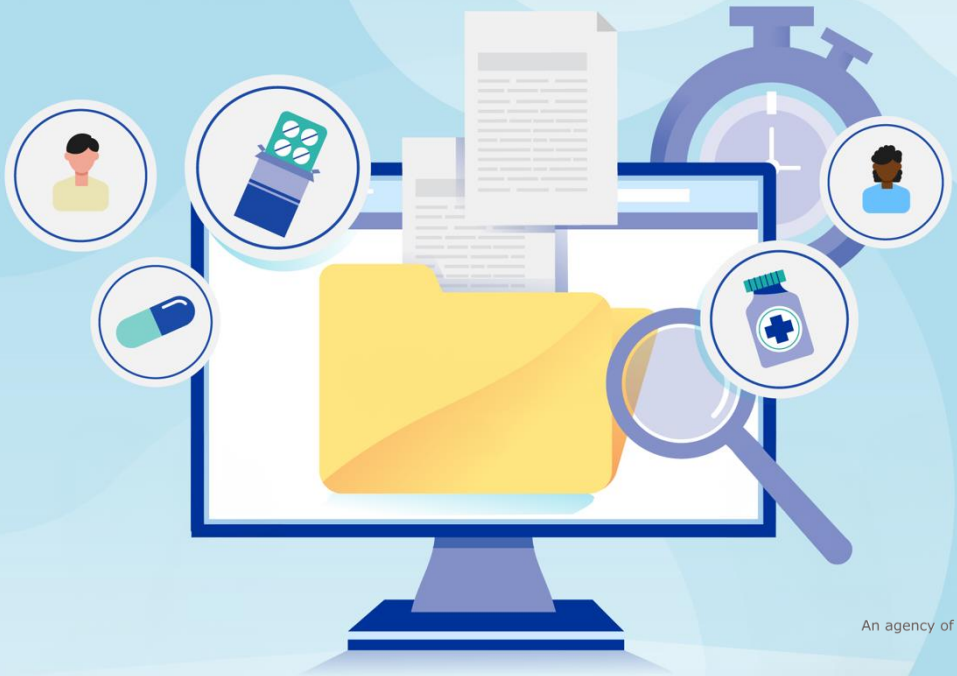
HMA
Heads of Medicines Agencies

EMA
EUROPEAN MEDICINES AGENCY

Proof-of-concept pilot on using data from clinical studies in medicines evaluation

Interim report on the experience gained with submission and analysis of patient-level data from clinical studies from September 2022 to December 2023



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Executive summary

In 2020, the joint Big Data Task Force of the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA) published ten priority recommendations for the European Medicines Regulatory Network (EMRN) to unlock the potential of 'big data'[1]. A key action involves enhancing the EMRN's capability to analyse big data including '**raw data**' - notably individual patient data from clinical studies[2] in structured format from which statistical analyses and clinical insights are derived.

While regulators can already request clinical study data from applicants/marketing authorisation holders (MAHs) as per the current European Union's pharmaceutical legislation, the European Commission's proposal for a reform of the legislation foresees a systematic submission of clinical study data at the time of filing of initial marketing authorisation applications. Overseen by the HMA-EMA Big Data Steering Group (BDSG) and the Committee for Medicinal Products for Human Use (CHMP), the EMRN is conducting a **Proof-of-Concept (PoC) pilot** (hereinafter "the pilot") to explore the benefits of visualising and analysing data from clinical studies in support of the scientific assessment of medicinal products. In addition to the **regulatory benefit** when clinical study data is available at the time of submission (i.e. faster assessment and enhanced decision-making), the pilot aims to determine the EMRN's **capacity and capability requirements,** a **target operating model** and **technical prerequisites** regarding a systematic submission of clinical study data in the regulatory setting in the future.

The pilot has initially been designed with an inclusion target of approximately ten centralised regulatory procedures and an estimated duration of two to three years (from September 2022). It encompasses initial Marketing Authorisation Applications (iMAAs) and post-authorisation applications, such as variations or extensions of indication that include data from clinical studies. Particular focus is given to **analyses supporting the assessment** (clinical efficacy and safety but also pharmacokinetics and pharmacodynamics, PK-PD) **and related decision-making**. Furthermore, the pilot includes **analyses to guide the selection of trial sites to verify compliance with Good Clinical Practice** (GCP). Analyses are planned to be performed by different resourcing scenarios; either the CHMP Rapporteur teams at the National Competent Authorities (NCAs) of Member States, EMA staff or EMA contractors.

