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Health Solutions

20 November 2024

Giving Voice to Rare Diseases During Joint Clinical Assessment

ISPOR Europe 2024 Issue Panel

The power of **knowledge.**
The value of **understanding.**

Our Panelists

Caroline Ling
PhD

Panel moderator

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Emma Hawe
MSc

Evidence generation perspective

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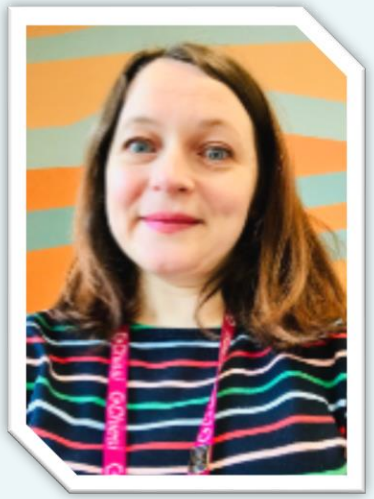


Abigail Stevenson
DPhil

Industry perspective

Chiesi

Martin Višňanský
MBA, PhD, PharmD

Patient Advocacy / Carer perspective

Chiesi

Questions

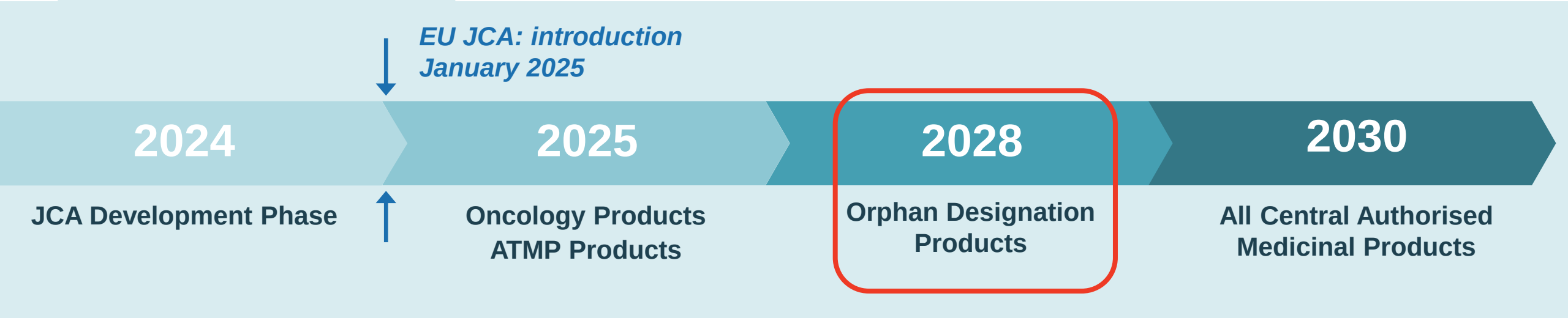
- In which sector do you work?
  - Pharma or MedTech industry
  - Academia
  - Public sector (e.g. HTA body)
  - Patient organisation
  - Other

- Do you think JCA is appropriate for rare diseases?
  - Yes
  - No
  - Don’t know

