Introduction to HTA

Julia Chamova, François Houyez, Conor Teljeur
Introductions

• Moderator
  - Julia Chamova, Director of Operations, EUnetHTA Secretariat (at the Danish Health Authority)

• Speakers
  - François Houyez, Director of Treatment Information and Access, European Organisation for Rare Diseases (EURORDIS)
  - Conor Teljeur, Senior statistician, Health Information and Quality Authority (HIQA, Ireland)
Why are we doing this webinar?

• Offered to the participants of the Multi-stakeholder Symposium on Improving Patient Access to Rare Diseases Therapies (24 - 25 February 2016, Hotel Le Plaza, Brussels)

• Aim: to ensure that all participants have a common knowledge base about the principles and concepts of HTA to further explore value determination, appraisal, pricing and reimbursement of orphan medicines at the symposium
Purpose of the webinar

• **Scope**
  - Fundamentals of HTA and relative effectiveness assessment

• **Objective**
  - To discuss REA and HTA from a European perspective

• **Learning outcomes**
  - Understand the distinction between HTA and REA
  - Appreciate how and where stakeholders can get involved
  - Have an overview of cost considerations in HTA
Presentation recording

• This webinar is recorded

• Playback and presentation slides will be available from 8 February at the EURORDIS website:

• Accessible from the homepage (http://www.eurordis.org) here:
Part 1: HTA methodology
Health Technology Assessment (HTA)
What is HTA?

HTA is “the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informed decision making regarding health technologies.”

(NIHR)
Timeline of HTA

1960s: Growing appreciation that technologies could have harmful effects as well as intended benefits

1970s: Office of Technology Assessment established in the US. Increasing use of technology assessment

1980s: Beginnings of health technology assessment (HTA) as a formal discipline

1990s: Introduction of HTA programmes to support reimbursement decisions

2000s: The European Commission and Council of Ministers targeted HTA as ‘a political priority’
Who uses HTA?

- Payers
- Providers
- Policy makers
- Regulatory agencies
- Clinicians and patients
- Health care technology companies
HTA Core Model®
The HTA Core Model® is a generic methodological framework for production and sharing of HTA information. It enables international collaboration in HTA.

- Developed through the EUnetHTA collaboration.
- Work carried out as part of cross-European collaboration.
- Applications available for specialised topics such as screening technologies and diagnostics.
Structure of the Core Model®

• The model consists of three components:
  
  A standardised set of HTA questions within a hierarchical structure
  
  Methodological guidance to assist in answering the research questions in a transparent manner
  
  A common reporting structure for presenting findings in a standardised "question-answer pair" format

• The model is structured into 9 domains
Core Model domains

1. Health Problem and Current Use of the Technology
2. Description and technical characteristics of technology
3. Safety
4. Clinical Effectiveness
5. Costs and economic evaluation
6. Ethical analysis
7. Organisational aspects
8. Patients and Social aspects
9. Legal aspects
How is a HTA carried out?
Sequence of activity

• The domains are addressed in approximate order, as the outcome of one may influence how subsequent domains are considered. For example, if there is no evidence of superior clinical effectiveness, then a full economic evaluation may not be required.

• The evaluation team must have multi-disciplinary expertise and access to clinical expertise.

• A HTA typically culminates in a report which, in the interests of transparency, includes a large amount of detail on how the assessment was carried out.
What will be addressed in a HTA?

• A HTA is a decision-support tool and must therefore address the needs of the decision-maker.

• An initial scoping of the HTA will also inform what questions will be addressed, as it may become clear from what is known. For example, a cost-minimisation analysis may be appropriate.

