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An interactive tool to select comparative efficacy and safety analysis methods for rapid feasibility assessment

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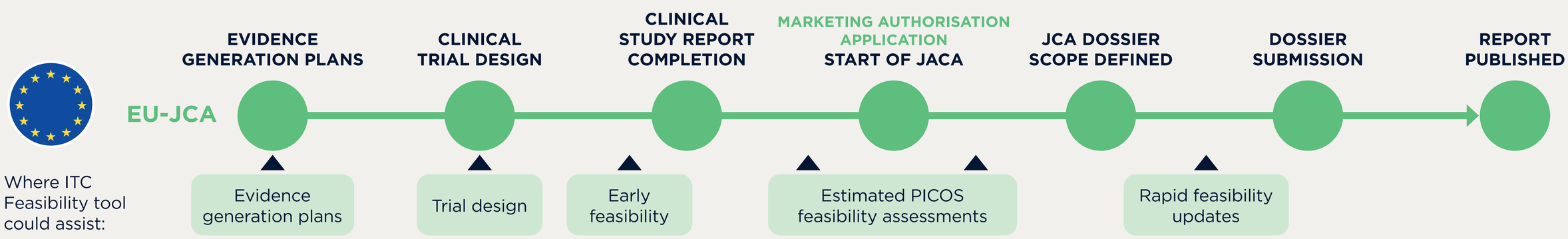
Summary

- We developed an interactive R Shiny-based tool to rapidly assess the feasibility of comparative efficacy and safety analysis methods.
- It was designed to support Joint Clinical Assessment (JCA) and Health Technology Assessment (HTA) submissions under strict EU-HTAR timelines.
- This tool provides structured recommendations, evidence networks, and PowerPoint summaries with minimal manual editing.
- Tool outputs aligned with expert opinion and successfully identified correct methods across simulations and real-world case studies.



Background

- Indirect comparative efficacy and safety estimates are often needed in the absence of head-to-head trials.
- Suitable indirect treatment comparisons (ITCs) such as Bucher method, network meta-analysis (NMA), population adjusted indirect comparisons (PAIC), simulated treatment comparisons (STC), external control arm (ECA), and multilevel network meta-regression (ML-NMR) are increasingly expected by regulators and HTA bodies.
- Currently, feasibility assessments to identify the appropriate ITC methods are:
  - Time-consuming.
  - Dependent on methods expertise.
  - Lacking explicit standardised guidelines.
- The EU-HTAR (effective 2025) introduces shorter timelines and emphasizes harmonised, transparent evidence strategies, particularly for joint clinical assessments (JCA).
- Sponsors require faster, reproducible decision-making processes to map available evidence to feasible ITC methods.
- Feasibility assessments are required to inform processes across the drug development pipeline, including at these stages:
  - Trial design.
  - Regulatory and HTA submissions.
  - Post-launch assessments as new comparative data emerge.

Methods

We developed an interactive R Shiny tool that is aligned to JCA and HTA guidance, published ITC methodological reviews, and ITC expert input.

- **Inputs required by the tool:** (Figure 1)
  - Study information (characteristics, comparators, outcomes).
  - Endpoint availability.
  - Individual patient data (IPD) and/or aggregate-level data, depending on the studies included.
  - Effect modifiers and prognostic factors.
  - Real-world evidence data (where relevant).
- **Adjustments for nuances such as:**
  - Different outcome definitions or scales.
  - Variation in treatment dosing regimens or administration schedules through treatment coding.
  - Subgroup-specific outputs that may influence feasibility.
- **Features:**
  - Automated construction of evidence networks.
  - Baseline comparability checks across studies/arms.
  - Identification of feasible anchored vs unanchored methods.
  - Outputs in dashboard and PowerPoint report formats.
- The tool was tested on several studies that included data on multiple treatments:
  - Simulated case studies.
  - Published studies: a rheumatoid arthritis study is provided as an example in the results section (Fautrel et al, 2020).

Results

The tool generated automated recommendations that aligned with expert reviews; the time from inputs completion to outputs was just under 1 minute.

- The tool correctly identified the ITC methods to use in all published case studies:
  - NMA – where connected networks existed, with potential deviations to the NMA assumptions noted.
  - Anchored MAIC – where IPD and shared comparators were available but required adjustment.
  - Unanchored MAIC – where IPD were available but no shared comparator was available.
  - ECA – where suitable real-world comparators existed.
  - ML-NMR – for networks requiring effect modifier adjustment.
- The tool highlighted situations where nuanced input adjustment was necessary:
  - Differences in treatment dosing across trials.
  - Use of different outcome scales (e.g., composite vs. single endpoints).
  - Divergences in reporting outputs (e.g., mean change vs responder rates).
- For the rheumatoid arthritis case study, the ITC tool provided:
  - A clear visualisation of the evidence network and connectivity of the treatments (Figure 2).
  - Baseline comparability checks that highlighted key similarities and differences in treatment effects (Figure 3).
  - Recommendations with details and rationale, both within the dashboard (Figure 4) and a PowerPoint report, which required minimal adjustment during expert review.