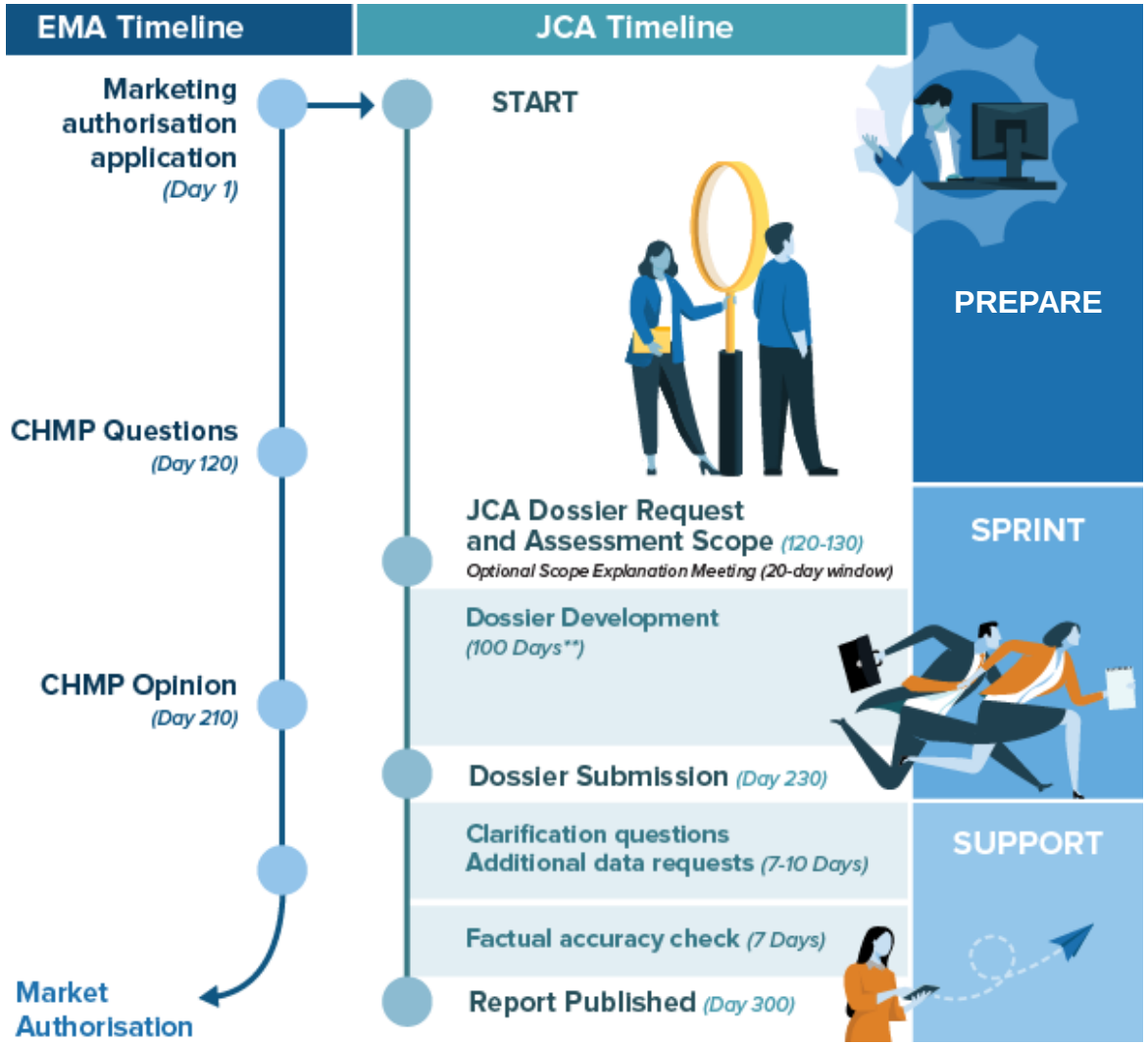
Recap of the Joint Clinical Assessment

- Joint Clinical Assessment (JCA) is a collaborative initiative among EU member states to streamline the clinical assessment of health technologies, including pharmaceuticals, medical devices, and in vitro diagnostics
- It involves a scientific compilation and comparative analysis of available clinical evidence on a health technology in comparison with other relevant technologies or existing procedures
- The JCA aims to inform decision-making and promote an equitable, efficient, and high-quality health system by assessing the value of health technologies at different points in their lifecycle. This process is formal, systematic, transparent, and uses state-of-the-art methods to consider the best available evidence

JCA Implementation Timeline



The JCA process activates from day 1 of Market Authorisation Application



Only 100 days between confirmation of the population, intervention, comparator(s), and outcomes (PICOs) and dossier submission, mean you must prepare in advance and refine JCA approach and submission one scope received

JCA process includes consultation with patients through the HTA Stakeholder Network

Includes over 40 patient associations, consumer organisations, health technology developer associations, health professional organisations and other relevant non-governmental organisations

Was a 2nd call for applicants in Sept-Oct 2024

CHMP = Committee for Medicinal Products for Human Use; EMA = European Medicines Agency.

