EU Joint Clinical Assessments

What happens when gold-standard evidence is out of reach?

7 November 2022 | HEOR Theatre

Presented by: Suzette Matthijsse, Miranda Cooper and James Horscroft

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Agenda

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1	European Regulation on Health Technology Assessment
2	The impact of the EU Regulation on estimation of comparative efficacy
3	Structured expert elicitation for exploring uncertainty
4	Closing remarks

Suzette Matthijsse, PhD

EU Head of Health Economics Analysis HEOR, Lumanity

Miranda Cooper, MSc

Head of Statistics HEOR, Lumanity

James Horscroft, PhD

Director, Insight HEOR, Lumanity

1.

European Regulation on Health Technology Assessment

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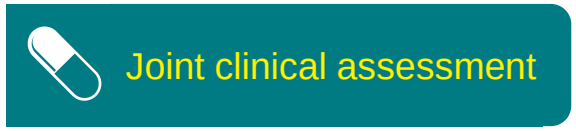
Aims

The Regulation replaces the current EUnetHTA system based on the voluntary network of national authorities (HTA Network) and the EU-funded project-based cooperation (Joint Actions EUnetHTA) with a **permanent framework for joint work.**

The Regulation aims to:

- Allow vital and innovative health technologies to be more widely available
- Ensure the efficient use of resources and strengthen the quality of HTA across the EU
- Save national HTA bodies and industry from duplicating their efforts
- Reassure business and ensure the long-term sustainability of EU HTA cooperation



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Key: EUnetHTA, European Network for Health Technology Assessment; HTA, health technology assessment.

Limited scope of JCA

JCAs will be restricted to **four clinical domains**:

- Identifying a health problem and current technology
- Examining the technical characteristics of the technology
- Relative safety
- Relative clinical effectiveness

- Non-clinical domains will be excluded
- The scope of JCAs should be inclusive and reflect all member states' requirements in terms of data and analyses
- The reports shall not contain any value judgement or conclusions on overall clinical added value of the assessed health technology and shall be limited to a description of (1) relative effects and (2) degree of certainty of the relative effects

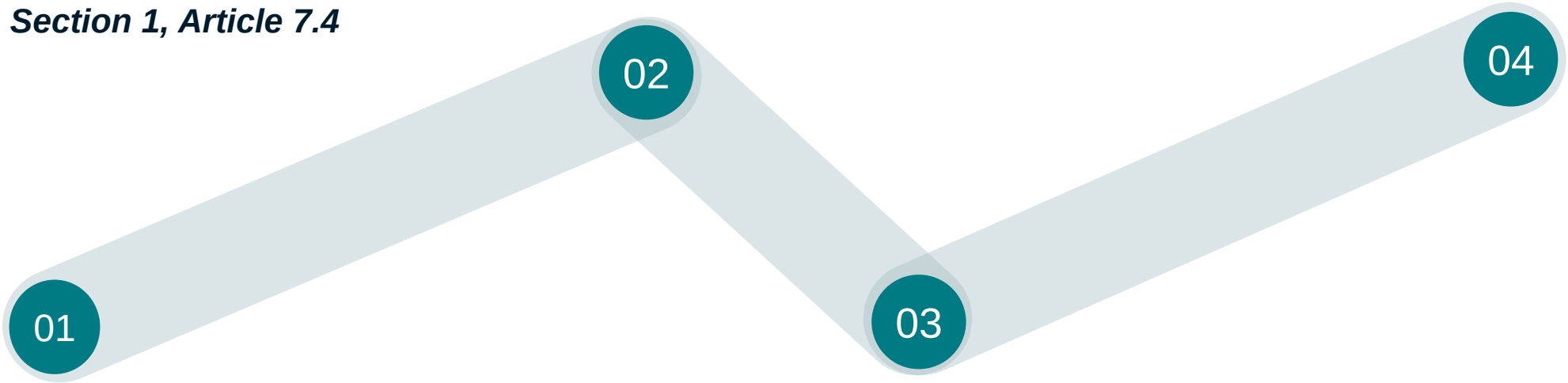
Key: JCA, joint clinical assessment.