While the pilot is still ongoing, in line with the BDSG fourth multiannual work plan (2023-2025), this report provides **preliminary insights gained from experience in conducting analyses of clinical study data voluntarily submitted by applicants or MAHs as part of the dossier** to support the respective marketing or post-marketing authorisation application. Using feedback sought from pilot participants (within the EMRN as well as applicants/MAHs) in **December 2023**, the report covers the time period from the inclusion of the first regulatory procedure in the pilot (September 2022) up to December 2023, marking the **inclusion of five procedures in the pilot**.

[1] The HMA-EMA Big Data Task Force defined big data as 'extremely large datasets which may be complex, multi-dimensional, unstructured and heterogeneous, which are accumulating rapidly and which may be analysed computationally to reveal patterns, trends, and associations. In general, big data sets require advanced or specialised methods to provide an answer within reliable constraints'.

[2] Clinical studies include clinical trials as well as non-interventional studies in accordance with the definitions set out in Article 2 of Regulation (EU) No 536/2014.

Building on initial insights, the report provides preliminary recommendations for future implementation of clinical study data submissions in support of regulatory assessments as well as recommendations for the second phase of the pilot.

In a survey of pilot participants to ascertain the regulatory benefit of access to clinical study data in assessment and decision-making, the vast majority of respondents (83%) highlighted an **added value of access to clinical study data at the time of submission** in at least one of the following areas:

Assessment and decision-making

- Improve understanding of the set of information in a product dossier via insights revealed from deeper analysis not apparent in summarised data, leading to enhanced quality of opinions and more informed decision-making;
- Reduce list of questions to applicants/MAHs as a proportion of the questions can be anticipated and resolved by clinical study data analysis leading to faster and more streamlined assessments;
- Further promote efficient multi-disciplinary teamwork;
- Foster consensus on methodological issues among regulators, therefore leading to potential reduction of outstanding issues during decision-making discussion;
- Support the development of a knowledge base for review of experience to guide assessment of future studies in similar setting and/or in similar patient groups.

Similarly, in the case of clinical study data analyses in support of GCP site inspection, 93% of the respondents noted the **added value of access to clinical study data** in its potential to:

GCP site inspection

- Shorten time needed to plan and conduct inspections via an earlier data-driven identification of suitable sites for inspection;
- Optimise the use of inspection resources across the EMRN.

Taking a closer look at the type of regulatory procedures benefiting the most from access and analysis of clinical study data, pilot participants responded that the specific value of statistical analysis of clinical study data is greatest for more complex dossiers and products with a contentious benefit risk balance. It is therefore recommended that, alongside **simple descriptive analyses and visualisation that could be provided by EMA for all dossiers**, **identification of criteria for applications that may benefit from more**

extensive targeted clinical study data analysis should be investigated. Such criteria will support EMRN resource planning for clinical study data analysis.

Several insights related to the EMRN's clinical study data readiness in terms of capacity and capability were gained. Based on feedback collected in respect of resource impact on the EMRN, there was **no evidence to suggest that assessment was impaired by the need to conduct additional tasks on clinical study data**, be it access to or analysis of clinical study data. The proposed risk-based approach for systematic simple descriptive analyses versus more in-depth analyses for selected dossiers will further ensure best use of available resources. Feedback received also pointed to the need for **enhanced expertise** across the EMRN to support access and analysis of clinical study data, notably in the field of **statistical programming, PK-PD modelling and biostatistics**. Subsequently, enhancement of the EMRN's **awareness of and training on clinical study data analysis and clinical trial data standards** are two areas highlighted of particular importance by pilot participants.

Feedback received on governance and processes, including operational and collaborative aspects explored in the pilot, indicated overall satisfaction from all pilot participants. An additional insight was that member states' comments provided on pilot procedures were informed by the clinical study data analyses conducted by member states other than the Rapporteur teams, thereby demonstrating the usefulness of **clinical study data access for all NCAs** and not only the Rapporteur teams. Furthermore, as noted by applicants/MAHs participating in the pilot, the available **public information on pilot requirements was deemed clear**, enabling a smooth communication amongst applicants/MAHs, NCAs and EMA. To optimise the operational model, EMRN pilot participants suggested sharing of experience between regulators and applicants/MAHs, reassess the timing of data submission meetings between the applicant/MAH and data analysts and consider the possibility for applicants/MAHs to discuss the electronic submission plan with EMA during the pre-submission phase.