• Once the research question or terms of reference for the HTA have been agreed, and the relevant domains have been defined, the assessment proceeds.
HTA data requirements
### Types of data

<table>
<thead>
<tr>
<th>Details of intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical or treatment pathways</td>
</tr>
<tr>
<td>Clinical effectiveness</td>
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<tr>
<td>Safety</td>
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<tr>
<td>Epidemiological data</td>
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<tr>
<td>Cost data</td>
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<td>Resource use data</td>
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<tr>
<td>Contextual data</td>
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</tbody>
</table>
## Sources of data

<table>
<thead>
<tr>
<th>Source of Data</th>
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</thead>
<tbody>
<tr>
<td>Manufacturers</td>
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<td>Randomised controlled trials</td>
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<td>Registries</td>
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<td>Observational studies</td>
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<td>Administrative databases</td>
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<tr>
<td>Health service providers</td>
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<tr>
<td>Clinicians</td>
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<tr>
<td>Patient representative groups</td>
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</tbody>
</table>
Methods of analysis

- Literature review
- Systematic review
- Evidence synthesis/meta-analysis
- Expert elicitation
- Epidemiological modelling
- Parameter estimation
- Economic modelling
- Sensitivity analysis
Relative Effectiveness Assessment (REA) versus HTA
Purpose of assessment

For market authorisation

• Show the extent to which an intervention does more harm than good under ideal circumstances [compared to one or more alternatives].

For relative effectiveness assessment (REA)

• Show the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice. Occurs within strict timeline just after market authorisation.

For HTA

• Summarise information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner.
## Domains

<table>
<thead>
<tr>
<th>Scope</th>
<th>Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full HTA</td>
<td>1. Health problem and current use of technology</td>
</tr>
<tr>
<td></td>
<td>2. Description and technical characteristics</td>
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<tr>
<td></td>
<td>3. Safety</td>
</tr>
<tr>
<td></td>
<td>4. Clinical effectiveness</td>
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<td></td>
<td>5. Costs and economic evaluation</td>
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<td></td>
<td>6. Ethical analysis</td>
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<td></td>
<td>7. Organisational aspects</td>
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<td></td>
<td>8. Social aspects</td>
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<tr>
<td></td>
<td>9. Legal aspects</td>
</tr>
<tr>
<td>Rapid REA</td>
<td>1. Health problem and current use of technology</td>
</tr>
<tr>
<td></td>
<td>2. Description and technical characteristics</td>
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<td></td>
<td>3. Safety</td>
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<td>6. Ethical analysis</td>
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<td></td>
<td>8. Social aspects</td>
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<tr>
<td></td>
<td>9. Legal aspects</td>
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</tbody>
</table>
Scope of an REA

• Due to the European Transparency Directive (Directive 89/105/EEC), some countries are legally obliged to assess pharmaceuticals within a specified time period (90/180 days).

• The Model for Rapid REA of Pharmaceuticals has been developed to facilitate these strict timelines.

• The ‘Cost and Economic Considerations Domain’ was explicitly excluded based on the recommendations of the High Level Pharmaceuticals Forum.

• The model includes a checklist of questions for the relevance of domains 6 to 9 (two questions per domain).
Outputs

• REA: reports the relative clinical effectiveness of an intervention relative to one or more comparators.

• HTA: provides advice to the decision maker or a binding recommendation to the payer about the provision of an intervention.
Local use of REAs
Adaptations

• A REA that is generated centrally or through international collaboration must be adapted for local use. For example, the comparators, included trials, clinical endpoints, and method of evidence synthesis may all vary by country.

• Local versions of REAs may also include contextual information about the local burden of disease and clinical pathways.
Key sources of variation in REAs

- What is the intervention compared to?
- Include non-pharmaceutical comparators?
- Allow composite outcomes?
- Allow surrogate outcomes?
- Allow utilities?
- Is the external validity considered?
- How is effectiveness estimated?
- Extrapolate long-term effects from short-term?
Extent of local adaptation

- Of 44 examples of local use of EUnetHTA rapid REAs: 22 were used directly in local decision making, and 18 were used for cross-checking evidence.
- Local use of EUnetHTA rapid REAs was most common in Austria, Spain and Slovakia.
- Adaptations typically include translation into the local language, and addition of more recent evidence where available.
End of part 1

Questions?
Part 2: stakeholder involvement
Stakeholders in HTA

End users of health technologies
- Patients, consumers, surrogate patients/consumers

Prescribers
- Doctors, nurses

Dispensers/purchasers
- Pharmacists, hospitals, home care organisations...