Rare diseases in Europe

In the EU, a rare disease is defined as one with a prevalence of **less than 5 in 10,000**

Over **6,000** diseases are recognised as rare

Around **80%** of rare diseases are genetic and the majority start in childhood

Rare diseases affect more than **27 million** people in Europe

Special considerations for rare diseases

- JCA guidance published to date suggests the same process and requirements will be followed for rare diseases as for other therapy areas
- Rare oncology products and ATMPs will be assessed from 2025 using the current guidance
- The HTA Stakeholder Network includes EURORDIS and some rare disease groups

Special considerations for rare diseases

There, are different challenges for the development of treatments for rare diseases:

- Patient numbers are low
- Diseases may be life-limiting
- Natural history of the disease may be unclear and populations heterogeneous
- Clinical outcomes need to be clearly defined and patient-relevant
- Trials are often single arm – and it may be unethical to withhold a potentially effective treatment from patients
- There is often a lack of effective available treatments and standard of care may vary between member states
- Small trials
- Comparative evidence is often based on external / real-world evidence
- There is less data available for decision-making and thus greater uncertainty

These challenges make it even more important that patients are **heard**

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Generating comparative effectiveness estimates for rare diseases

Generating comparative efficacy results overview

Define the Scope

Population: Identify the specific patient population affected by the rare disease.

Intervention: Detail the treatment or technology being assessed.

Comparator: Determine the standard of care or alternative treatments.

Outcomes: Specify the clinical outcomes to be measured, such as survival rates, quality of life, and symptom improvement.

Data Collection

Systematic literature review: Following best practice and guidelines. Including risk of bias.

Clinical Trials: Gather data from clinical trials, even if they are small due to the rarity of the disease.

Real-World Evidence: Include data from patient registries, observational studies, and real-world evidence, which are crucial for rare diseases.

Analysis

Statistical Methods: Use appropriate statistical methods to analyze the data, considering the small sample sizes typical in rare disease studies. Evaluate potential bias and uncertainty.

Subgroup Analyses: Perform subgroup analyses to understand the effects on different patient subgroups.

