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Introduction: The assessment of proarrhythmic risk associated with QT interval prolongation and Torsade de Pointes (TdP) is a regulatory requirement and a critical aspect of new drug development for which a guideline has been made by the International Conference on Harmonization (ICH) E14. Since the 2015 revision of the ICH E14 Thorough QT (TQT) studies which is considered the gold standard can be substituted by concentration-QT (C-QT) modelling. This approach offers several advantages over TQT studies, including ethical considerations, practical feasibility, cost-effectiveness, and regulatory flexibility. Consequently, C-QT modelling is increasingly being used in regulatory submissions to assess QT liability without the need for a dedicated TQT study. The present study provides a retrospective review of European Medicines Agency (EMA) scientific advice on C-QT modelling between January 2022 and January 2025, analyzing cases where applicants explicitly sought regulatory feedback on their clinical QT assessment strategy.

Objectives: The study aims to identify patterns in the regulatory acceptance and rejection of C-QT modelling, as well as to explore the rationale behind regulatory feedback.

Methods: A search was conducted in scientific advices using Scientific Explorer, the AI tool developed within the EMA with the keywords “QT” and “QTc” for the period January 2022 January 2025. The final Scientific advice were reviewed and sections related to QT assessment extracted in an anonymized manner. The general workflow is depicted in **Figure 1**.

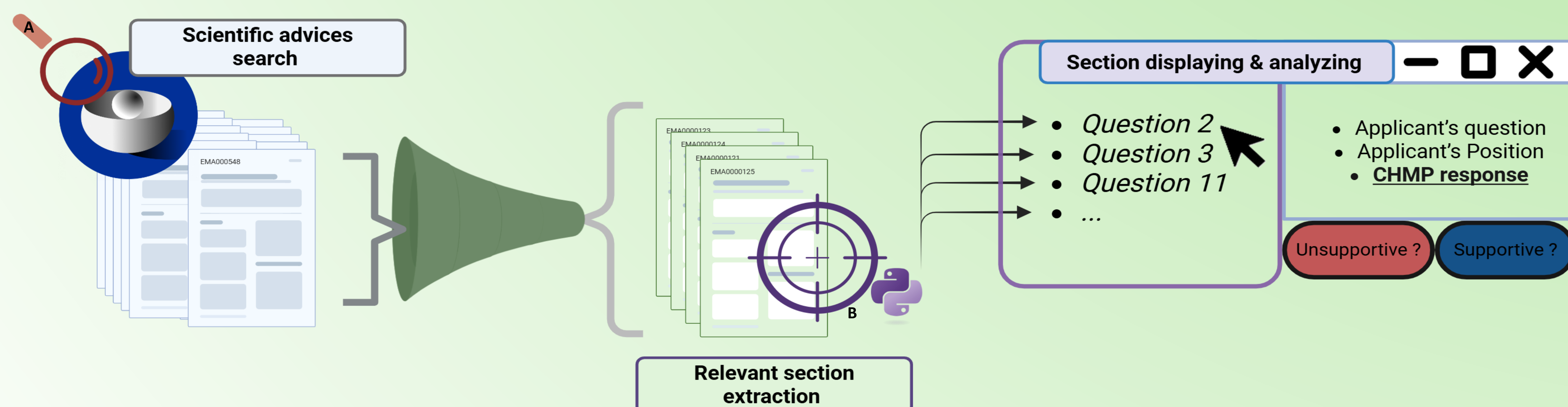


Figure 1: General extraction workflow. EMA scientific advices search was conducted using “QT” and “QTc”(A). Every documents found using the EMA IRIS tool and the specific key words were then reviewed in a systematic manner using a custom python tool (B). Relevant part from scientific advice were then extracted and analyzed. The sections where the keywords appeared were displayed as well as the corresponding discussion for each occurrence, including the applicant’s question, their position, and the Committee for Medicinal Products for Human Use (CHMP) response were eventually retained. Explicit requests for regulatory feedback were identified. For unsupportive CHMP responses, an in-depth analysis of the discussion was conducted to determine the rationale behind.

Results: A total of 253 cases were identified through the search using *Scientific Explorer*, comprising 1,735 questions, of which 70 explicitly requested feedback on assessment of QT prolongation. Among these, 13 cases (18%) received unsupportive responses from the CHMP (see Figure 2 for proportions).

Reasons for unsupportive responses were classified into seven categories: *study design issues*, *concerns with QTc interpretation*, *insufficient exposure*, *methodological issues*, *unclear methodological reporting*, *regulatory & compliance issues*, *study evidence gaps*.