JCA timelines

12 January 2025

Application for **medicinal oncology products** and **ATMP**:
Section 1, Article 7.2(a)

Medical devices and in vitro diagnostic medical devices can be selected for JCA based on criteria:
Section 1, Article 7.4



11 January 2022

The Regulation entered into force.

13 January 2028

Application for medicinal products which are designated as orphan medicinal products:
Section 1, Article 7.2(b)

13 January 2030

Application of Regulation for all other medicinal products:
Section 1, Article 7.2(c)

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Key: ATMP, advanced therapy medicinal products; JCA, joint clinical assessment.

Key considerations for JCA

Adapting to the new considerations will be crucial for successful reimbursement

Fewer interaction points between assessors and health technology developers

Tight timelines to adhere, especially for missing data or updates in dossier

Member states will be able to request additional analyses

Stringent evidence requirements

This could be particularly challenging for ATMP and orphan diseases

Multiple decision problems need to be considered for the JCA

All member states are supposed to participate in the PICOS survey

Consolidation of PICOS will take place

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Key: ATMP, advanced therapy medicinal products; JCA, joint clinical assessment; PICO, population, intervention, comparator, outcome.

Key considerations for JCA

Adapting to the new considerations will be crucial for successful reimbursement

Fewer interaction points between assessors and health technology developers

Tight timelines to adhere, especially for missing data or updates in dossier

Careful consideration of appropriate methods to support evidence generation needed

additional analyses

Stringent evidence requirements

This could be particularly challenging for ATMP and orphan diseases

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Key: ATMP, advanced therapy medicinal products; JCA, joint clinical assessment; PICO, population, intervention, comparator, outcome.

2.

The impact of the EU Regulation on estimation of comparative efficacy

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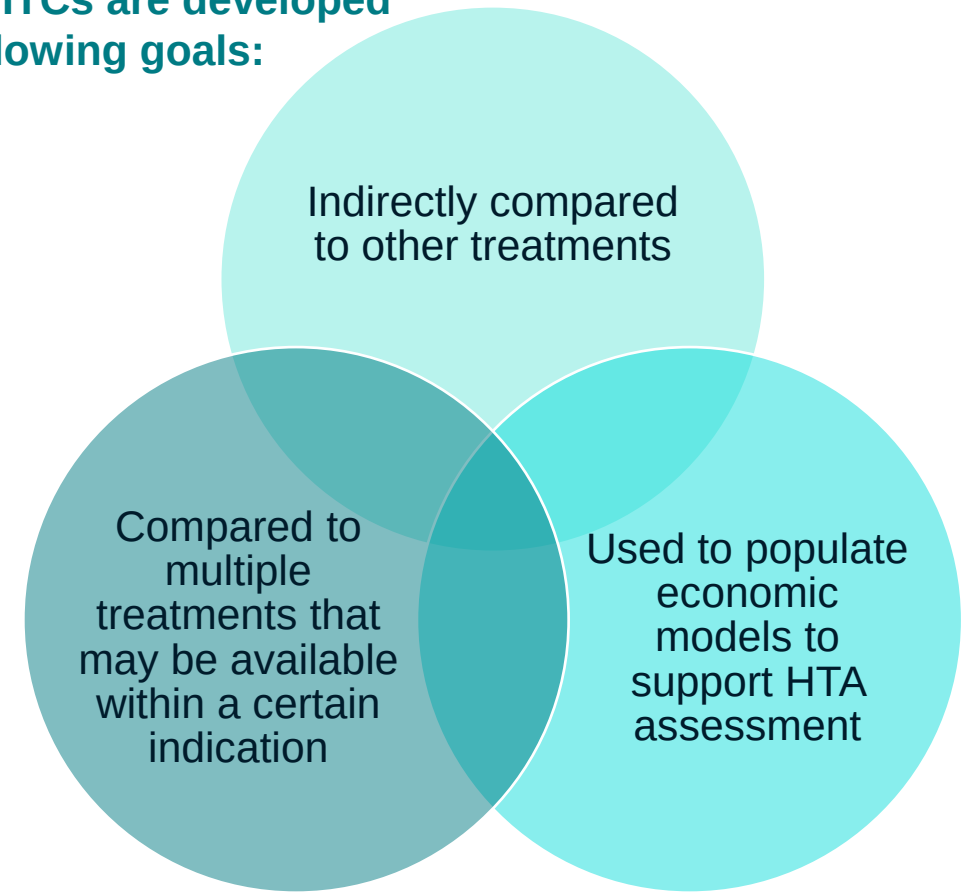
The regulation broadens the objectives for comparative efficacy

This leads to an increase in the demands on indirect treatment comparisons

Generally ITCs are developed for the following goals:



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Key: HTA, health technology assessment.

