Evaluation of the Acceptance of Real-World Evidence (RWE) in EUnetHTA joint clinical assessments (JCA) to Support Evidence for Reimbursement Decisions

#HTA244

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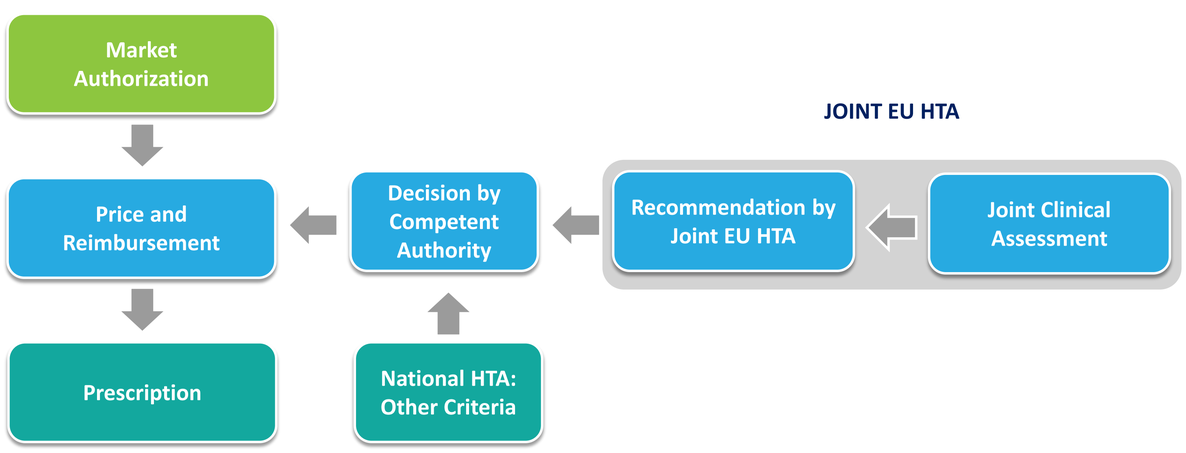
Introduction

- January 2025 is the date of application of the new European Union (EU) health technology assessment (HTA) Regulation 2021/2282 to harmonise methodological standards and to foster collaboration among EU HTAb (HTA bodies). One of the main pillars of the Regulation are the joint clinical assessments (JCAs).
- Current policies and guidelines from EUnetHTA direct JCAs to use randomised controlled trials (RCTs) as the best estimate of relative effectiveness. Real-world data/evidence (RWD/RWE) from observational studies are to be used to address the low external validity of RCTs. How RWD/RWE are being incorporated in JCAs remains unclear.



EU = European Union; HTA = health technology assessment

Objectives

- To evaluate the level of acceptance and use of RWD/RWE from observational studies in JCAs to support reimbursement decisions
- To describe trends of the value of RWD/RWE across JCAs

Methods

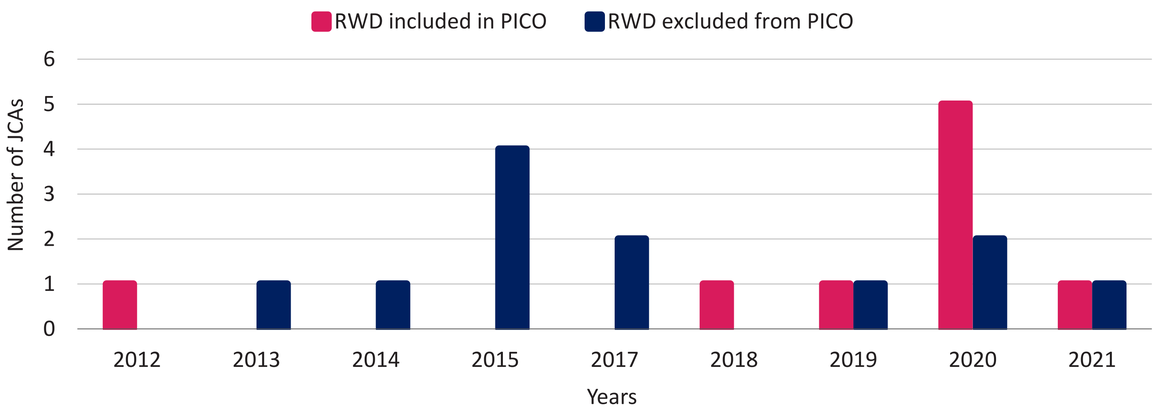
- Twenty-one JCA reports on medicines were identified and retrieved from the EUnetHTA website, all published between 2012 and 2021, of which 10 (48%) covered oncology products and eight (38%) covered orphan drugs.[1]
- Full-text final reports from each JCA were screened and extracted into a standardised data extraction form. Extraction was done twice by two independent reviewers.
- Based on the data extraction:
  - **acceptance** (i.e., inclusion of RWD in the PICO (**p**opulation, **i**ntervention, **c**ontrol, and **o**utcomes) model for evidence synthesis and intended use of RWD [i.e., primary or supportive evidence of safety and effectiveness])
  - **actual use** (i.e., inclusion of RWD in the evidence body)
  - **interpretation** of the evidence from RWD was identified and analysed.
- Appraisals of the validity of RWD/RWE use were examined by identifying judgements in JCA reports regarding the strengths and weaknesses of data sources.
- Descriptive statistics were used to summarise the information collected. Standard comparative statistics were used on data categorised by subgroups of interest (i.e., indication, JCA publication year) (two-sided P<0.05).