Sensitivity Analysis: For example removing outliers, subgroups, around priors

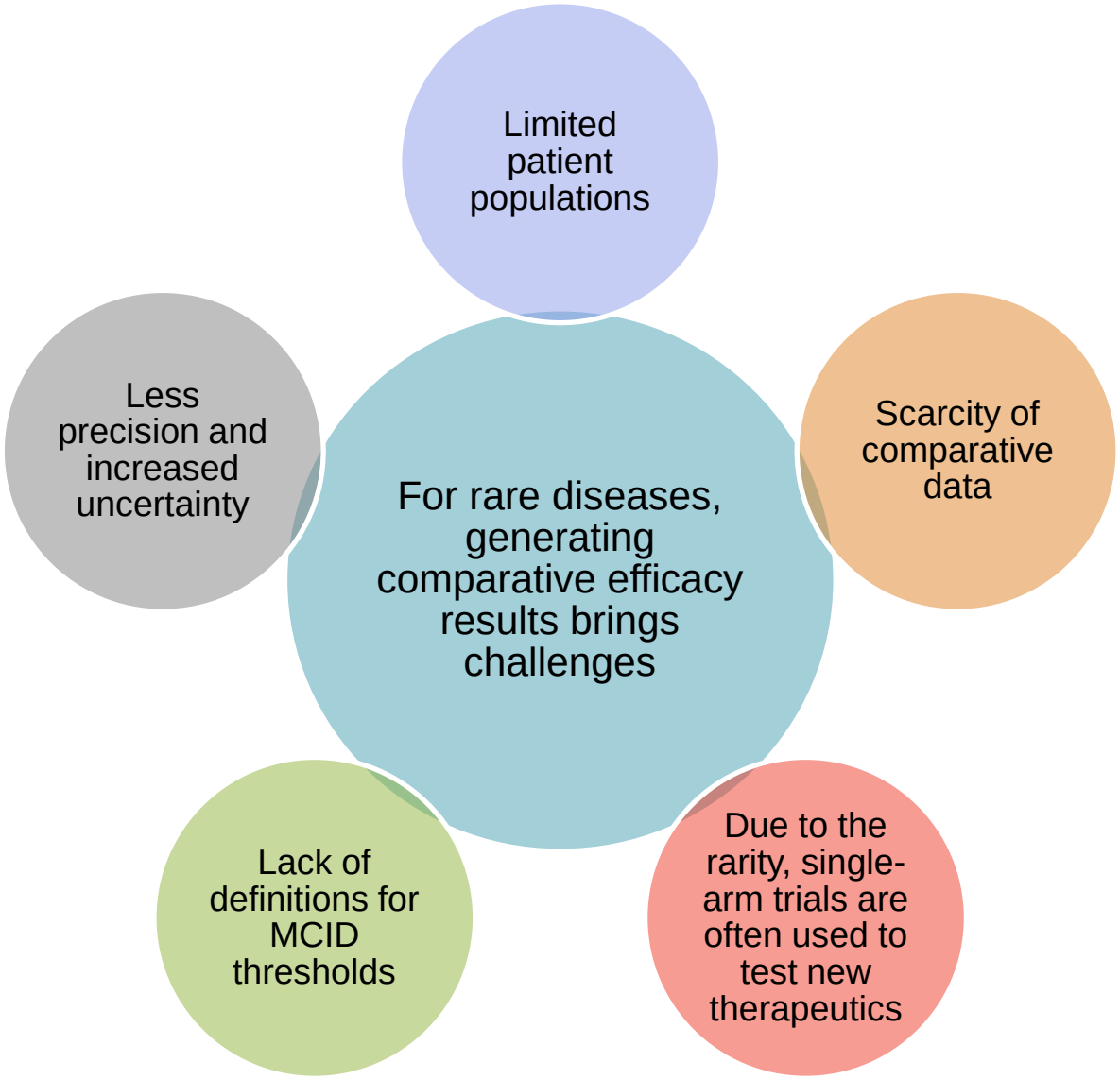
Reporting

Transparency: Ensure that the JCA report is transparent and includes all relevant data and methodologies.

Uncertainty: Describe uncertainty, report precision intervals, when uncertainty beyond statistical precision, report results against shifted hypothesis.

Feasibility assessment(s)

Analysis Challenges in Rare Diseases

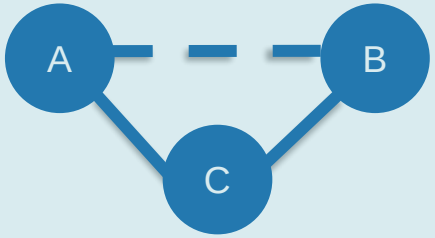


- The use of RWE is increasingly important in HTA for rare diseases. RWE can help address uncertainties in clinical evidence
- However, generating and using RWE poses challenges, such as patient selection, data quality, and appropriate adjustment for confounding factors

Statistical Methods

Anchored/direct comparisons

Pairwise Meta-Analysis



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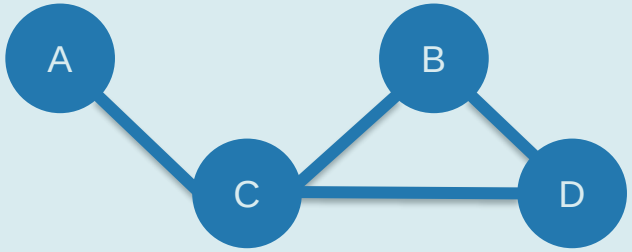
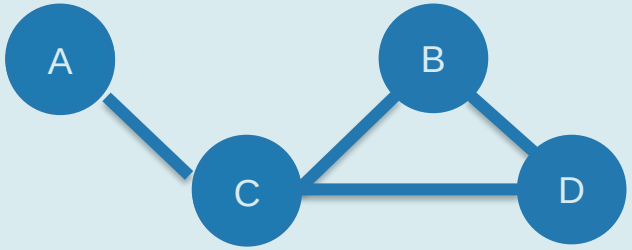