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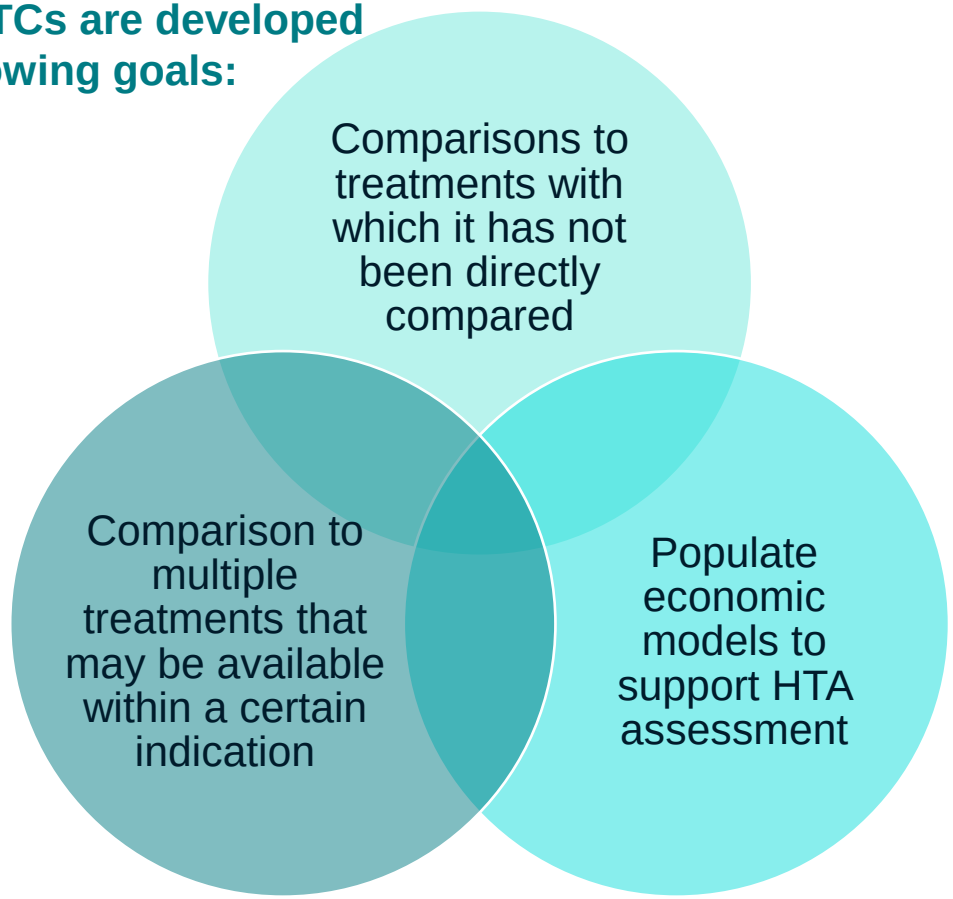

Importantly, these goals are tailored by country that each have specific requirements and preferences related to:

- Comparators, endpoints and populations
- Preferred ITC methods

The relevant body of evidence of interest is captured through the PICOS, which defines **P**opulation, **I**ntervention, **C**omparators, **O**utcomes and **S**tudy design.

The different country preferences and needs can impact the demands of any ITCs related to these factors.

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Key: HTA, health technology assessment; ITC, indirect treatment comparison.