Industry
- Pharmaceuticals, medical devices, diagnostics, connected devices...

Health authorities / decision makers
- Price negotiators, reimbursement/coverage deciders, public/private insurances

Note: external collaborations exist, e.g. regulators, INATHA...
Points of involvement in HTA (not exhaustive)

1. Guidelines
2. Early dialogues / parallel with regulators
3. Horizon scanning
4. HTA topic selection
5. Scoping
6. Assessment
7. Final Report
8. Evidence generation / further studies / re-HTA
9. Appraisal per se is more a post-HTA activity
## Procedures

<table>
<thead>
<tr>
<th></th>
<th>EUnehtHTA</th>
<th>Other EU level</th>
<th>National level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strategic and political guidance</strong></td>
<td>NA</td>
<td>HTA Network</td>
<td>?</td>
</tr>
<tr>
<td><strong>Guidelines development</strong></td>
<td>SAG consultation</td>
<td>(Reflection papers)</td>
<td>Expert consultation</td>
</tr>
<tr>
<td><strong>Horizon scanning</strong></td>
<td>?</td>
<td>NA</td>
<td>In some</td>
</tr>
<tr>
<td><strong>Early scientific discussion</strong></td>
<td>Multi HTA early dialogues</td>
<td>EMA/HTA SA SEED project (2014-15)</td>
<td>In some MS (e.g. UK, DE). local language</td>
</tr>
<tr>
<td><strong>HTA project prioritisation</strong></td>
<td>POP database Topic selection process</td>
<td>NA</td>
<td>Different procedures in each MS</td>
</tr>
<tr>
<td><strong>Scoping</strong></td>
<td>SAG consultation</td>
<td>NA</td>
<td>Expert consultation</td>
</tr>
<tr>
<td><strong>Assessment</strong></td>
<td>REA / Full HTA Joint assessment</td>
<td>NA</td>
<td>National procedures Own or re-use</td>
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<tr>
<td><strong>Reporting</strong></td>
<td>See <a href="#">here</a> and also EVIDENT DB</td>
<td>NA</td>
<td>See local agencies See <a href="#">here</a></td>
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<tr>
<td><strong>Appraisal</strong></td>
<td>NA</td>
<td>NA</td>
<td>Decision making</td>
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</table>

Introduction to HTA
## Who actually participates? Where?

<table>
<thead>
<tr>
<th></th>
<th>Users</th>
<th>Prescribers</th>
<th>Dispensers</th>
<th>Deciders</th>
<th>Industry</th>
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<td><strong>Strategy / policy</strong></td>
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<td>✔</td>
<td>✔</td>
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<td><strong>(1) Guidelines</strong></td>
<td>✔</td>
<td></td>
<td>✔</td>
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<td>✔</td>
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<tr>
<td><strong>(2) Early dialogues</strong></td>
<td>✔</td>
<td></td>
<td>✔</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td><strong>(3) Horizon scanning</strong></td>
<td></td>
<td></td>
<td>✔</td>
<td></td>
<td>✔</td>
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<tr>
<td><strong>(4) HTA topic selection</strong></td>
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<td>✔</td>
<td>✔</td>
<td>✔ ✔</td>
<td>✗</td>
</tr>
<tr>
<td><strong>(5) Scoping</strong></td>
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<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td><strong>(6) Assessment</strong></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td><strong>(7) Final Report</strong></td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td><strong>(8) Evidence generation</strong></td>
<td>+/-</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td><strong>(9) Appraisal/decision</strong></td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>✔</td>
<td>✗</td>
</tr>
</tbody>
</table>

*When box empty, unsure and/or to be discussed*
Modalities of involvement vary

- **To which extent?**
  - Consultation (answering questions, not taking part in discussions)
  - Participation (participation in discussions)
  - Document review
  - Post hoc information (once decision made)

- **How?**
  - Face to face meetings / interviews
  - In writing
  - Providing expert opinion / providing data

- **Each stakeholder group to define its preferences for involvement modalities**
Resources for involving stakeholders