Network Meta Analysis



Anchored Population Adjusted Indirect Comparisons

Multilevel-Network Meta Regression

Indirect treatment comparisons

Unanchored comparisons

Unanchored Population Adjusted Indirect Comparisons

External Control Arms

Possible Analytical Solutions for Unanchored Comparisons

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Crude/Naïve comparison

- No adjustment is made with this method for any differences in patient characteristics
- Naïve comparisons between treatment arms are prone to bias due to confounding and should not be performed

MAIC

- The matching factors would need to be carefully selected, and likely limited due to the sample sizes
- Bootstrapping may be used assess weight stability and robustness of results
- Weights may be expected to be unreliable even with limited factors
- Effective sample size would be very small following matching

STC

- Sample sizes may be too small to fit a robust regression model
- May only feasible for regression model to adjust for limited covariates
- Large amount of uncertainty in predictions would be expected

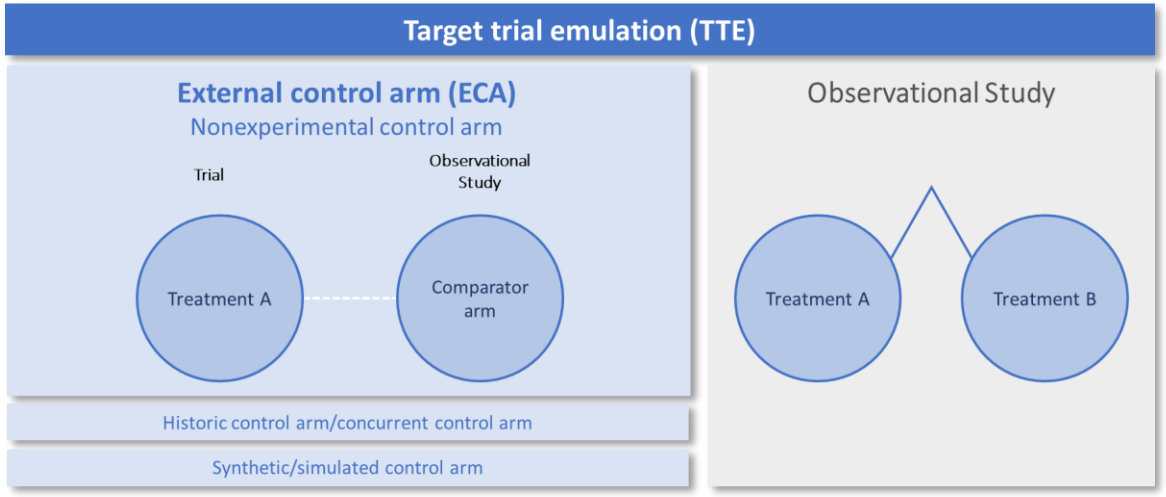
MIM

- May have greater power with smaller sample sizes, but less well known
- Similar strong assumptions as for unanchored STC and MAIC

MAIC = matched adjusted indirect comparison; STC = simulated treatment control arm; MIM = multiple imputation marginalisation

External Control Arms

What is an ECA?



- In the case of a single-arm trial, an external control arm may be used to enable comparative estimates to be generated.
- Considerations should be given (in advance) to the observational data source(s) and approach for the analysis.

Why perform an ECA?

