A comparative analysis of four countries in assessing orphan drugs

Elena Nicod, London School of Economics

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AGENDA

• Motivations for this research
• Research question & methods
• Results
  – Methodological framework
  – Sampling
  – Evidence
  – Interpretation of the evidence (uncertainty, value judgment, stakeholder input)
• Lessons learnt & Policy implications
• Future research agenda
Motivations

Different HTA recommendations for the same drugs (Nicod & Kanavos 2012)
- 53% (N 293) differing HTA recommendations (5 countries, 2007-2009)
- Different expectations depending on disease areas

⇒ Objectives: to understand the criteria driving HTA recommendations for a sample of orphan drugs across countries, and identify the reasons for cross-national differences

- Orphan drugs* not cost-effective (Drummond 2007)
- Orphan drugs > more prevalent conditions (Dupont 2012, Simoens 2011)

Work Packages 2.1b (framework) & 3.2 (orphan drugs)

*Orphan drugs: treat rare conditions (5<50,000 people in Europe), granted an orphan designation by the European Medicines Agency, and received a number of incentives to encourage R&D. A similar process is done in other countries (US etc.).
A mixed methods research design

**Sub-research questions**

- Is the decision-making process comparable across countries, and how?
- For each case, what are the decision-making criteria and how do these differ across countries?

**Sampling** (scope of research)

**Stage I:**
Case study analyses (Pilot study)

**Stage II:**
Qualitative data collection (vertical / horizontal component)

**Stage III:**
Quantitative data analysis

**Research question**

What are the criteria driving HTA-based recommendations and why are these different for a same drug and indication pair across countries?

**Instrument-based model**

To derive a **methodological framework** enabling the systematic comparison of HTA decision processes across countries, drugs and therapy areas

Source: Nicod and Kanavos, under peer review 2015
Methodological framework

- 3 stage decision-process
- Scientific and social value judgments because evidence is always incomplete or imperfect

Framework allows for a systematic identification of:

- Taxonomy of criteria
- Influence of criteria on final decision
- Differences of these criteria across countries
- Agency-specific preferences & agreement levels (quantitative analysis)

- Interviews to obtain insights from HTA bodies on cross-country differences

Source: Nicod & Kanavos, under peer review 2015
<table>
<thead>
<tr>
<th>HTA Body</th>
<th>Scientific assessment</th>
<th>Social or societal preferences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HTA criteria &amp; perspective</strong>&lt;br&gt;-quantified-</td>
<td>Preferential status&lt;br&gt;-elicited-</td>
<td>Orphan drug&lt;br&gt;preferential status&lt;br&gt;-elicited-</td>
</tr>
<tr>
<td><strong>England - NICE</strong>&lt;br&gt;National Institute for Health and Care Excellence</td>
<td>Clinical cost-effectiveness and cost-effectiveness (ICER)&lt;br&gt;Societal perspective</td>
<td>End-of-life&lt;br&gt;implantations and intravenous&lt;br&gt;infusions&lt;br&gt;HIV&lt;br&gt;Palliative&lt;br&gt;care&lt;br&gt;End&lt;br&gt;end&lt;br&gt;life&lt;br&gt;End&lt;br&gt;life&lt;br&gt;end&lt;br&gt;life&lt;br&gt;End&lt;br&gt;life&lt;br&gt;end&lt;br&gt;life&lt;br&gt;End&lt;br&gt;</td>
</tr>
<tr>
<td>Generic name/Brand name</td>
<td>Indication</td>
<td>ICD10 code</td>
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<td>---------------------------------------</td>
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</tr>
<tr>
<td>Eltrombopag REVOLADE</td>
<td>Thrombocytopenic purpura</td>
<td>D2</td>
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<tr>
<td>Romiplostim NPLATE</td>
<td>Chronic idiopathic thrombocytopenic purpura</td>
<td>D2</td>
</tr>
<tr>
<td>Everolimus AFINITOR</td>
<td>Renal cell carcinoma (2nd line, advanced)</td>
<td>C</td>
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<tr>
<td>Lenalidomide REVLIMID</td>
<td>Multiple myeloma (3rd line)</td>
<td>C</td>
</tr>
<tr>
<td>Mifamurtide MEPACT</td>
<td>Osteosarcoma</td>
<td>C</td>
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<tr>
<td>Azacitidine VIDAZA</td>
<td>Myelodysplastic syndrome</td>
<td>D1</td>
</tr>
<tr>
<td>Imatinib GLIVEC</td>
<td>Gastro intestinal stromal tumour (adjuvant, after surgery)</td>
<td>C</td>
</tr>
<tr>
<td>Mannitol dry BRONCHITOL</td>
<td>Cystic fibrosis</td>
<td>E</td>
</tr>
<tr>
<td>Ofatumumab ARZERRA</td>
<td>Chronic lymphocytic leukemia</td>
<td>C</td>
</tr>
<tr>
<td>Trabectedin YONDELIS</td>
<td>Soft tissue sarcoma</td>
<td>C</td>
</tr>
</tbody>
</table>
Criteria captured through thematic coding (Coding Manual, 3 groups of codes)