The frequency of each category is illustrated in Figure 3. Additionally, it was noted that in 9 cases, safety margin calculations were either missing or unclearly reported, and in 3 cases, sample size information for planned, ongoing, or completed studies was not clearly provided in the joint report.

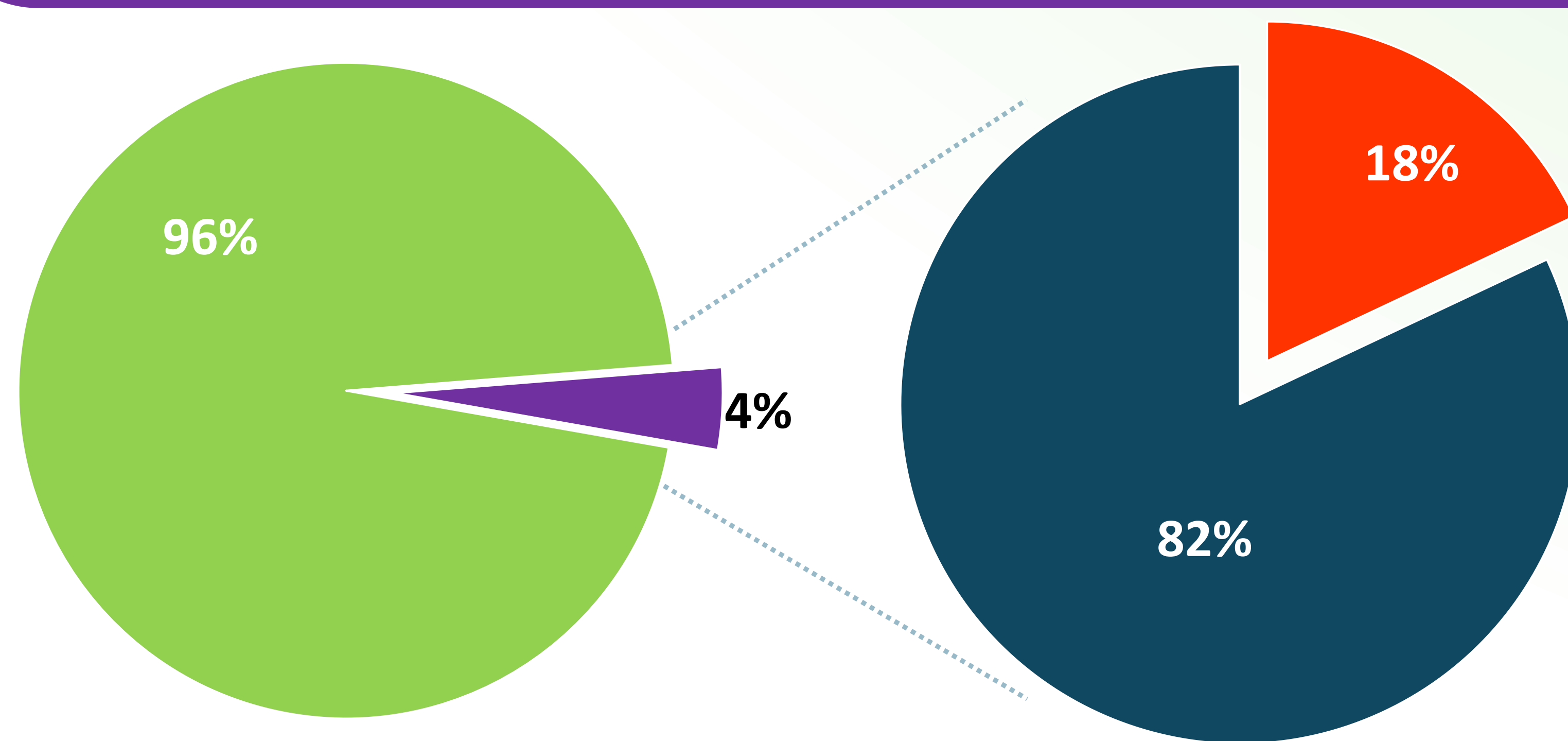


Figure 2: Proportion of QT-related queries and CHMP responses. **Left panel:** Distribution of questions explicitly related to QT assessment (purple) versus other regulatory questions (green). **Right panel:** Proportion of supportive (blue) versus unsupportive (red) CHMP responses to QT-related questions.