- **Guidelines for Stakeholder Engagement in HTA in Ireland**
- **HTAi Patient Group Submission Templates**
  - that can be modified by any HTA process to support patient organisations to submit information to an HTA
  - Medicine’s HTA – [Guidance](#) and [Template](#)
- **Values and Quality Standards for Patient Involvement in HTA**
  - [Questions that are asked about Patient and Citizen Involvement](#)
  - [A Methods and Impact Working Group perspective (FAQ)](#)
- **HTAi Glossary for Consumers and Patients**
  - available in English and Greek
- **Health Equality Europe: A Guide to Understanding HTA for Patients and the Public**
  - available in English, Spanish, Swedish, Mandarin, Italian, Polish and Greek
Illustration: POP Statistics (Quarterly Updates)

In Spring 2014, POP Database contained: **1,230** planned, ongoing and recently published projects from **44** EUnetHTA JA partners and **24** countries

**Sept/Dec 2013** POP Request

Out of **63** EUnetHTA JA partners:
- **28** responded and entered/updated projects in the database
- **11** responded but DID NOT feed the database
- **24** did not respond at all (38%)
- Total number of projects: **1,219**
- Alert (SAME) topics: 101 (8%)
- Similar projects (within alert topics): **249**
- Access-rights: **41** partners

**Jan/March 2013** POP Request

Out of **68** EUnetHTA JA partners:
- **35** responded and entered/updated projects in the database
- **8** responded but DID NOT feed the database (no current changes in the projects)
- **25** did not respond at all (37%)
- Total number of projects: **1,216**
- Alert (SAME) topics: 103 (8%)
- Similar projects (within alert topics): **247**
- Access-rights: **46** partners

Visit York Univ / NIHR database: [http://www.crd.york.ac.uk/CRDWeb](http://www.crd.york.ac.uk/CRDWeb)
Illustration: Methodological Guidelines for Rapid REA

Endpoints used for REA of pharmaceuticals
1. Clinical endpoints
2. Composite endpoints
3. Surrogate endpoints
4. Safety
5. Health-related quality of life

Comparators and comparisons
6. Criteria / choice of the most appropriate comparator(s)

7. Direct and indirect comparison

Levels of evidence
8. Internal validity
9. Applicability of evidence in the context of a relative effectiveness assessment

Link to the guidelines
http://www.eunethta.eu/eunethta-guidelines
For the moment REA doesn’t include cost and economic evaluation.
Early dialogues between developers and HTA doers

The objective of an early dialogue is to reduce the risk of inadequate data when products are presented for evaluation in aim of reimbursement by national health insurance.
• briefing book sent by developer to the SEED coordinator (HAS) for pre-validation

• Updated briefing book sent to SEED coordinator (+/- EMA). Briefing Book sent to HTA bodies

• Consolidated list of points for clarification: **Teleconference** developer/coordinator (+/- EMA)

• Responses from developer to SEED (+/- EMA)

• EMA list of issues to developer

• HTA bodies sent draft answers to SEED coordinator. Answers are shared

• **E-meeting** between HTA bodies. Key issues discussed. List of key issues sent to developer.

**Patients come in**

• Early Dialogue **Meeting**. Closed discussion (morning), with developer (afternoon)

• Written answers sent to developer. Developer sends minutes
Patients in ED: 13 patients/20 slots (60%), 35 contacts (35%), 57 organisations, Total 284+ emails (+ phone)

<table>
<thead>
<tr>
<th>Date</th>
<th>Condition</th>
<th>Patients</th>
<th>Type</th>
<th>Technology</th>
<th>Developer</th>
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</thead>
<tbody>
<tr>
<td>16 May 2014</td>
<td>Relapsed/refractory multiple myeloma</td>
<td>-</td>
<td>Multi-HTA</td>
<td>Medicine</td>
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<td>Solid tumors</td>
<td>-</td>
<td>Multi-HTA</td>
<td>Medical device</td>
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<td>Medicine</td>
<td>Transgene</td>
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<td>1 / 2</td>
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<td>Multi-HTA</td>
<td>Implant. Device</td>
<td>St Jude Medical</td>
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<td>Medicine</td>
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<td>Sanofi/ Regeneron</td>
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<td>2 / 5</td>
<td>Multi-HTA</td>
<td>Diagnostic test</td>
<td>Diaxonhit / Voisin</td>
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<td>EUnetHTA</td>
<td>Medicine</td>
<td>Lysogene</td>
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<td>Haemophilia A</td>
<td>1 / 2</td>
<td>EMA-HTA</td>
<td>Medicine</td>
<td>Roche</td>
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<td>7 Sept 2015</td>
<td>Insulin dependent diabetes</td>
<td>1 / 2</td>
<td>EUnetHTA</td>
<td>Med. Dev.</td>
<td>Roche Diag</td>
</tr>
</tbody>
</table>