**Evidence**

- Main reason for decision
- Positive or negative influence
- Stakeholder input
- Considered by all

**Interpretation of the evidence**

- Considered by all
- Not included by NICE
- Not included by SMC
- Not included by NICE

**HTA recommendation**

- Main positive
- Main restrict
- Main negative
- Same unit of analysis as, and to be coded with "uncertainties" and "other considerations".

**Double coding:**
- Main reason for decision
- Positive or negative influence
- Stakeholder input
- Considered by all

**Third-order theme**

- Clinical evidence
- Economic models
- Safety

**Second-order theme**

- Clinical endpoints
- Comparative treatment
- Economic/comparator

**First-order theme**

- Comparator type
- Day 1
- Economic model

**Definition**

- Clinical uncertainty
- Clinical evidence
- Economic model uncertainty

**UNIT OF ANALYSIS**

- Clinical evidence
- Economic model uncertainty
- Safety
Methodological framework

HTA PROCESS
- Qualitative strand
  - Identification & comparison of HTA decision-making criteria

OUTCOMES
- Quantitative strand
  - Decision-making criteria (vertical component)
  - Reasons for differences in HTA recommendations (horizontal component)

Evidence
- Clinical & cost-effectiveness
  - Preferences in the type of evidence
  - Different evidence

Interpretation of the evidence
- Uncertainties
- Other considerations
- Stakeholder input
  - Risk and value preferences
  - Different interpretation of same evidence

HTA recommendation
- List / Restrict / Reject
  - Influence of preferences on final outcome
  - Influence of differences on final outcome
Evidence & preferences in the type of evidence

<table>
<thead>
<tr>
<th>Primary trial</th>
<th>Trial type</th>
<th>Subgroup/trial population</th>
<th># trial participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eltrombopag</td>
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<td></td>
<td>What do we see...</td>
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<td></td>
<td>• Same primary trials</td>
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<td>• All phase III except:</td>
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<td></td>
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<td>• Ofatumumab: phase II, prospective, nonrandomised, noncomparative (conditional marketing approval)</td>
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<tr>
<td></td>
<td></td>
<td>• Trabectedin: phase II, randomised (exceptional marketing approval)</td>
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<td></td>
<td></td>
<td>• 5/10 drugs relied on subgroup data</td>
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<td>• 8/10 drugs relied on surrogate endpoints</td>
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<td>• 8/14 trials enrolled &lt; 300 patients</td>
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<td></td>
<td></td>
<td>≈ trial characteristics of rare conditions (Kesselheim 2013)</td>
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<td></td>
<td></td>
<td>Same trials, different ways of reporting outcomes</td>
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<tr>
<td>Romiplostim</td>
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<tr>
<td>Everolimus</td>
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<td>Lenalidomide</td>
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<tr>
<td>Mifamurtide</td>
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<td>Azacitidine</td>
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<td>Imatinib</td>
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<td>Mannitol dry</td>
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<tr>
<td>Ofatumumab</td>
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<td></td>
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<tr>
<td>Trabectedin</td>
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</tbody>
</table>

What do we see...

• Same primary trials

• All phase III except:
  • Ofatumumab: phase II, prospective, nonrandomised, noncomparative (conditional marketing approval)
  • Trabectedin: phase II, randomised (exceptional marketing approval)

• 5/10 drugs relied on subgroup data

• 8/10 drugs relied on surrogate endpoints

• 8/14 trials enrolled < 300 patients

≈ trial characteristics of rare conditions (Kesselheim 2013)

Same trials, different ways of reporting outcomes
Differences in the evidence appraised

- Levels of reporting endpoints
- Selecting the appropriate endpoints
- Using non-primary evidence
- Different economic models and comparators