- Randomized trial known as gold standard
- However, sometimes there are justifiable reasons to perform and utilize an observational study to construct an external control arm
  - Reduced associated costs
  - Ethical considerations
  - Time efficiency
  - **Rare diseases (small number of eligible patients)**

Accelerated access to beneficial treatments for patients

Concerns on distinguishing treatment effects from other factors

JCA Statements Relevant to Rare Diseases

- ***Indirect treatment comparisons***

For some interventions, single-arm or non-randomised evidence may be the only evidence available for consideration. However, it may well be that this evidence is insufficient for estimation of the relative treatment effectiveness in the context of JCA.

In general, the inclusion of additional effect modifiers reduces bias at the expense of increased variance, resulting in wider confidence/credible intervals for estimated treatment effects. As a result, when sample sizes are small it may not be possible to include all relevant effect modifiers and therefore population adjustment may not be appropriate.

The use of such evidence [single arm study compared to a group elsewhere] in JCA is highly problematic as it carries a high risk of not providing valid and reliable estimates

In the context of JCA, assessors should be aware that the inclusion of evidence from non-randomised studies [in a network] may lead to results that are highly uncertain and unlikely to provide a valid and reliable estimate

JCA Statements Relevant to Rare Diseases

- ***Indirect comparisons***

In the situation of binary data with rare events, the Peto method can be applied. However, this method should not be used when treatment effects are large and the trial arm sizes are unbalanced. In the situation of many double-zero studies (i.e., no observed events in both treatment arms), the beta-binomial model can be applied

Bayesian approaches are especially useful in situations with sparse data.

If between-trial heterogeneity is too strong to justify an evidence synthesis, but the heterogeneity can be explained, appropriate evidence synthesis should be performed in the corresponding groups of trials or subgroups of patients or by means of meta-regression

In some cases, it may be possible that the lack of randomisation can be compensated by rigorous adjustment for confounding. However, in general, this requires access to the full IPD information…. Clear cut recommendations regarding treatment effects on the basis of indirect comparisons with adjustment for confounding on the basis of IPD are only possible if the size of the estimated treatment effect is so large that the effect could not be induced by bias due to missing confounders or effect modifiers

JCA for (Ultra) Rare Disease: The Industry Perspective

Considerations and challenges of evidence generation in rare disease: across all 27 European Union member states

Challenges

Burden on small/midsize pharma

Limited HTA experience; smaller teams/budgets for larger data packages needed across EU27; conflicting priorities and unclear responsibilities

PICO scoping

Few clinical/patient experts (strict CoI); lack of capacity in local HTA to input within deadline; companies must plan ahead of PICO for analyses

Lack of industry input

No opportunity for consultation, other than fact check

100-day timing with other processes and stakeholders

Lack of preparation time and clinical/stats resources for FDA/EMA/NICE/JCA etc

Inherent clinical uncertainty and limited datasets: sufficient flexibility?

Small populations; often heterogeneous, slowly progressing, affecting children and adults; limited natural history data; ITCs not always feasible

Appropriate outcomes for rare?

Are selected outcomes in PICO clinically valid or patient/carer-relevant in (ultra) rare?

Early data may be surrogate outcomes, single-arm, lack statistical significance/MCID, lack of QoL

Limited guidance on data requirements and impact of assessment

Burden of additional data package for unclear impact?
EU27: same package won't fit all: published/unpublished data
Lack of legal framework: *"informs decision-making, not a value judgement":* what is its purpose?

Opportunities

Efficiency/alignment across EU and all stakeholders: 'one and done'

Earlier access to patients (?)
Joint reg/HTA scientific advice more important

Hope and Lessons Learned

Harmonization similar to the EMA centralized procedure, BeneLuxIA, Joint Nordic-HTA

Expertise is out there!

HTAi RDIG; EURODIS;
ISPOR Rare Disease SIG;
EUPATI HTA4Patients Initiative

Chiesi
global rare diseases

JCA for (Ultra) Rare Disease: The Patient and Carer Perspective

The patient and carer voice in rare disease: urgency of access to new treatments and importance of patient-relevant outcomes in JCA

Questions

- Do you think JCA is appropriate for rare diseases?
  - Yes
  - No
  - Don’t know

- What practical steps can be taken to overcome the issues identified?