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ISPOR | November 2025

EU Joint Clinical Assessment for Orphan Drugs: Methodological Challenges, Solutions, and Early Learnings

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

Your Presenters

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JCA Process and Challenges for Orphan Drugs

PATRICK HOPKINSON

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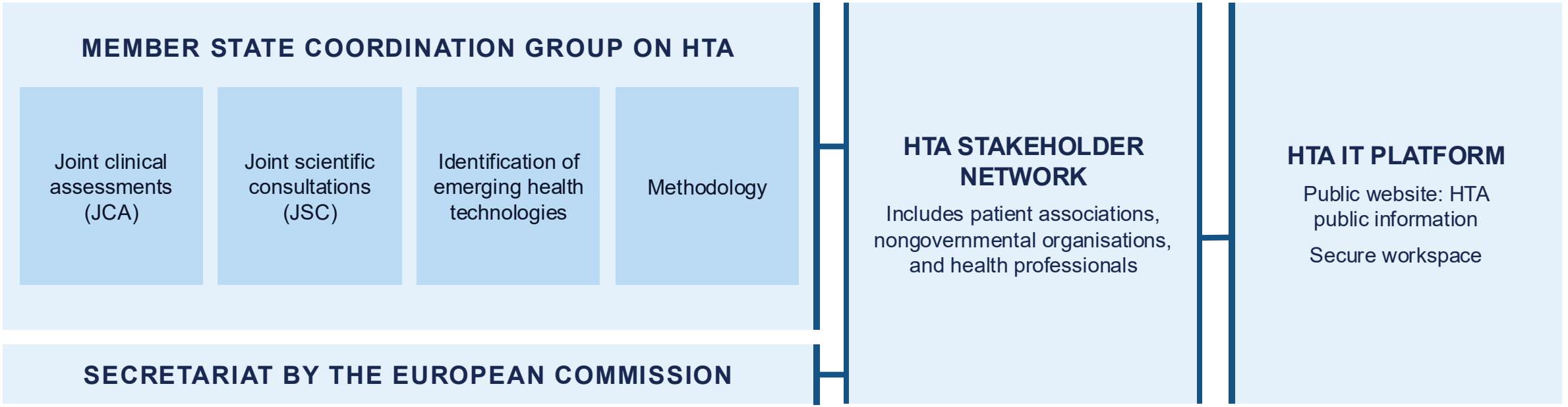
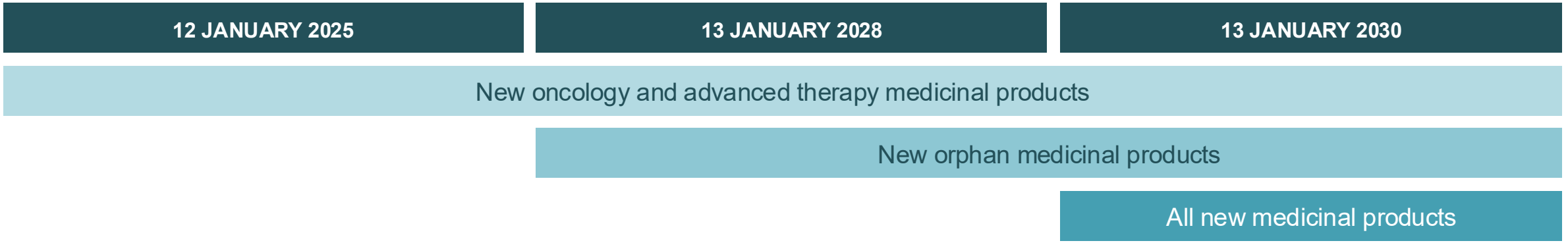
EU HTA Regulation Launched January 2025 – Will Expand to Orphan Products in 2028





Source: EU Commission (2025).