Multiple PICOS may be required to meet country requirements

There are a number of potential challenges of covering multiple PICOS

Covering multiple PICOS can:

Dilute the main objective of the ITC into multiple possible objectives

Create an unwieldy evidence base and large body of resulting evidence that can be difficult to manage, particularly within the timeframes

Mean an increased likelihood of a large, poorly connected network given the potentially broader range of relevant comparators

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Key: ITC, indirect treatment comparison; PICOS, population, intervention, comparator, outcome, study design.

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Mean an increased likelihood of a large, poorly connected network given the potentially broader range of relevant comparators

A clear understanding of the likely treatment landscape and careful upfront planning for analysis timing will be essential to address these challenges

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Key: ITC, indirect treatment comparison; PICOS, population, intervention, comparator, outcome, study design.

What to do when RCTs are not viable

Orphan indications and ATMPs for example

- When we cannot assess a new treatment through an RCT, such as when researching orphan diseases or when aiming to speed up patient access, this leads to situations where the gold standard for indirect comparative efficacy analysis is not feasible.
- However, the comparative efficacy for a new therapy still needs to be estimated to support HTA submissions, as this will avoid delaying access for patients to potentially life-saving treatments
- We must therefore consider other approaches that allow us to estimate comparative efficacy, despite their limitations

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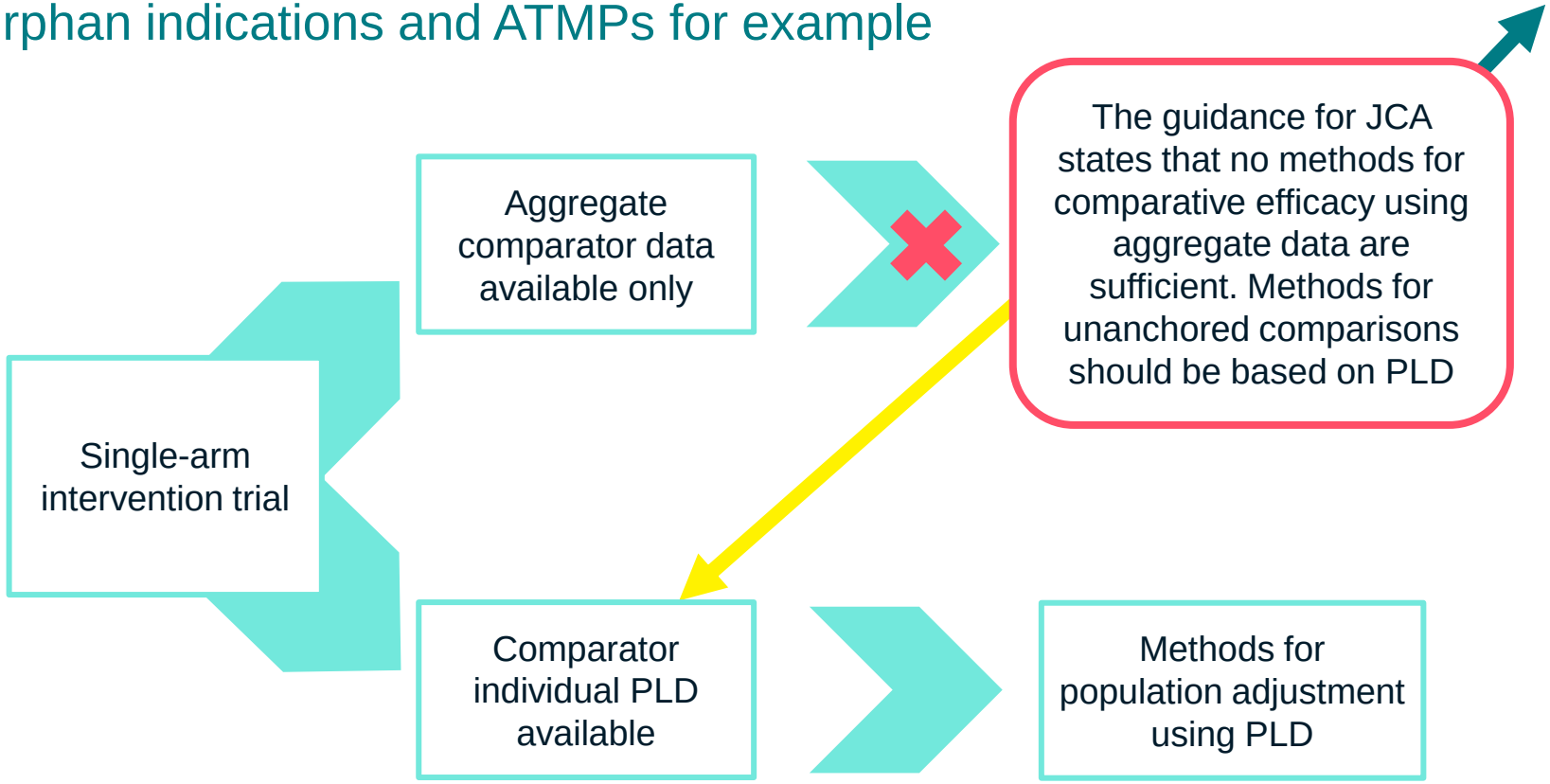
Key: ATMP, advanced therapy medicinal products; HTA, health technology assessment; RCT, randomized controlled trial.

