07 July 2025
EMA/658116/2022
European Medicines Agency

Questions and Answers about the clinical study data proof-of-concept pilot for industry

Scope, terms of participation and data submission process

This document provides Answers to commonly asked Questions about the proof-of-concept (PoC) pilot on the submission and analysis of data from clinical studies[1] as part of selected initial marketing authorisation applications (iMAAs) and post-authorisation applications submitted to the European Medicines Agency (EMA). This Questions and Answers document relates to the 'Information about the clinical study data proof-of-concept pilot for industry'.

Clinical study data, also referred to as 'Standardised Study Data', mean individual patient data from clinical studies[2] in electronic structured format.

[1] Formally referred to as proof-of-concept pilot on the submission and analysis of raw data
[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.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Contents

1. General questions about the PoC pilot

1.1. Why is the clinical study data PoC pilot performed?

The PoC pilot is performed to investigate the benefits of having access to clinical study data from regulatory submissions to support the scientific assessment of medicinal products and to identify the associated operational, resource and technological needs. Learnings from the PoC pilot will be systematically collected and evaluated. This will include asking for feedback from the Rapporteurs' assessment team, the Agency, and the applicant or marketing authorisation holder (MAH) of the regulatory procedures concerned by the PoC pilot phase.

The ultimate aim of the pilot is to generate learnings that will be translated into recommendations to the European Medicines Regulatory Network on the future role of access to clinical study data to support the regulatory assessment.

1.2. How were relevant stakeholders consulted on the design of the PoC pilot and how will they be consulted on the execution of the PoC pilot?

The EMA has engaged continuously with relevant stakeholders, e.g. via presentations at various fora. In addition, advisory bodies were set up to foster dialogue with relevant stakeholders during the design phase of the pilot. Further interactions are foreseen during the execution of the pilot as needed.

- European Medicines Regulatory Network Advisory Group on Raw Data: This group was established in July 2021 and includes representatives from the European Medicines Regulatory Network as well as patients' and health care professionals' representatives. Meetings take place on an ad-hoc basis, while written updates are provided approximately once per quarter.
- Industry Focus Group on Raw Data: This group was established in July 2022 following an open call via EMA's industry stakeholder trade associations. Meetings take place on an ad-hoc basis, while written updates are provided approximately once per quarter.

1.3. When has the PoC pilot started and how long will it run?

The PoC pilot has been launched in September 2022. It was initially envisaged to run for up to 2 years with an aim to include approximately ten centralised applications submitted to the EMA.

Building on the insights the pilot has generated so far and captured in the pilot's interim report (link), the pilot is now extended until further notice.

Interested applicants or MAHs should be aware that the pilot currently accepts expressions of interest for procedures until further notice.

1.4. Which regulatory procedures are in scope for the PoC pilot?

Initial Marketing Authorisation Applications (iMAAs) and post-authorisation applications (e.g. variations or extension applications) submitted centrally to EMA are in scope for the PoC pilot with a focus on iMAAs. For clinical variations, Type II variations with proposed change(s) to therapeutic indication(s) will be targeted.

1.5. Are decentralised procedures or referral procedures in scope for the PoC pilot?

Decentralised procedures or referral procedures are not in scope for the PoC pilot.

1.6. Are procedures concerning Advanced Therapy Medicinal Products (ATMPs) eligible to be included in the PoC pilot?

Procedures concerning ATMPs are eligible to be included in the PoC pilot.

1.7. Are procedures with accelerated assessment eligible to be included in the PoC pilot?

Procedures with an accelerated assessment are in principle eligible for inclusion. However, procedures without accelerated assessment will be prioritised.

1.8. Is it mandatory for applicants/marketing authorisation holders to participate in the PoC pilot?

Applicants/MAHs with a centralised application to EMA that falls within the scope of the PoC pilot (see Question 1.4) are invited to participate in the pilot on a voluntary basis. Pilot participation allows the applicant/MAH to share feedback on their experience and support the European Medicines Regulatory Network in making relevant learnings about the future role of access to clinical study data to support the regulatory assessment (see Question 1.1). A procedure will only be included in the PoC pilot if both the Agency/Rapporteurs and the applicant/MAH agree to their participation. If a specific procedure has been selected for the pilot, the concerned applicant/MAH will formally confirm their voluntary participation by signing a participation letter (see Question 2.3).