Figure 1. Data entry page for inputting study information

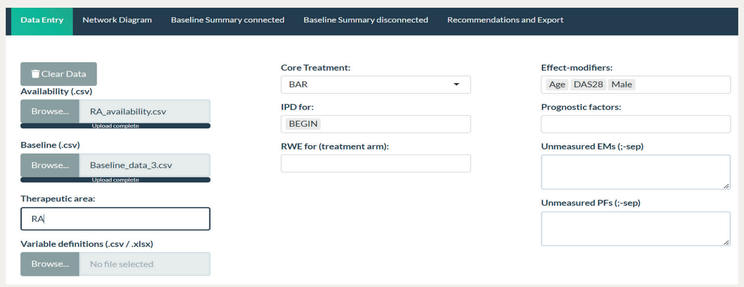
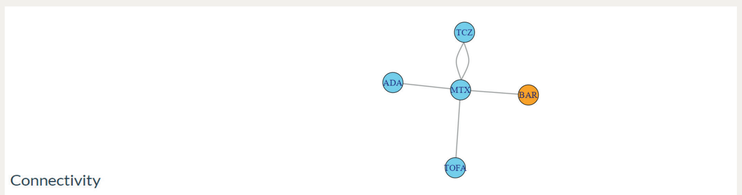


Figure 2. Network diagram of treatment connectivity and list of connectivity types, for the rheumatoid arthritis case study



Connectivity

Treatment	Connectivity
ADA	Indirect
BAR	Core
MTX	Direct
TCZ	Indirect
TOFA	Indirect

Figure 3. Treatment effect plot for connected studies, which form part of the baseline comparability checks, for the rheumatoid arthritis case study

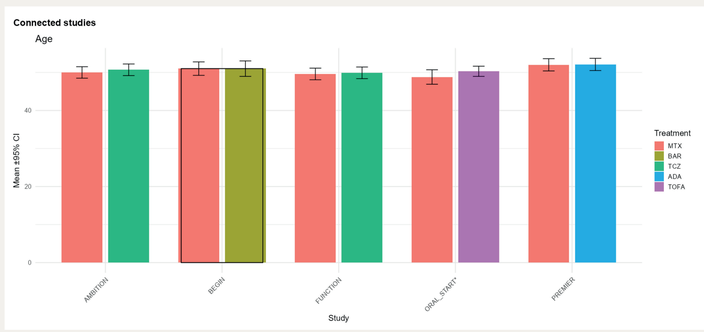
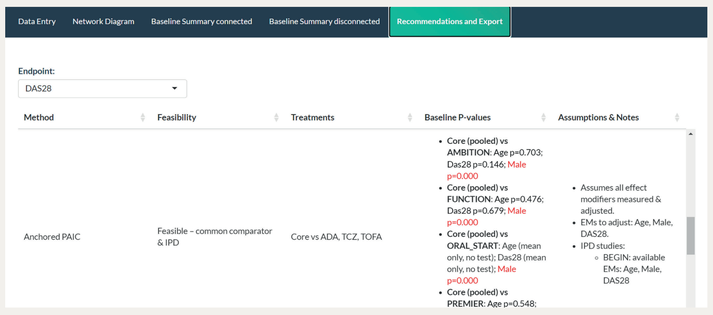


Figure 4. Example ITC method recommendation with supporting details, for the rheumatoid arthritis case study



Conclusions

This tool accelerates, standardises, and document ITC feasibility, and can support JCA and evidence planning from trial design to post-launch assessment.

Benefits:

- The tool speeds up evidence planning across trial design, regulatory/HTA submissions, and post-launch updates under strict JCA timelines.
- It guides method selection by linking available data to feasible ITC approaches and providing rationales.
- It generates submission-ready outputs, minimising manual editing.

Limitations:

- Its recommendations are dependent on the quality and completeness of the study and IPD input information provided.
- It requires adjustments for differences in endpoints, dosing schedules, and output definitions.

Future work:

- This tool will be integrated with automated analytical tools for running NMA and ML-NMR.
- Continuous updates will be made to the tool to align with evolving JCA and HTA guidance.

Reference for case study:
Fautrel B., Zhu B., Taylor P.C., van de Laar M., Emery P., De Leonardis F., Kannowski C.L., Nicolay C., Kadziola Z., De La Torre I., Fleischmann R. (2020). Comparative effectiveness of improvement in pain and physical function for baricitinib versus adalimumab, tocilizumab, and tofacitinib monotherapies in rheumatoid arthritis patients who are naïve to treatment with biologic or conventional synthetic disease-modifying antirheumatic drugs: a matching-adjusted indirect comparison. RMD Open, 6(1), e001131.

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