What to do when RCTs are not viable

Orphan indications and ATMPs for example



Early considerations for trial design

- Ensures that relevant outcomes are collected
- Consider early on in the process how treatment comparisons will be made, what the most appropriate comparator is, whether an RCT is viable?

Proactive RWE data collection/generation

- Better-quality data can potentially be accessed
- Preferred ITC methodologies can be used in the case of single-arm trials
- Analyses can be more flexible (possibly)

However, generating/gaining access to IPD to sufficiently address a potentially broader PICOS remains challenging

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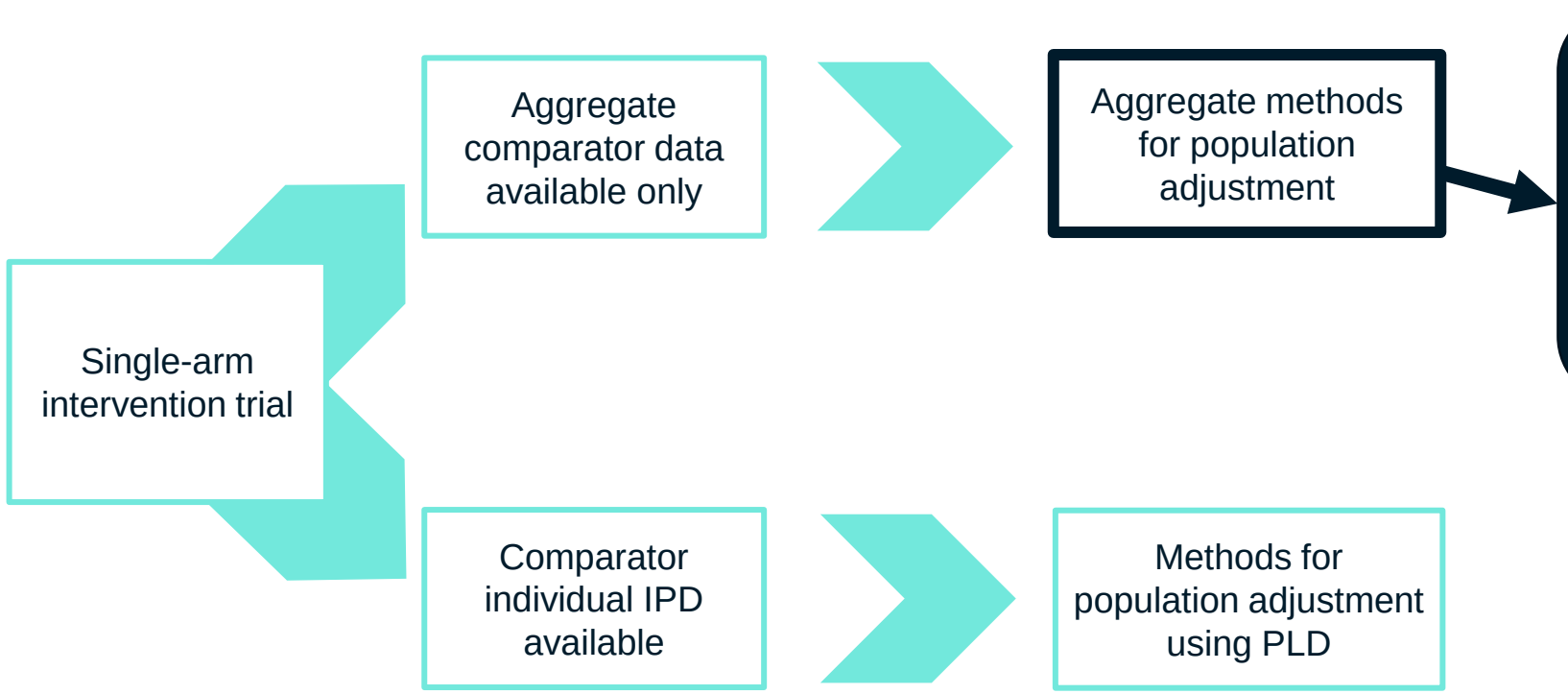
Key: ATMP, advanced therapy medicinal products; ITC, indirect treatment comparison; JCA, joint clinical assessment; PLD, patient-level data; RCT, randomized controlled trial; RWE, real-world evidence.