Results

JCA RWD acceptance in evidence synthesis

- RWD from observational studies were accepted in 9 of 21 (43%) JCAs (**Figure 1**):
  - All nine accepted RWD from prospective observational studies; more than half (5 of 9 [56%]) accepted RWD from other study designs as well.
  - In all nine, the intended use of RWD was to support the safety assessment of the new drug beyond RCTs; fewer JCAs (6 of 9 [67%]) aimed at using RWD to support effectiveness.
- JCAs acceptance of RWD sources was higher for orphan drug indications (4 of 8 [50%]) compared with non-orphan drugs (5 of 13 [38%]), but this difference was not significant (P=0.604).
- JCAs acceptance of RWD increased significantly from 20% (2 of 10) in 2012–2018 to 64% (7 of 11) in 2019–2021 (P=0.044), irrespective of the intended use, i.e., safety or effectiveness (P=0.044 and 0.006, respectively).

Figure 1. JCAs that included RWD in the PICO for evidence synthesis



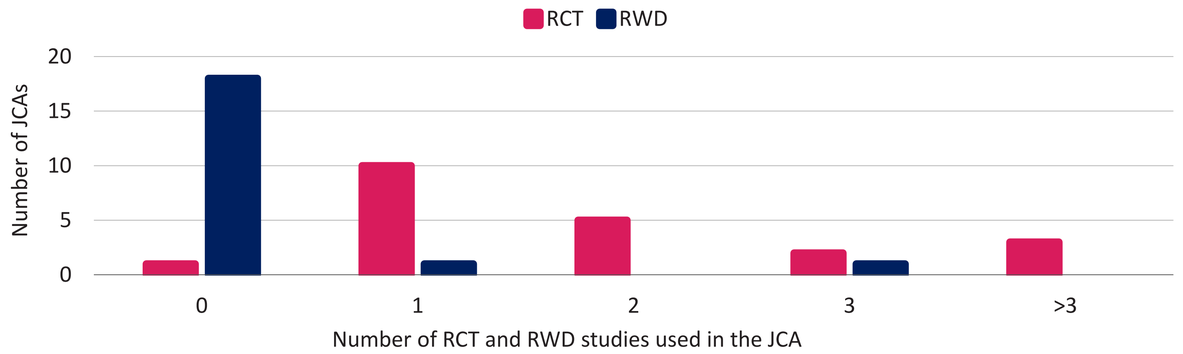
RWD = real-world data; PICO = population, intervention, control, and outcomes

Results (cont'd)

JCA RWD usage

- In 48% of JCAs (10 of 21), data from only one RCT were used to support evidence of the relative effectiveness and safety of the new drug; 24% of JCAs (5 of 21) based relative evidence on two RCTs.
- Only 10% of JCAs (2 of 21) included RWD as additional supportive evidence (**Figure 2**).