Special Considerations for Rare Diseases

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

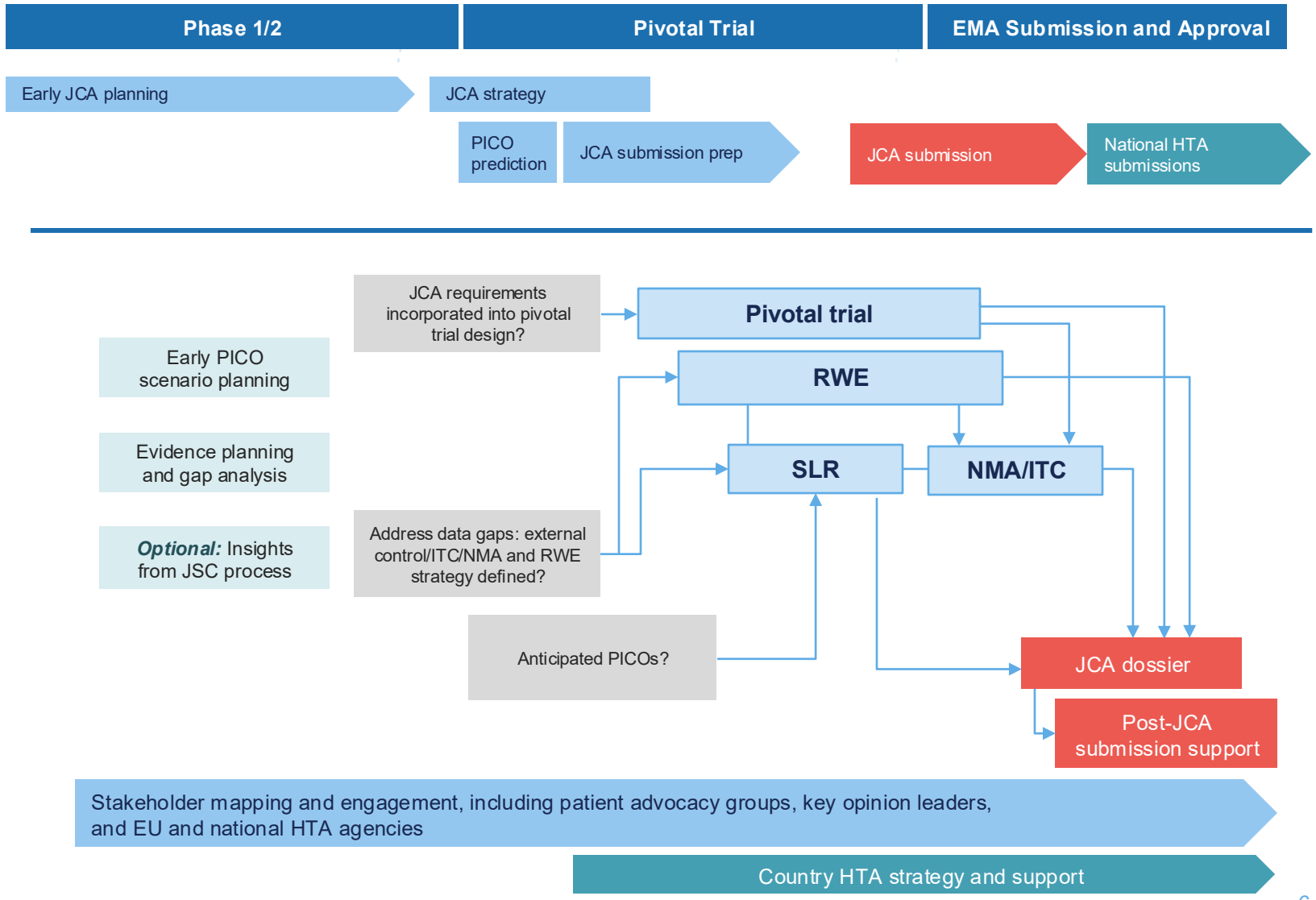
Disease characteristics	Evidence generation challenges	Outcome definition/ assessment challenges
Patient numbers are low	Clinical outcomes need to be clearly defined and relevant to patients	There is often a lack of available effective treatments and standard of care may vary between member states
Natural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

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

Embedding JCA Requirements Into the Product Development Process

Access landscape analysis

- Review of HTA assessments
- Standard of care
- Stakeholder mapping
- Early value proposition
- Clinical trial planning



Technical and Methodological Challenges for Orphan Submissions in JCA

SORREL WOLOWACZ

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Preparing Comparative Effectiveness Estimates – Overview

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DEFINE THE PICOs

- Population
- Intervention
- Comparator
- Outcomes

DATA COLLECTION

- Systematic Literature Review
- Clinical Trials
- Real-World Evidence

ANALYSIS

- Statistical Methods
- Subgroup Analyses
- Sensitivity Analysis

REPORTING

- Transparency
- Uncertainty

Anticipating PICOs for 27 EU Member States

Strategy

- Early engagement and market research
- Multiple guideline reviews and HTA recommendations
- Real-world evidence