What to do when RCTs are not viable

Orphan indications and ATMPs for example



Generate estimates of comparative efficacy using aggregates despite issues. Ensure clear justification and a comprehensive suite of scenarios are developed to explore the known limitations of these methods

This approach could be:

- Vital – we have no other option that doesn't delay access to patients
- Necessary given we are unlikely to have access to IPD for all possible comparators
- Required if countries request specific analyses
- The best way to make the most of the data that are available

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Key: ATMP, advanced therapy medicinal products; ITC, indirect treatment comparison; JCA, joint clinical assessment; PLD, patient-level data; RCT, randomized controlled trial; RWE, real-world evidence.

Impact of the regulation by scenario

- The challenges introduced by the JCA regulations on preferred approaches to comparative efficacy are likely to affect different indications and treatments in diverse ways
  - Issues related to study design and statistical methods for comparative efficacy are anticipated to cause greater challenges for orphan drugs or ATMPs (when assessed via single-arm trials).
  - The demand for capturing all relevant information for a broader PICOS may cause bigger challenges for other treatments

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  - Issues related to study design and statistical methods for comparative efficacy are anticipated to cause greater challenges for orphan drugs or ATMPs (when assessed via single-arm trials).
  - The demand for capturing all relevant information for a broader PICOS may cause bigger challenges for other treatments

In either case, these methods make best use of the empirical data that are available. When considering these methods, it will be important to acknowledge their limitations and comprehensively explore the impact of these limitations.

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Key: ATMP, advanced therapy medicinal products; ITC, indirect treatment comparison; JCA, joint clinical assessment; PICOS, population, intervention, comparator, outcome, study design.

3.

Structured expert elicitation for exploring uncertainty

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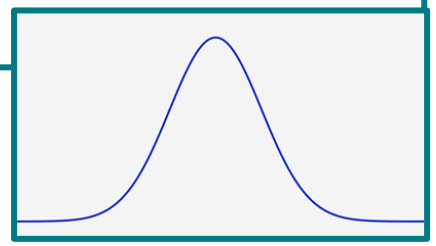
What is SEE?

A method for obtaining judgements from experts that minimizes bias and reflects uncertainty

Obtaining judgements from experts

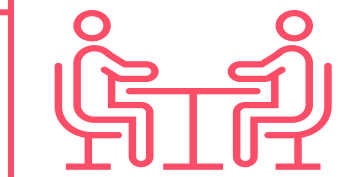
SEE

Obtaining beliefs from experts in a quantitative or statistical form, for example, as **probability distributions** for uncertain quantities



Expert opinion

Obtaining **qualitative information** from experts



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Key: SEE, structured expert elicitation.

What is SEE?