05/02/2016 Introduction to HTA
All sequences are seen

- FDA → EMA → SEED
- FDA → SEED → EMA
- FDA → Parallel SEED EMA
- EMA → FDA → SEED
Other interactions

- **Stakeholders’ Forum**
  - Different colleges
  - (EUnetHTA JA2: 4 patients/consumers, 3 payers, 4 providers, 9 industries (pharma, medtech, diag)
  - Call for expression of interest to participate
  - Terms of Reference
  - Interacts with scientific/technical and/or strategic/political cooperation (progress report, general issues on HTA...)
  - HTA Network SF: to be renewed in 2016

- **Scientific Advice Groups**
  - With confidentiality arrangements

- **Trainings**

- **Evaluation / impact / improvement**
End of part 2

Questions?
Part 3: Economic aspects
Economic evaluation
The need to address cost

• Cost data are usually included to address two questions in a HTA:
  - Is the intervention efficient? (cost-effectiveness)
  - Is the intervention affordable? (budget impact)

• The reimbursement process in most countries includes cost-effectiveness and/or budget impact as key considerations.

• Cost-effectiveness information is sometimes generated in the course of randomised controlled trials.
Data requirements

Need cost data for:

- Capital costs (e.g., new equipment or facilities)
- Ongoing costs (e.g., medicines)
- Staff
- Housing (e.g., operating theatre)
- Additional service utilisation arising from intervention
- Treatment of adverse events
- Savings from treatment avoided
- Depending on perspective, societal costs (e.g., productivity)

The data are needed for the intervention and the comparators.
Why economic modelling?

• Trial-based economic analyses are subject to numerous limitations, such as being underpowered for economic outcomes. If the trial represents ideal care, then it is unlikely to be applicable to the real-world context.

• Economic models allow for data to be incorporated from numerous sources.

• Long-term outcomes can be modelled where trials may have short-term outcomes.

• Economic models can be helpful for conveying decision uncertainty.
Economic model outputs

Economic models can provide a range of information, such as:

- Incremental cost-effectiveness (in the form of cost per unit benefit, such as quality-adjusted life years)
- Budget impact
- Resource implications (e.g., number of specialists)
- Decision uncertainty (e.g., cost-effectiveness acceptability curves)
- Expected value of perfect information
Reimbursement

- Economic evaluation is one of the domains of the Core Model® and clearly relevant for decision making.

- It is, however, not the only consideration for reimbursement.
Reimbursement considerations

Reimbursement decisions are typically informed by a range of considerations, including:

- Therapeutic value
- Cost-effectiveness
- Budget impact
- Importance in clinical practice
- Innovation
- Ethical arguments
- Political climate
Transferability of economic data
Given the value of economic information in the decision making process, why do we not do centralised evaluations?
Methodological variation

A number of aspects vary across countries such that a single economic analysis would not be applicable to all countries, including:

- Costs (how much different elements cost)
- Epidemiology (target population, disease progression, outcomes)
- Comparators (which alternatives are considered)
- Discount rate (our expression of time preference)
- Perspective (the payer or societal perspective)
- Time horizon (over what time period we measure benefits)
- End points (which clinical endpoints are considered acceptable)
End of part 3

Questions?
Closing reminders


Full information about the symposium can be found at the above web link, including:

• Playback recording and presentation slides from this webinar (from 8 February)

• Additional preparatory documents - we encourage you to read them!

• Advanced programme for the symposium
Thank you!