However, irrespective of the participation to the pilot, it is important to note that under the existing legal framework related to the assessment of marketing applications, the Agency has the possibility to request additional information, including clinical study data. In accordance with Article 7(c) of Regulation (EC) No 726/2004, the CHMP may request that the applicant supplements the particulars accompanying the application within a specific time period in order to further qualify, as appropriate, the quality, safety and efficacy of a medicinal product. Article 16.3 of Regulation (EC) 1234/2008 provides a similar possibility for Type II variations applications. Under the terms of these Regulations, the applicant/MAH must answer such requests fully and promptly according to the agreed timelines.

1.9. How will procedures be selected for the PoC pilot?

Procedures can be selected irrespective of the disease area, the therapeutic indication, or the type and number of clinical studies presented in the application. However, it is intended to include a variety of regulatory procedures among the procedures that will be part of the pilot. Furthermore, it is intended to select regulatory procedures before the submission of the dossier.

CHMP Rapporteurs as well as applicants/MAHs are invited to express their interest in participating in the PoC pilot. Based on the expressions of interest received, the Agency together with the CHMP Rapporteurs will decide whether a procedure may be included in the PoC pilot. If a specific procedure is deemed suitable for the PoC pilot by the CHMP Rapporteurs, applicants/MAHs may also be contacted directly by the Agency and asked whether the applicant/MAH would be willing to participate.

1.10. How will the clinical study data analysis results be used?

Visualisation and analysis of clinical study data will be used to support the benefit-risk assessment (clinical efficacy and modelling and simulation, including e.g. population pharmacokinetic/dynamic modelling, physiological based pharmacokinetic modelling) of the regulatory procedure. For some procedures the clinical study data will be used to support the selection of sites for GCP inspections. The

type of clinical study data analyses will include re-analyses, additional analyses and visualisations. No cross-product analyses will be performed as part of the PoC pilot.

The decision as to which analyses are performed will be driven by the Rapporteur teams' needs and individual to each submission. The focus will be on additional analyses that are deemed of relevance by the Rapporteur teams in the context of reviewing the dossier. Since, without pilot participation, the applicant/MAH likewise would have been asked to provide the additional analyses, it is per se not expected that pilot participation will increase the number of questions to the applicant/MAH.

The applicant/MAH will not be consulted prior to running the analysis, however, information about the analysis method and the results will be shared allowing the applicant/MAH to respond (see Question 2.8). Furthermore, the results from the Agency may be included in the Assessment Report (AR) and the European Public Assessment Report (EPAR) and, if applicable, this will be clearly stated, e.g. "Analysis by EMA: …". The appointed Rapporteur teams and the CHMP will decide whether certain analyses will be included in the AR and the EPAR. In general, those will be results that are considered of relevance to the scientific assessment of the dossier.

Clinical study data submitted may also be used to explore the added value of pre-specified analyses, visualisations and characterisation of data packages in the form of user-friendly interactive dashboards or reports aiming to enhance understanding of the data underlying the clinical evidence supporting an application.

1.11. Who is going to analyse the clinical study data submitted for the PoC pilot?

For each regulatory procedure, clinical study data analysis will be performed by either the CHMP Rapporteur teams at the NCAs, EMA staff or an EMA contractor (the Data Analytics Centre at Lægemiddelstyrelsen, Danish Medicines Agency). Lægemiddelstyrelsen has been awarded the contract with EMA via a procurement procedure under one of EMA's framework contracts (EMA/2020/46/TDA[3]). Please note that combinations of the entities listed above might also be explored for a procedure.

Although the data analysts' affiliation will depend on the regulatory procedure, for simplicity, the analysis results generated will throughout this Q&A be referred to as 'results by the Agency'.

1.12. How will learnings from the PoC pilot be shared with the public?

The Agency will organise a workshop with external stakeholders towards the end of the PoC pilot to present and discuss its learnings. An interim and final summary of the outcomes of the pilot will also be published, respecting commercially confidential information. The summaries will include high-level aggregate information on most relevant outcomes such as the regulatory benefit of access to clinical study data in support of the regulatory assessment and decision-making, while the final summary will also include information about which procedures were included in the pilot.

1.13. Does the Agency plan to request clinical study data for future applications following the PoC pilot?

The objective of the pilot is to gather experience and provide recommendations to the European Medicines Regulatory Network on the benefits as well as the operational and technical requirements of early access to clinical study data. The pilot is therefore expected to inform any decision on future clinical study data submission requirements.