<table>
<thead>
<tr>
<th>Differences in the evidence appraised</th>
<th>Eltrombopag</th>
<th>Mifamurtide</th>
<th>Trabectedin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Idiopathic thrombocytopenic purpura</td>
<td>Osteosarcoma</td>
<td>Soft tissue sarcoma</td>
</tr>
<tr>
<td>Main reasons</td>
<td>Non-primary endpoint</td>
<td>Appropriate endpoint</td>
<td>Non-primary evidence</td>
</tr>
<tr>
<td></td>
<td>✗ Severe bleeding events (WHO 3-4) (NICE)</td>
<td>✔ Progression-free survival = primary endpoint (SMC, TLV HAS)</td>
<td>✔ Historical controls (NICE)</td>
</tr>
<tr>
<td></td>
<td>✗ Quality of life data</td>
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<td></td>
<td>✗ Lack of QOL data (HAS) Not included for HAS, TLV</td>
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<tr>
<td></td>
<td>✗ Economic models</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>✗ CUA-Standard care (NICE) ✔ CUA-romiplostim (SMC) ✔ CMA-romiplostim (TLV)</td>
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</tr>
</tbody>
</table>

Legend: NICE: National Institute for Health and Care Excellence (England), SMC: Scottish Medicines Consortium (Scotland), HAS: Haute Autorité de Santé (France), TLV: Dental and Pharmaceutical Benefits Board (Sweden); QOL: quality of life; CUA: cost-utility analysis; CMA: cost-minimisation analysis
Differences in the evidence appraised

- **Levels of reporting endpoints**
  - Levels of evidence: best/all available evidence, clinical claim, consequence of the decision, situation of the disease (prevalence)
  - Appropriate endpoint: survival (proxy), benefit
  - Surrogates: validated, survival and/or HRQoL, orphan drugs
  - Subgroups: pre-specified, restriction
  - Registry data & other forms of evidence: natural disease progression, historical controls, long term data
  - HRQoL: hard or soft endpoint
  - Economic models: cost-utility models only, others accept & prefer other models (e.g. cost-minimisation) when appropriate

Orphan drugs ≈ lower levels of evidence => smaller trial populations, surrogate endpoints, heterogeneous diseases (=> subgroup data)), unknown natural course of the disease (shorter trials), high financial, psychological, and physical burden on patients and carers.
Methodological framework

**HTA PROCESS**
- Qualitative strand
  - Identification & comparison of HTA decision-making criteria

**OUTCOMES**
- Quantitative strand
  - Decision-making criteria (vertical component)
  - Reasons for differences in HTA recommendations (horizontal component)

**Evidence**
- Clinical & cost-effectiveness

**Interpretation of the evidence**
- Uncertainties
  - Other considerations
  - Stakeholder input

**HTA recommendation**
- List / Restrict / Reject

- Preferences in the type of evidence
- Risk and value preferences
- Different interpretation of same evidence
- Influence of preferences on final outcome
- Influence of differences on final outcome
### Differences in interpreting the evidence and dealing with uncertainty

- **14.5% of concerns (Nu=114)** about the same evidence were common across countries

<table>
<thead>
<tr>
<th>Main reasons</th>
<th>Eltrombopag Idiopathic Thrombocytopenic Purpura</th>
<th>Imatinib GIST (adj, unresectable and/or metastatic)</th>
<th>Mannitol dry Cystic fibrosis</th>
<th>Mifamurtide Osteosarcoma</th>
<th>Trabectedin Soft tissue sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Same evidence appraised</strong></td>
<td>Short trial duration X NICE, SMC Not raised by HAS</td>
<td>No reduction in hospital days and use of antibiotics X HAS Not raised by SMC, NICE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Same uncertainties raised addressed differently</strong></td>
<td>Short trial duration X NICE (experts), SMC, TLV ✓ HAS (comparator)</td>
<td>Overall survival not significantly improved X NICE ✓ SMC (orphan) ✓ HAS (ongoing trial)</td>
<td>Risk of bronchospasms X HAS ✓ NICE (expert opinion) Not raised by SMC</td>
<td>Risk of interaction between treatments X HAS (other study) ✓ NICE, SMC (expert opinion)</td>
<td>Lack of comparative evidence (phase II non-comparative pivotal trial) X HAS ✓ NICE (rarity, early marketing authorization, historical controls) ✓ SMC (rarity, investigational treatment)</td>
</tr>
</tbody>
</table>

- **Different concerns** (raised by some and not by others): trial duration, resource use, safety, HRQoL improvement

- **Different ways to deal with the same concerns:** stakeholder input, orphan status, investigational nature, other trial or “other considerations” (=social value judgments)
“Other considerations” - value judgments

Proportion of cases that accounted for other considerations, by cluster and most commonly included (Noc=123)