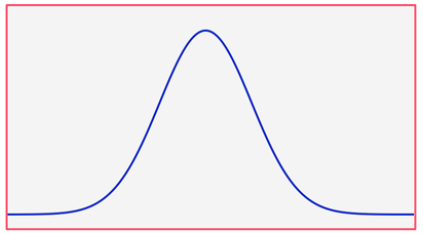
Frequency versus subjective probability

Coin toss

Frequency probability based on data → 50% heads, 50% tails

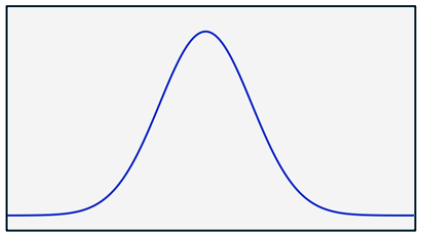
Commute time

Frequency probability based on data →



Commute time tomorrow

Subjective probability based on data and **prior beliefs** →



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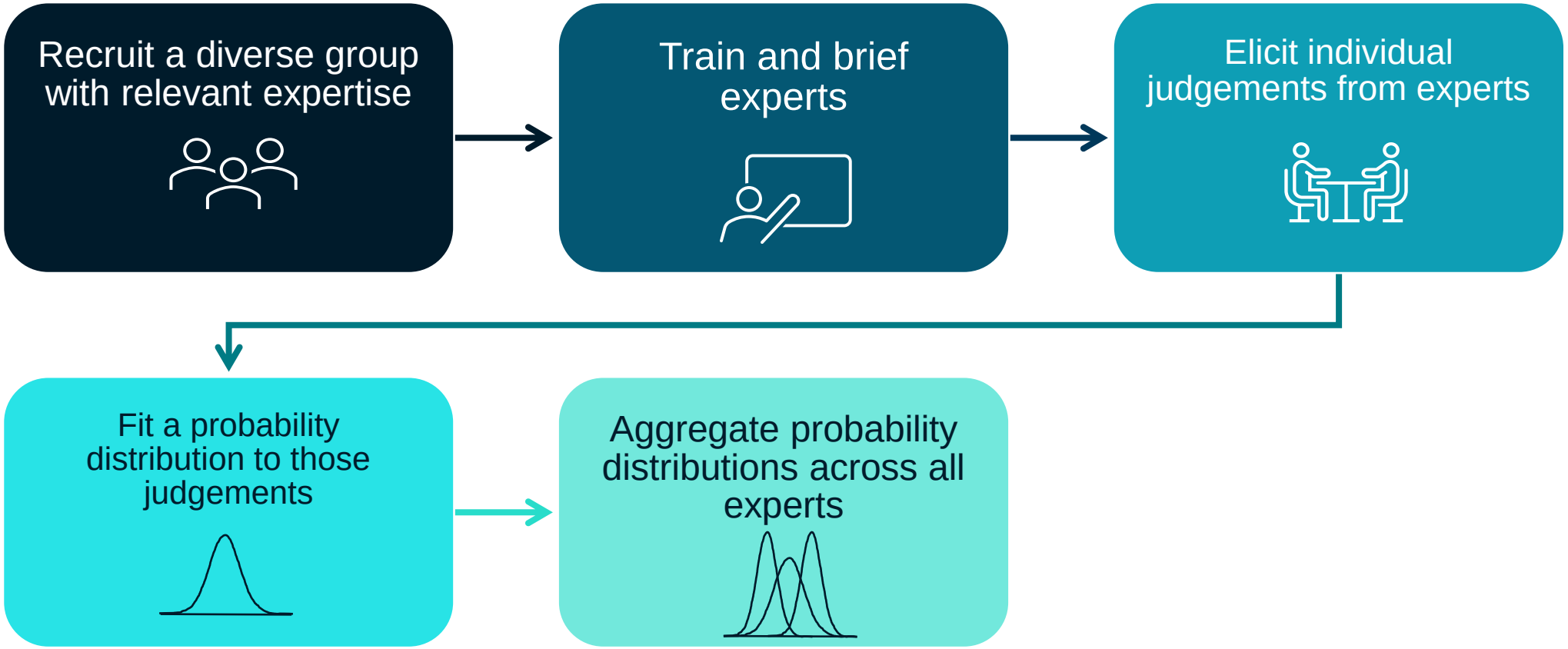
Key: SEE, structured expert elicitation.

How is SEE conducted?