[3] Services - 575628-2021 - TED Tenders Electronic Daily (europa.eu)

2. Questions on the terms of participation

2.1. How can applicants/MAHs ask questions about the PoC pilot?

Applicants/MAHs can contact EMA via rawdatapilot@ema.europa.eu to ask questions about the PoC pilot.

2.2. How and when can applicants/MAHs express interest to participate in the PoC pilot?

The process of volunteering for pilot participation involves two steps: (1) expression of interest, (2) formal confirmation of intention to participate (see Question 2.3).

In order to express interest in pilot participation, applicants/MAHs are encouraged to contact the EMA via rawdatapilot@ema.europa.eu. Alternatively, interest may also be expressed via one of the existing communication channels such as during pre-submission interactions. Expression of interest may happen via one of two ways:

i. By expressing general interest to participate without suggesting a specific upcoming submission. Expressing interest in pilot participation via e-mail will result in 'shortlisting' the applicant's/MAH's interest which will help in establishing dialogue with interested CHMP Rapporteurs.

ii. By suggesting a specific upcoming submission that is in scope for the PoC pilot (see Section 1). If a specific submission has been suggested, the appointed CHMP Rapporteurs will be contacted to establish if they agree for the suggested procedure to be included in the pilot (see Question 1.8).

Since the PoC pilot will include procedures providing the CHMP Rapporteurs' agreement, not all applicants/MAHs who express interest might be able to participate. There is no firm deadline in expressing interest in pilot participation. However, applicants/MAHs are advised to indicate interest as early as possible to increase the likelihood that a procedure can be included in the pilot.

2.3. How and when can applicants/MAHs confirm their intention to participate in the PoC pilot with a specific procedure?

The process of volunteering for pilot participation involves two steps: (1) expression of interest (see Question 2.2), (2) formal confirmation of intention to participate.

If both the applicant/MAH as well as the appointed CHMP Rapporteurs have expressed interest in pilot participation with a specific procedure, a direct dialogue will be established (see Question 2.7) to ensure that both agree on the data package to be submitted. In order to formally confirm pilot participation for a specific procedure, applicants/MAHs will be asked to submit a signed pilot participation letter (link) in which they confirm that they agree to the terms of participation. The signed participation letter should be submitted at the latest together with the clinical study data package for the concerned procedure (see Section 3), i.e. at the time of submitting the rest of the dossier.

2.4. Will participation in the PoC pilot cause a delay to the adoption of the opinion by the CHMP?

Participation in the PoC pilot will not delay the adoption of the scientific opinion by the CHMP. The Agency shall ensure that the opinion is adopted within the legal timeframes as laid out in Article 6 of

Regulation (EC) No 726/2004 for iMAAs or in the Commission Regulation (EU) No 712/2012 for variations.

2.5. Can an applicant/MAH withdraw their participation in the PoC pilot?

Once an applicant/MAH has confirmed their intention to participate in the PoC pilot with a regulatory procedure (see Question 2.3), the applicant or MAH cannot withdraw pilot participation for this procedure. Following consultation with EMA, exceptions can be made in case of force majeure.

2.6. How will the applicant/MAH communicate with the Agency and the Rapporteurs on pilot/clinical study data related aspects?

In general, existing regulatory channels shall be used to discuss questions related to the pilot participation. However, the Agency will follow a flexible approach to allow for sufficient dialogue with the applicant/MAH and additional interactions are planned or may be facilitated as needed.

- Before submission: The pre-submission interactions shall be used to agree on the data package to be submitted. As part of these interactions, applicants/MAHs are encouraged to request a joint pre-submission meeting with the appointed (Co)Rapporteur and the EMA to discuss the submission modalities.
- At the time of submission: For procedures chosen for the PoC pilot, the concerned applicant/MAH is expected to organise a data submission meeting to introduce the data analysts from the European Medicines Regulatory Network to the submitted data package. The applicant/MAH experts attending the data submission meeting are expected to explain the scope and structure of the submitted data package. The data submission meeting should happen around the time of the dossier's submission, i.e. usually within five working days after the data package has been submitted to the Agency (in particular, this meeting should take place before the start of the procedure).
- During the assessment: See Question 2.8.
- After the issuance of an opinion by the CHMP: The applicant/MAH is expected to provide feedback to the Agency on their pilot participation.

2.7. How will the applicant/MAH communicate with the Agency and the Rapporteurs about the benefit-risk analyses from the Agency?

In general, existing regulatory channels will be used for communication on the analyses by the Agency.