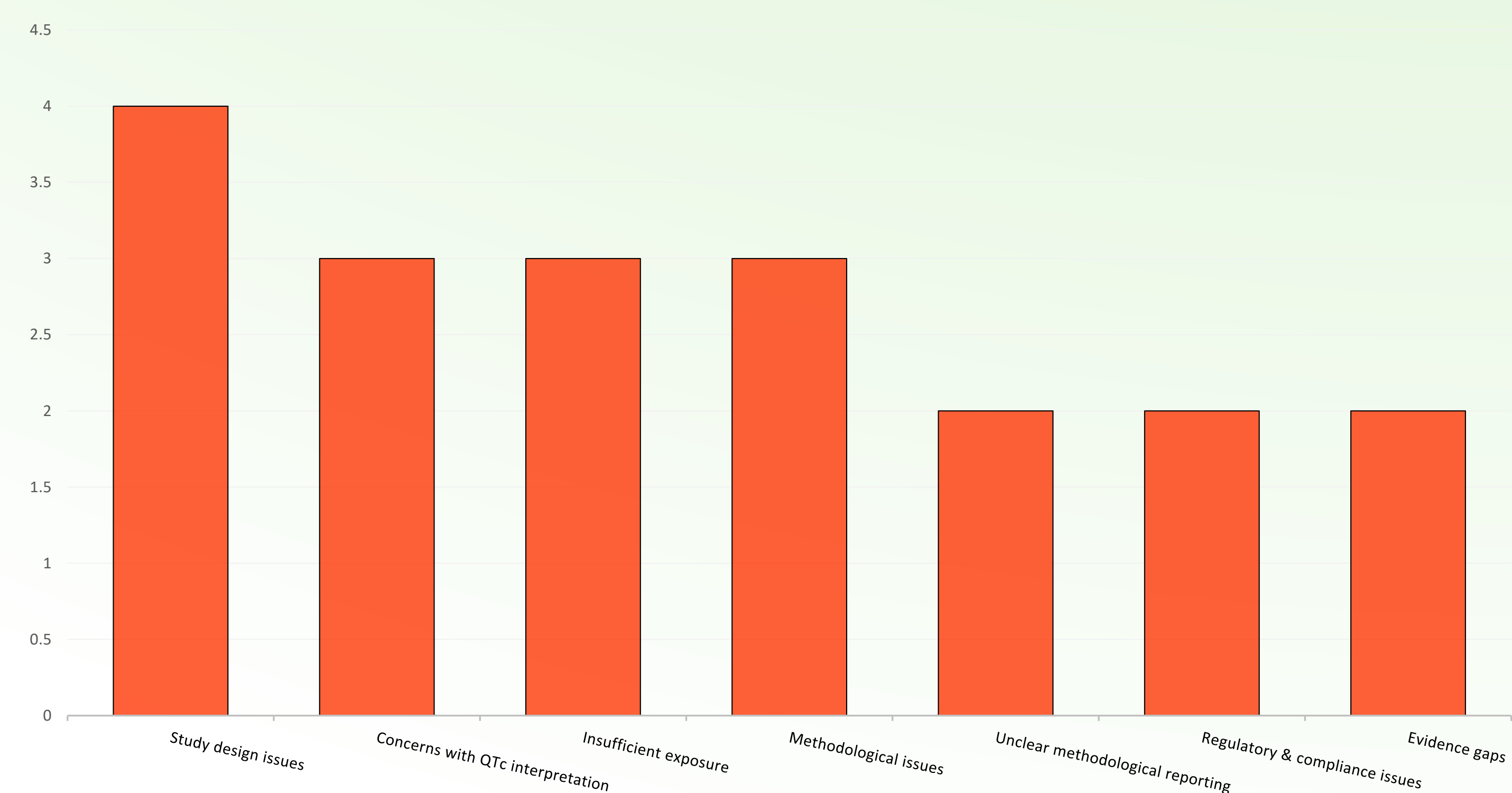


Figure 3: Reasons of Unsupportive response and frequency of occurrence. *study design issues* (4 cases), *concerns with QTc interpretation* (4 cases), *insufficient exposure* (3 cases), *methodological issues* (3 cases), *unclear methodological reporting* (3 cases), *regulatory & compliance issues* (2 cases), *study evidence gaps* (2 cases).

Conclusion: The present study highlights key regulatory concerns surrounding the use of C-QT modelling as an alternative to the TQT study in drug development. The main reasons hampering regulatory support are discussed. The analysis of unsupportive responses showed that main issues identified were related to study design and interpretation of C-QTc results. This emphasizes the need for adequate study designs and robust QTc modelling approaches. These findings suggest that clearer regulatory guidance and training, in particular on the technical aspects, and early engagement with regulatory agencies could enhance the acceptance of C-QT modelling. Future efforts should focus on populating best practices for C-QT study design to ensure better alignment with regulatory expectations .

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