Finally, in the field of technical aspects, EMRN pilot participants noted that a **suitable technological analytics infrastructure** is key, including to make **statistical software** available. Applicants/MAHs pilot participants' feedback indicated the need to engage with the EMRN to **clarify electronic data submission requirements**. Additionally, technical aspects of the **electronic submission process for applicants/MAHs** were highlighted as an area requiring further attention.

Overall, building on the insights the pilot has generated so far, an **extension of the pilot** is recommended. This will allow for inclusion of additional regulatory procedures, possibly beyond the initially targeted number of ten applications in the pilot's second phase. The extension would aim to generate **further learnings on the use of clinical study data in support of regulatory assessment, with a focus on addressing remaining knowledge gaps and further validation of the already identified benefits of clinical study data into regulatory decision-making**. To optimally deliver on this recommendation, some adjustments to the initial **pilot design** are proposed. In addition, recommendations for complementary steps to be undertaken in parallel to the second phase of the pilot are made to ensure readiness in anticipation of larger volumes of clinical study data submissions in the future.

The table below provides an overview of all initial pilot insights/learnings and recommendations for the second phase of the pilot. These recommendations were derived from pilot participants' feedback as well as feedback gathered from EMRN subject matter experts.

	Learnings	Recommendations for the second pilot phase
Added value for assessment and decision-making 	• Beneficial for assessment and decision-making, **improving understanding of the set of information in a medicinal product dossier** • Fewer **questions to the applicant/MAH**, as a proportion of the answers were anticipated and consequently, questions resolved from clinical study data analysis leading to **faster and more streamlined assessments** • More value of statistical analysis for complex applications and medicinal products with a **contentious benefit-risk profile** • **Consensus on methodological issues** amongst regulators fostered leading to potential **reduction of outstanding issues during decision-making discussion** • **Increased awareness of pitfalls in statistical analysis** that should therefore not be routinely requested to applicants/MAHs • Potential to optimise the use of limited inspection resources by **early risk identification through** faster familiarisation of a product dossier and **shorter time needed to plan and conduct inspections**	• Consider inclusion of procedures where **clinical study data is requested from applicants/MAHs** when it is considered necessary for the assessment (as per current legal basis) in the pilot • Strengthen understanding of which dossiers benefit most from **more extensive targeted analysis** • Consider inclusion of a pilot procedure with **high modelling and simulation impact** • Consider inclusion of a pilot procedure for a **generic** application • Further investigate the benefit of **standardised descriptive clinical efficacy and safety data summaries** to support an efficient understanding of the set of information in a product dossier
Capability and capacity 	• Limited EMRN **knowledge on clinical trial data standards** which is key to foster quality and efficiency • Heterogeneous EMRN **expertise on clinical study data analysis** in support of regulatory assessment and decision-making • **Additional EMRN expertise** needed in the field of **statistical programming, PK-PD modelling and biostatistics** • No **evidence to suggest that assessment was impaired** by the need to conduct additional tasks on clinical study data	• **Continue raising awareness of stakeholders** regarding use of clinical study data analysis in regulatory assessment and decision-making, by providing regular updates to the EMRN and public fora • **Foster knowledge sharing** on clinical study data analysis and clinical trial data standards, e.g. by leveraging ongoing EMRN fora • **Continue to investigate EMRN resource needs** in support of use of clinical study data in regulatory decision-making; in particular need for training in statistical programming, PK-PD modelling and biostatistics