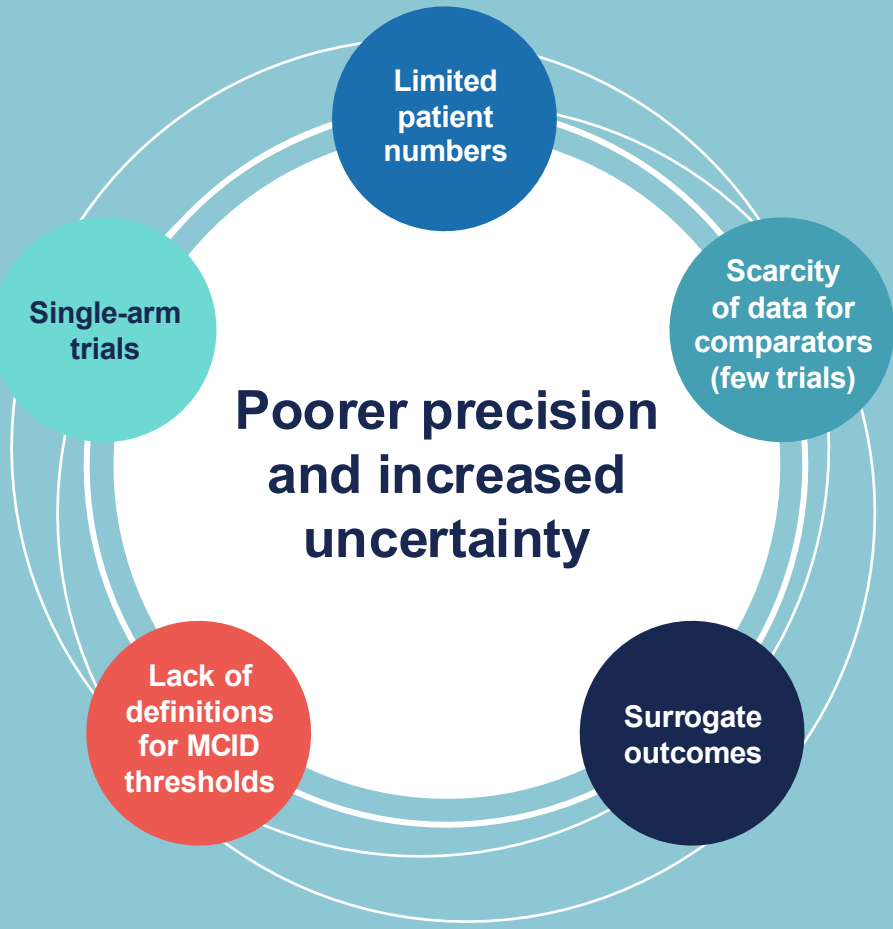
Challenges in rare diseases

- Heterogeneity
- No standard of care
- Limited HTA experience
- Few clinical experts and scarce clinical guidelines
- Non-validated outcomes

Additional strategies for rare diseases

- De novo RWE studies and market research
- Patient advocacy groups and registries
- Early engagement with clinical experts, preceding JCA invitation

Challenges for Comparative Effectiveness in Rare Diseases



Single-arm trials may be performed for ethical reasons and/or speed of recruitment

Surrogate outcomes allow for accelerated access to beneficial treatments

Preparing Comparative Effectiveness Estimates

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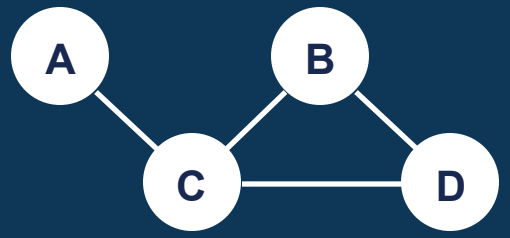
Anchored comparisons | **Unanchored comparisons**

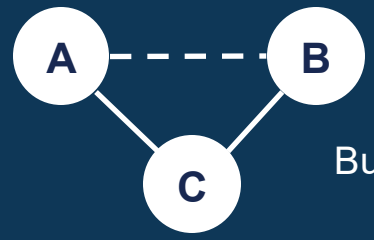
Direct comparisons

Pairwise Meta-Analysis

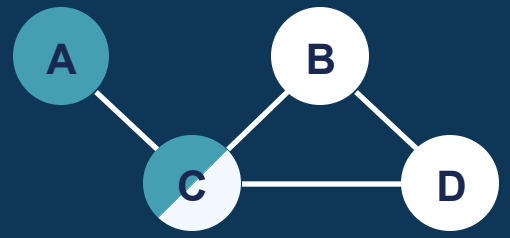


Mixed Treatment Comparisons

Indirect comparisons



Bucher/NMA



Anchored-Population–Adjusted Indirect Comparisons

Multilevel Network Meta-Regression

Unanchored-Population–Adjusted Indirect Comparisons

External Control Arms

JCA Statements Highlight Potential Challenges…
…and Also Recognise Possible Approaches

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.

Bayesian approaches are especially useful in situations with sparse data.

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***.

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.