- The Agency/Rapporteurs inform the applicant/MAH about the analysis methods and results: Analysis results that are considered relevant for the benefit-risk assessment will be discussed in the assessment report and shared with the applicant/MAH together with the name of the data analyst(s). In addition, the Agency/Rapporteurs will share information about the analysis method and statistical software used as well as optionally the statistical software code. Furthermore, applicants/MAHs might be asked to replicate the analysis via the list of questions (LoQ), list of outstanding issues (LoOI) or requests for supplementary information (RSI) as relevant.
- Clarification needed about the analysis: Clarification on requests for replication of analyses received via the LoQ, LoOI or RSI should be sought via the existing EMA clarification meetings.
- Applicant/MAH responds to the analysis: The applicant/MAH is expected to respond in writing to the requests for replication as for any other question included in the LoQ, LoOI or RSI.

- Comparison of results: The following outcomes are possible:
    - The applicant/MAH replicates the analysis reaching the same results as the Agency. The results may be included in the AR and EPAR, indicating that the results were first generated by the Agency and then replicated by the applicant/MAH.
    - The applicant/MAH replicates the analysis reaching different results or conclusions. In such a situation it will be crucial to understand the reasons for reaching different results. A dialogue between the Agency/Rapporteurs and the applicant/MAH shall ensure that the reasons are understood such that an informed decision can be taken as to whether the results by the applicant/MAH or those by the Agency may be reflected in the AR and EPAR. In the unlikely event that the reasons for different results are not understood despite direct dialogue, this will need to be addressed on a case-by-case basis. However, the results from the Agency would not be included in the EPAR.
    - The applicant/MAH chooses not to replicate the analysis, responding that they accept the results from the Agency. The results from the Agency may be included in the AR and EPAR, indicating that the results were first generated by the Agency and accepted by the applicant/MAH.
    - The applicant/MAH chooses not to replicate the analysis and either no justification is given, or the given justification is not considered adequate by the Agency/Rapporteurs. The results from the Agency may be included in the AR and EPAR, acknowledging the fact that the applicant/MAH elected not to run the analysis proposed.

2.8. When data are analysed to select sites for GCP routine inspection, will this lead to an increase of the number of sites which are selected for GCP routine inspection as compared to procedures which are not part of the PoC pilot?

Participation in the PoC pilot will not per se increase the number of sites selected for the routine GCP inspections programme. Instead, the data analyses will support the decision-making process. As laid down in the 'Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for 'routine' and/or 'for cause' inspections, their investigation and scope of such inspections' (EMA/INS/GCP/167386/2012, link), all clinical trials that are part of a marketing application dossier could merit closer scrutiny, e.g. by an inspection.

2.9. How will the clinical study data files be processed by the EMA?

In processing the clinical study data, the Agency will ensure personal data are protected in full compliance with the provisions set in the Regulation (EU) 2018/1725 on the protection of personal data by the European Institutions and bodies. A Data Protection Impact Assessment for the clinical study data PoC pilot has been performed in 2022. The corresponding Data Protection Notice (link) and the Records of Processing Activity (link) are available on EMA's website.

2.10. How long will the clinical study data files be stored by EMA?

The retention period for the clinical study data files is the same as for the rest of the dossier which is submitted to the Agency. In particular, according to EMA's existing records policies, the clinical study data files will be retained up to 30 years after the withdrawal of the product from the market (see SOP_EMA_1004.pdf (eudra.org)).

2.11. How will EMA's transparency principles be applied to the clinical study data?

The Agency has published a paper that describes the Application of EMA's transparency principles to the clinical study data proof-of-concept pilot (europa.eu).

3. Questions on the data package to be submitted

3.1. Are data packages as prepared for other international regulators suitable to be submitted to the Agency for the PoC pilot?

In principle, data packages prepared for other international regulators, such as FDA, PMDA or Health Canada, may be submitted to the Agency for the PoC pilot, provided they meet the mandatory criteria listed in Question 3.3. Accordingly, all versions of standards as supported by other international regulators are permissible for the pilot.

Furthermore, a direct dialogue between the appointed CHMP Rapporteurs and the applicant/MAH shall confirm that the data package contains data for all clinical studies which are considered of interest by the Rapporteurs (see Question 3.2).

3.2. Does the data package need to contain clinical study data for all clinical studies included in the application or only for certain clinical studies?