	Learnings	Recommendations for the second pilot phase
Governance and processes 	• Two out of three **resourcing scenarios** (NCAs and EMA contractor) **were carried out successfully** for analyses supporting the assessment and selection of sites for GCP routine inspection • The **contractor resourcing scenario has a risk of lower flexibility** if associated with predefined timelines and scope of deliverables • NCAs **providing member state comments** on the assessment **conducted clinical study data analyses** • **Data protection processes** in place (e.g., the pilot's data protection notice and records of data processing) worked for the pilot with no incidents reported • **Public information on pilot requirements** reported as clear and useful by applicants/MAHs	• **Update guidance to applicants/MAHs** for the second phase of the pilot, e.g. change in timelines, modes of participation • **EMA to carry out analyses** in support of assessment and decision-making • Foster **knowledge sharing between NCAs** to optimise the operational model, e.g. in relation to pre-submission interactions and data submission meetings
Technical aspects 	• The **data sharing** process between EMA and NCAs worked adequately for the pilot but will require changes in case of larger volume of clinical study data submissions • **Diverse feedback received** in relation to the **preferred data storage and analytics infrastructure** for the EMRN (e.g. centralised, decentralised or hybrid solution) • **Heterogeneity in software preferences** by the EMRN for **clinical efficacy and safety analyses** was reported • For **PK-PD** analyses, **relevant software** should be available • The **process** and **guidance** for applicants/MAHs on the **technical submission of the clinical study data package** could **be improved** • Clinical trials clinical study data submitted by applicants/MAHs **complied with CDISC standards** (SDTM and ADaM); a **format that proved adequate for the review of the data**	• Refine the business requirements and assess feasibility of a **suitable to-be clinical study data receipt, storage and analytics infrastructure** • Explore the use of **software to systematically validate compliance with agreed data standards of clinical study data files** and activities related to content validation of a dossier at EMA • Explore the feasibility of a small set of **standardised analyses and visualisations** to support the understanding of a dossier's characteristics • **Explore the establishment of a repository** hosted and curated by EMA for sharing templates and statistical codes within the EMRN • Identify necessary upgrades of systems and processes to **optimise applicants'/MAHs' eSubmission process**, e.g. the inclusion of the clinical study data package in eCTD structure

	Learnings	Recommendations for the second pilot phase
		• **Leverage EMRN Data Standardisation Strategy** to reflect on adoption of clinical trial data standards • **Strengthen exchange** with other international regulators on activities related to **data standardisation** and data governance, fostering **alignment regarding data submission requirements** and **electronic submission plans** • **Foster engagement with applicants/MAHs** (e.g., via the Industry Focus Group on Raw Data or relevant industry fora)

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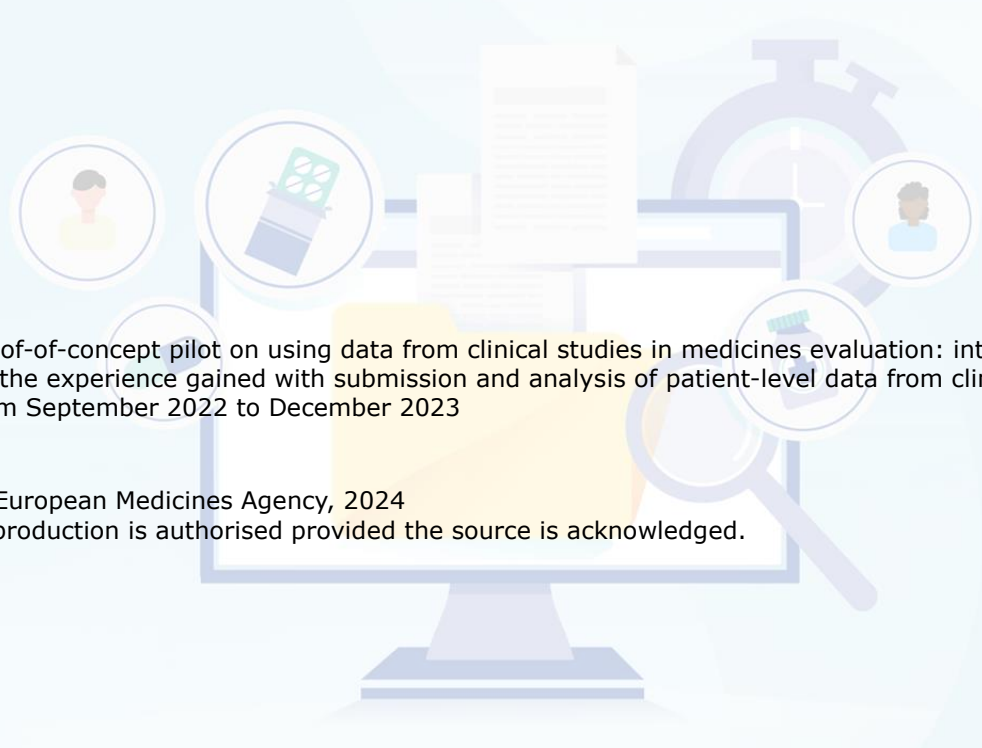

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