Figure 2. RCT and RWD usage in the JCAs

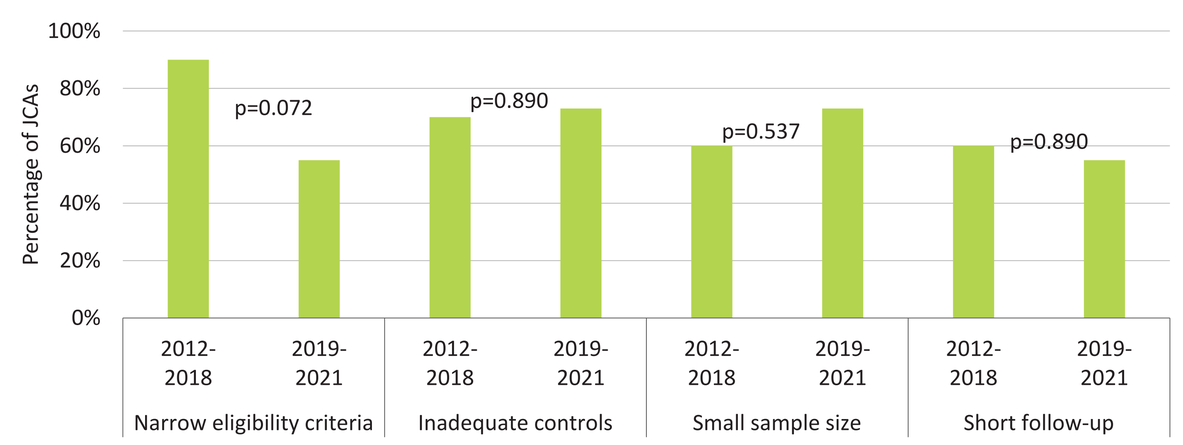


JCA= joint clinical assessments; RCT= randomised control trial; RWD= real-world data

Data insufficiencies at the time of HTA

- JCAs often reported a relatively low degree of certainty of the relative effects based on available data submitted by the manufacturer (**Figure 3**). The most common research questions were:
  - Limited extrapolations to community patients due to the narrow eligibility criteria and exclusion of those older/with comorbidities (reported in 71% of JCAs [15 of 21])
  - Inadequate comparison therapy that does not reflect use in current practice (15 of 21 [71%]).
  - Small sample sizes (14 of 21 [67%])
  - Limited long-term effect claims (12 of 21 [57%])
- Data insufficiency at the time of HTA submission was high, irrespective of JCA year of publication or drug indication type.

Figure 3. Most common critiques of RCT data



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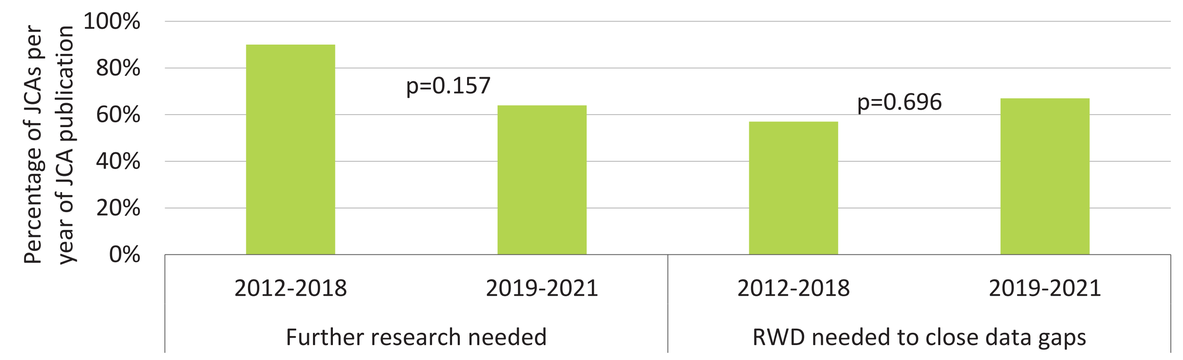
Handling incomplete clinical and safety data at the time of HTA

- The statement "more research is needed" was cited by 76% of JCAs (16 of 21). These JCAs identified unanswered clinically important research questions (**Figure 4**).
- Ten of 21 JCAs (48%) formulated research recommendations to use RWD/RWE to address remaining uncertainties (**Figure 4**), but rarely specified the design of subsequent primary research (i.e., only 30% of JCAs (3 of 10) were guided toward prospective studies)
- JCA recommendation for additional research was high irrespective of JCA year of publication or drug indication type.

Figure 4. JCA recommendations to address RCT uncertainties



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Conclusions

- JCAs primarily rely on RCTs to support their conclusions of relative effects, but clinically important research questions often remain unanswered by RCTs.
- JCAs' acceptance of RWD/RWE from observational studies to support RCT evidence in HTA decision-making is increasing, and RWD/RWE are often recommended to close the evidence gap for both effectiveness and safety. However, RWD are not yet widely used in JCAs, suggesting that barriers for the use of RWD remain.

References

1. https://www.eunethta.eu/jca/