

Development of a Unique Tool for Assessing the Feasibility of an External Control Arm Study

HTA109



Jason C. Simeone¹, Thomas Wilke²

[1] GIPAM Inc., Winchester, MA, USA; [2] GIPAM GmbH, Wismar, Germany.

Background

External control arms (ECAs) are used to generate comparative evidence (e.g., effectiveness) when only a single-arm trial has been conducted during the drug development process. However, key stakeholders often face substantial delays in determining the feasibility of an ECA; a responsive tool could streamline this process in a structured, rigorous manner.

Methods

- A comprehensive review was performed to identify ECA guidelines and reflection papers from relevant agencies such as the US Food and Drug Administration (FDA)¹ and the European Medicines Agency (EMA)² as well as other literature describing best practices for the conduct of an ECA.
- A structured questionnaire was first developed to assess general topics, data feasibility and design feasibility. Questions were coded with skip logic when appropriate.
- A checklist indicating positive (i.e., supportive of the ECA feasibility) and negative (i.e., challenges to the ECA feasibility) responses was created to allow the user to easily identify potential gaps at the strategic planning stage.
- A report summarizing the responses and recommended advice per question based on expertise from relevant literature was generated.
- The ECA Questionnaire Tool was developed as an interactive web application using a modern JavaScript framework for the frontend, enabling dynamic question logic, progress tracking, and automated report generation. User responses are transmitted via a RESTful API to a C# backend, where they are securely stored in a SQL database. This architecture supports structured data collection, real-time feedback, and seamless integration of feasibility checklists and reporting features.

Results

ECA Feasibility Questionnaire: A total of 24 questions including 2 general questions, 13 data feasibility questions, and 9 design feasibility questions were developed. Sample questions from the general domain (Figure 1) and the design feasibility domain (Figure 2) are provided below.

Figure 1: Example General Question from ECA Questionnaire

The screenshot shows a question from the 'General' domain. The question is: "[2] Have you reviewed previous ECA submissions to the regulatory or HTA body that you are preparing to submit to, especially in the same indication?". Below the question are 'YES' and 'NO' buttons. At the bottom are 'BACK', 'PROCEED TO NEXT QUESTION', and 'CONTACT GIPAM FOR SUPPORT' buttons.

Figure 2: Example Design Feasibility Question from ECA Questionnaire

The screenshot shows a question from the 'Design feasibility' domain. The question is: "[23] Have you considered key sensitivity analyses that may be necessary to account for uncertainty in, for example, the selection of patients included in the study or the identification of study outcomes?". Below the question are 'YES' and 'NO' buttons. At the bottom are 'BACK', 'PROCEED TO NEXT QUESTION', and 'CONTACT GIPAM FOR SUPPORT' buttons.

Checklist: Following the questionnaire, the completion status of all feasibility questions is summarized for user review (Figure 3).

Figure 3: Selected Output from ECA Questionnaire Checklist

The screenshot shows a table of checklist results. The columns are '#', 'Category', 'Feasibility question', and 'Checklist Symbol'. The data is as follows:

#	Category	Feasibility question	Checklist Symbol
1	General	Do you have a justifiable rationale (e.g., not for budgetary reasons) for conduct...	✓
2	General	Have you reviewed previous ECA submissions to the regulatory or HTA body t...	✓
3	Data feasibility	Have you already conducted a data landscaping and feasibility assessment fo...	✓
4	Data feasibility	Have you selected a source of data for your external control arm (ECA)?	✓

Report: A comprehensive explanation of all responses along with associated guidance is then generated (Figure 4).

Figure 4: Selected Output from ECA Questionnaire Report

The screenshot shows a report section for the 'General' domain. It includes a summary table and a detailed list of responses. The detailed list for 'General' includes:

- You stated that you have an acceptable rationale for conducting the ECA. GIPAM still recommends checking against any ECA guidelines issued by the agency you are submitting to, to confirm that the rationale meets their recommendations, as this point is critical for the success of the submission overall.
- You stated that you have already reviewed previous related ECA submissions. GIPAM highly recommends that you note any feedback provided by the agency on the submission, particularly including criticisms, as this information can help to inform the selection of data and design of your study.

The report also includes a section for 'Data feasibility' with a detailed list of responses.

Conclusion

- A user-friendly electronic tool to assess the feasibility of an ECA across multiple domains can de-risk the evidence generation process, saving time and financial resources; the tool is available in GIPAM's EVIGATOR platform or independently.
- The use of a feasibility tool does not replace required analyses of patient-level data. However, a structured, rapid assessment can quickly identify gaps for focus during a full feasibility analysis.

Disclosure statement and Acknowledgements

No disclosures other than those related to the listed affiliations need to be reported.

The authors thank Axel Dittmar, IPAM, for programming the ECA Questionnaire Tool.

References

- [1] United States Department of Health and Human Services Food and Drug Administration. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (Draft). 2023 Feb. Accessed at: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products>
- [2] European Medicines Agency. Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation application. 2024 Sept. Accessed at: <https://www.ema.europa.eu/en/establishing-efficacy-based-single-arm-trials-submitted-pivotal-evidence-marketing-authorisation>