Approaches To Address the Challenges

Specialist statistical approaches

- Target trial emulation/external control arm estimation for single-arm trials
- MAIC, STC, ML-NMR, propensity score methods
- Sensitivity analyses, testing of shifted null hypotheses
- Comparison of treatment effect with MCID
- Specialist methods for small sample sizes and limited number of studies

Important to develop comparative effectiveness strategy early to identify need for additional data and/or research

Additional data requirements

- Identification of prognostic factors and treatment-effect modifiers
- Individual level data from single-arm trials
- Individual level data for comparators with as large a sample size as practicable to reduce uncertainty
- Surrogate validation
- Research to establish MCID

5 Steps to Success – Strategy and Planning

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STEP 1

EARLY JCA PLANNING

Success starts with strategic planning
– ideally phase 2 or earlier

STEP 2

DEVELOP A JCA STRATEGY

Build your pivotal trial strategy on solid foundations

STEP 3

PREDICT AND VALIDATE PICOs

Forecast potential PICOs and test them with local experts

STEP 4

PREPARE A ROBUST SUBMISSION

STEP 5

COUNTRY HTA SUBMISSIONS

Plan for country-specific requirements

Lessons Learned:
Prediction results in large numbers of PICOs

- Current PICO prediction exercises saw up to 13 PICOs for seen for some indications
- All 27 EU member states input into the JCA scope
- Heterogeneous rare diseases without a single “standard of care” that is consistent across all EU member states may result in even larger numbers of PICOs
- Consolidation and prioritization of PICOs will be required
- Assessment of the need for – and validity of – potential ITCs is vital
- Developing a rationale for not presenting any ITC for some PICOs will be key

Lessons Learned: Designing a clinical SLR to meet both JCA and future HTA requirements

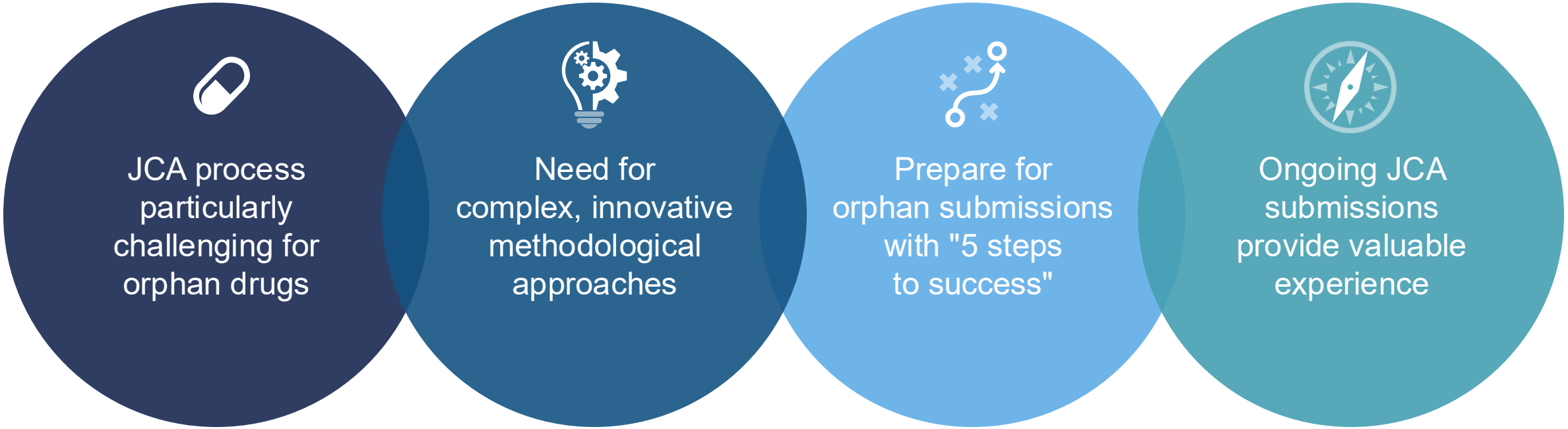
JCA has some specific requirements for SLRs that differ from those of national HTA bodies

JCA	National HTAs
Searches of Medline and Cochrane	Searches of multiple databases, usually including Embase
Searches of multiple trial registries	Searches of Clinicaltrials.gov
Does not accept conference materials	Accepts conference materials
Requires indirect comparisons for many outcomes	Usually only requires indirect comparisons of primary and key secondary outcomes or those used in any models

RECOMMENDATIONS

- ☑ Keep searches and inclusion/exclusion criteria specific
- ☑ Ensure extraction includes all aspects required by JCA
- ☑ Wait for confirmation of inclusion in ITC to complete certain elements
- ☑ Plan for SLR updates

Key Takeaways



And finally… start early and partner with an **experienced team**!

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Get in touch with our presenters if you'd like a more in-depth conversation about JCA

Continue the conversation at **booth 607**

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