In general, clinical study data should be submitted only from the clinical studies pivotal for the benefit-risk decision-making. However, for some procedures, upon agreement with the Agency and the appointed CHMP Rapporteurs, data from other studies such as dose-ranging studies may be asked for as well. Agreement on the set of clinical studies for which data will be submitted should be sought before submitting the data package (see Question 2.7).

3.3. Which files are mandatory to be included in the data package?

The data package should as a minimum contain the following data files as well as ancillary files:

- If not shared with the Agency before, the signed pilot participation letter (link).
- Pseudonymised data sets from the clinical studies as described in Question 3.2.
    - In accordance with the requirements of other international regulators, the data sets may be submitted in SAS Transport format (XPORT). However, the Agency will also consider other file transport formats such as Extensible Markup Language (XML) or JavaScript Object Notation (JSON) upon mutual agreement between the Agency and the applicant/MAH.
    - The data sets from clinical trials should comply with Clinical Data Interchange Standards Consortium (CDISC) Analysis Data Model (ADaM) and CDISC Study Data Tabulation Model (SDTM) data standards.
    - For data from non-interventional clinical studies, different requirements to data formats and standards may be agreed to with the Agency.
    - For analyses involving the use of modelling and simulation methods (e.g. population pharmacokinetic/dynamic modelling, physiological based pharmacokinetic modelling),

different requirements to data formats and standards may be agreed to with the Agency.

- The data definition files in CDISC Define-XML format.
- The Analysis Data Reviewer's Guide and the Study Data Reviewer's Guide.
- The software programs for (i) creation of the ADaM datasets and (ii) related to the primary and secondary efficacy analyses including programs to generate figures and tables.

3.4. Which files are optional to be included in the data package?

The submission of additional files may be agreed upon on a procedural basis. For example, the following files are optional to be included in the data package that is submitted to the Agency:

- It is highly recommended to submit the Analysis Results Metadata (ARM) for the primary and key secondary endpoints. The ARM may be submitted in XML or in a non-machine readable format such as PDF.
- The Bioresearch monitoring (BIMO) datasets and ancillary documents, with technical conformance guidance issued by the Office of Scientific Investigations (OSI), which are provided in FDA applications (link).
- The annotated case report forms (aCRF).
- Data on the Integrated Summary of Safety and Integrated Summary of Efficacy.
- Pooled data analyses packages, if they support the underlying submission.

3.5. Are there any requirements on naming convention for the files?

Applicants/MAHs are asked to use the naming conventions already specified by the data standards and agreed upon by other international regulators.

3.6. Could issues with the data formats/standards or missing files impact the start of the procedure?

Technical issues with the data format/standard or missing files will not impact the start of the procedure since the Agency will not invalidate submissions for these reasons. However, a delayed submission of the required files or of the data in the required format/standard might lead to the procedure being excluded from the PoC pilot.

3.7. Who should be contacted regarding general questions on the required data to be submitted?

Questions related to the data package for a specific submission should be discussed during the pre-submission interactions (see Question 2.7). General questions concerning the data package should be sent to rawdatapilot@ema.europa.eu.

4. Technical questions on the submission of the clinical study data

4.1. How can datasets be submitted to the EMA?

The files as specified in Section 3 should be submitted via the eSubmission Gateway:

- The clinical study data packages should be submitted with a specific xml delivery file for submission type 'Raw data submission'.
- The submission should be provided in the format as described in Section 3. The clinical study data package should be provided as a zip file.
- A cover letter (link) can be included within the zip package to provide more information on the clinical study data submission.
- It is recommended that the zip file will have a short, simple name which doesn't contain any special characters (for example: 009999 WonderPill Raw data).
- The zip file should be zipped together with the xml delivery file. There must be no working documents folder or any eCTD content submitted using this submission type.
- Further details on how to create the delivery file can be found from the User guide to XML delivery file creation.
- Further details can be found in How to send submissions via the Web Client.

4.2. What is the maximum size of the data package that can be submitted?

Data packages of up to 25 GB can be submitted via the submission type 'Raw data submission'.

4.3. How can additional data be submitted?

In general, a single data package including all required files should be submitted at the time of submitting the rest of the dossier. In case submission of additional data not included in the initial data package is agreed between the CHMP Rapporteurs and the applicant/MAH, this can be done the same way as the initial clinical study data submission (see Question 4.1).

4.4. How can data from several clinical studies be submitted?

Datasets from different studies can be submitted within the same zip package or as a separate submission. A cover letter can be included within the submission to provide more information.