- Disease nature affecting the patient
- Unmet need
- Rarity, orphan status, small patient population
- Issues around current treatment alternatives
- Complex pathway, no best practices or advances
- Clinical benefit and type of benefit
- Innovative nature of the treatment
- Indirect benefits from the treatment
- Adverse events manageable/non significant

<table>
<thead>
<tr>
<th>Cluster</th>
<th>NICE</th>
<th>SMC</th>
<th>TLV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

100%
“Other considerations”: elicited versus non-elicited (NICE)

<table>
<thead>
<tr>
<th>Main reason for recommendation</th>
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<th></th>
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<tbody>
<tr>
<td>HFA recommendation</td>
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</table>

[Diagram showing data with yellow and blue sections]
### “Other considerations”: elicited versus non-elicited (SMC)

<table>
<thead>
<tr>
<th>Main reason for recommendation</th>
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<tbody>
<tr>
<td>HFA recommendation</td>
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</tbody>
</table>

Social value judgments: unmet need, severity, innovation

- Accounted for as part of the deliberative process
- Elicited or not
- Overlap of terminologies

Innovation
- Treatment benefits (ICER or deliberative process)
- Intrinsic to decision (no definition)
- New mode of action
- Covers an unmet need

Unmet need
- Consequence of the decision (disease severity)
- Lack of treatment options (no differentiation for severity)

Disease severity
- Consequence of the decision (unmet need)
- Intrinsic to the decision (no definition)
- Severe, life-threatening, short life-expectancy, affects quality of life, etc.

⇒ Consistency
⇒ Accountability for reasonableness
### Disease characteristics

<table>
<thead>
<tr>
<th>Disease symptoms</th>
<th>Impact of disease on quality of life</th>
<th>Disease severity</th>
<th>Other effects from the disease</th>
<th>Unmet need</th>
<th>Issues around current treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Patients, carers, family, friends</td>
<td></td>
<td>Social stigma (e.g. from bruises)</td>
<td>lack of alternatives</td>
<td>Negative effects (e.g. taste)</td>
</tr>
<tr>
<td></td>
<td>Limiting life style choices (daily or leisure activities)</td>
<td></td>
<td>Anxiety of symptoms, relapse, or surgery</td>
<td>need for options (relapse)</td>
<td>Adherence issues</td>
</tr>
<tr>
<td></td>
<td>Functional capacity</td>
<td></td>
<td>Stress at work</td>
<td></td>
<td>Dependence on rescue therapy, blood transfusions</td>
</tr>
</tbody>
</table>

### Treatment characteristics

<table>
<thead>
<tr>
<th>Adverse events from the treatment</th>
<th>Disease management</th>
<th>Quality of life improvements</th>
<th>Measures of quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well tolerated, tolerable</td>
<td>decreased need for rescue therapy</td>
<td>Functional capacity</td>
<td>Do not capture the consequences of living with the disease</td>
</tr>
<tr>
<td>Safe</td>
<td>Preference for oral therapy versus transfusions</td>
<td>Patients, carers, family, friends</td>
<td></td>
</tr>
<tr>
<td>Relief from fatigue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event preferences</td>
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</tr>
</tbody>
</table>


Lessons learnt and policy implications
Recommendations & research contributions

**Tool to better understand HTA decision processes across settings**

≈ Methodological framework ≈ captures the full taxonomy of criteria considered at each stage of the decision process, systematically and in a structured and comparable manner

- Extent of cross-national differences => *differences matter (for patients & society)*
- Reasons for cross-national differences => *legitimacy of these differences*
- Awareness about different ways of conducting HTA => *cross-country learning (European collaboration)*
- Value judgments => *eliciting societal preferences, defining social values*
- Accountability for reasonableness => *criteria and its influence*
- Consistency across decisions => *retrospective identification*
- Dealing with orphan drugs (e.g. lower levels of evidence, common issues related to small patient populations) => *further the debate about how to approach rarity (cross-country learning)*
Future research agenda

Further application of the methodological framework

❖ Greater sample of drugs, indications, countries
  – Comparison across therapy areas, orphan versus ultra-orphan drugs, cancer versus non-cancer orphans, orphan versus non-orphan cancer, etc.
  – European collaboration (e.g. EUnetHTA)

❖ For different stakeholders
  – Patients / clinicians: understand what input was meaningful
  – HTA bodies: consistency, accountability for reasonableness, social values
  – Industry: criteria, dealing with uncertainty
  – Regulatory bodies: duplication

❖ Dealing with issues related to rarity
THANK YOU FOR YOUR ATTENTION

Questions?

Do not hesitate to contact me:

e.m.nicod@lse.ac.uk