There are several different approaches to SEE, all following the same broad principles

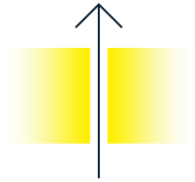


See **STEER** co-developed by University of York and Lumanity, to be published online later this month, for more details

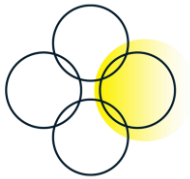
Key: SEE, structured expert elicitation; STEER, Structured Expert Elicitation Resources.

Why is SEE valuable in healthcare decision-making?

Global trends are leading to higher **uncertainty** at the point of decision-making



Recognized as a **preferred method** where empirical evidence is lacking[1,2]



Minimizes known **biases** associated with expert judgements[3]

Can be used **longitudinally** to predict clinical outcomes[4]

Provides **bounds to uncertainty** for key clinical or economic parameters[3]

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Key: SEE, structured expert elicitation.

References: [1], NICE. 2022. https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation. Accessed: 20 October 2022; [2], CADTH. 2017. https://www.cadth.ca/guidelines-economic-evaluation-health-technologies-canada-4th-edition. Accessed 20 October 2022; [3], Bojke et al. *Health Technol Assess,* 2021; 25(37), 1.; [4], Cope et al. *BMC Med Res Methodol,* 2019; 19.1: 1-11.

What role could SEE play in European HTA processes?

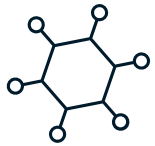
Pre-clinical to Phase 2

- Supporting strategic decision making
- Inputs to early economic models
- PTRS assessments

Phase 2 to launch

- Supporting extrapolation of trial outcomes
- Exploring generalizability to new populations
- Inputs to economic models for HTA

SEE is particularly useful where there are high levels of uncertainty due to challenges associated with generating empirical evidence. For example:



ATMPs

(Ultra)-rare diseases

Long-term outcomes

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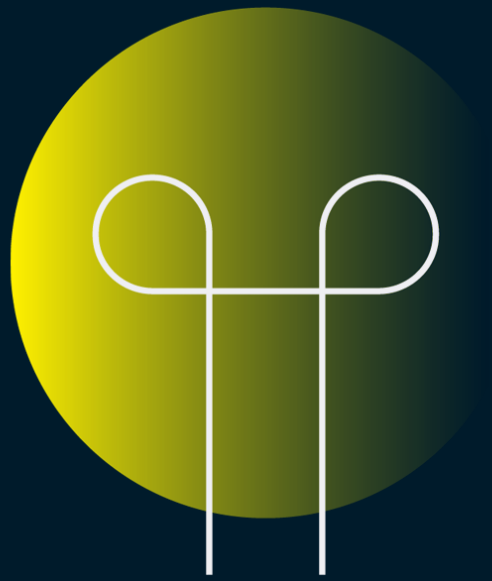
Key: ATMP, advanced therapeutic medicinal product; HTA, health technology assessment; PTRS, probability of technical and regulatory success; SEE, structured expert elicitation.

Closing remarks



01 **Challenges affect different indications in different ways:**

- **Multiple PICOs are more challenging for large disease areas, e.g. oncology**
- **Challenges related to study design and statistical analyses create more difficulties for ATMP and orphan diseases**

02 **Proactive planning for comparative efficacy will be vital whatever the type of trial. This will help us to clearly understand what is of interest to different countries, explore whether PLD access/generation is a possibility and carry out a comprehensive scenario investigation if it is not**

03 **SEE captures the expert uncertainty that surrounds key parameters of interest, and is particularly relevant when generating empirical evidence is complicated (e.g. ATMPs, ultra-rare diseases, long-term outcomes)**

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Key: ATMP, advanced therapy medicinal products; ITC, indirect treatment comparison; PICO, population, intervention, comparator, outcome; PLD, patient-level data; SEE, structured expert elicitation.

EU Joint Clinical Assessments: What happens when gold-standard evidence is out of reach?

If you have any queries, please do get in touch or come to see us at our stand

Suzette Matthijsse: Suzette.Matthijsse@lumanity.com

Miranda Cooper: Miranda.Cooper@lumanity.com

James Horscroft: James.Horscroft@lumanity.com