Comparing the challenges of comparative effectiveness Research in France, Italy and the Netherlands

Current Situation and Perspectives

Issue Panelists:
F. Meyer, MD Advisor to President, France
E. Xoxi, PhD AIFA, Italy
C. Van der Meijden, PhD CVZ, Netherlands

Moderator: J van Loon, MSc Mapi

Panelists

Francois Meyer, MD
Advisor to the President, Head of International Affairs, HAS France

Entela Xoxi, PhD
Pharmacologist, Medicines protocols monitoring Registers & AIFA experts data management Unit, Italy

Caroline van der Meijden, PhD
Senior Advisor to Dutch Health Insurance Board (CVZ), the Netherlands

Jeanni van Loon, MSc (Moderator)
Global Managing Director Mapi HEOR
Objective of Issue Panel

- Provide insight into the French, Italian and Dutch requests for comparative effectiveness research (CER) and the specific issues per country:
  - Process
  - Challenges
  - Impact on decision making
  - Future changes

- You will be asked to share your experience and thoughts on these requirements and the impact on the decision making process and how a European collaboration could add value.

Comparative Effectiveness

- 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 circumstance of health care

*Pharmaceutical forum 2006-2008*
*ISPOR good research practices taskforce report, 2011*
CER-CI

- AMCP, ISPOR and NPC have joined forces to establish the Comparative Effectiveness Research Collaborative Initiative (CER-CI) for advancing appropriate use of outcomes research including comparative effectiveness research (CER) to improve patient health outcomes.

- The goal of CER-CI
  - greater uniformity and transparency in the use and evaluation of outcomes research information
  - providing a user-friendly toolkit to help decision makers in evidence-based health care decision making.

Performance Based Risk Sharing Arrangements (PBRSAs)

- The request for CER data is linked to the use of Performance Based Risk Sharing Arrangements (PBRSAs):
  - Outcomes based schemes
  - Risk sharing agreements
  - Coverage with evidence development
  - Patient access schemes
  - Conditional licensing
  - Managed entry schemes

* ISPOR Taskforce Reports, Garrison et al., Value in Health, 16; 2013 703-719
PBRSAs taxonomy

- Cost sharing arrangement
  - Performance-based risk sharing arrangement
    - To manage utilization in the real world
    - Coverage with evidence development
    - Outcomes guarantees
    - Process of care
    - Only with research
    - Pre-specified agreement
  - Performance-based reimbursement
    - Budget capping
    - Utilization
    - Co-payments
    - Price/evaluation

- Clinical endpoint
- Intermediate endpoint

* ISPOR Taskforce Reports, Garrison et al., Value in Health, 16; 2013 703-719
The request for Additional Data Collection (ADC) for Health Technologies

Dr François Meyer
Advisor to the President, HAS
ISPOR 2013, Dublin
HAS: the only national HTA institution in France

- Covers all health technologies / interventions
  - Drugs
  - Medical devices
  - Procedures
  - Public health interventions
- Provides advice to decision makers
  - Decision making institution(s) depend on the type of « technology »

From HTA to reimbursement

- Drugs
- Medical Devices
- Procedures
- Public Health Interventions (Screening programmes…)

HTA → CEPS (Economic Committee for Healthcare Products) → Decision making

HTA → UNCAM (Nat. Health Insurance Union) → Decision making
ADC: For which technologies?

- Performance Based Risk Sharing Arrangements and conduct of ADC more developed for drugs and medical devices
  - Same decision maker
  - Key institution = CEPS (Pricing Committee)
  - CEPS signs contracts with companies, for each reimbursed product
  - Inclusion in this contract of the commitment by the company to perform additional data collection

HAS Guidance Content for a new drug

1. Eligibility to reimbursement (SMR)
   - Full indication or restricted to situations or subpopulations
2. Assessment of clinical added value (ASMR)
   - What is the clinical added value and for what population?
3. Target population
   - Quantitative estimate
4. Uncertainty
   - and need for additional data collection
5. Recommendations
   - for use in clinical practice
Request for Additional Data Collection

How does it work?

- Request expressed by HAS, CEPS, Ministry
- Included in the Contract signed between Pricing committee and the company
- The company has to:
  - Draft a study protocol
  - Submit it to HAS for approval
  - Implement and conduct the study
  - Submit data to HAS and MoH.
- Data are taken into account at the time of reassessment.
  - Summary of the results published with HTA report
ADC for Drugs and Medical Devices

• **Re-assessment for drugs and medical devices mandatory after max. 5 yrs on the market**
  - Even in the absence of a formal Performance Based Risk Sharing Arrangement, some adjustment in the conditions of reimbursement or on the price of the product can be decided at that time.
  - To better inform re-assessment and review of pricing/reimbursement conditions, HAS, as well as pricing committee and ministry of health, can request the conduct of ADC at the time of initial assessment/decision

ADC in France: where are we now?

• **What did we do yet?**
  - The example of drugs: non-comparative data collection
  - Coverage with evidence development for some devices (TAVI)

• **What is currently changing?**
  - Economic evaluation will complement the evaluation of added clinical benefit
  - Possibility to request data collection
Requests for ADC 2004 – 2011 - Drugs

- 815 appraisals made for a new product or a new indication
- ADC request: 165 /815 (20.2%)
- Situations where request is made
  In comparison with products without ADC request):
  - applicability in real life uncertain (91 vs 50 %, p<0.001),
  - expected impact on mortality, morbidity was high or medium (7 and 16 vs 1 and 5%, p<0.001)
  - when an impact on the organization of health care was expected (26 vs 10%, p<0.001).

ADC Requests according to Added Clinical Benefit (ASMR) level (2005-2010)

<table>
<thead>
<tr>
<th>ASMR</th>
<th>Added clinical benefit</th>
<th>Total ADC</th>
<th>ADC /ASMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>II – Important</td>
<td>7%</td>
<td>16%</td>
<td>33%</td>
</tr>
<tr>
<td>III – Moderate</td>
<td>10%</td>
<td>20%</td>
<td>29%</td>
</tr>
<tr>
<td>IV – Minor</td>
<td>29%</td>
<td>28%</td>
<td>17%</td>
</tr>
<tr>
<td>V – None</td>
<td>54%</td>
<td>36%</td>
<td>12%</td>
</tr>
</tbody>
</table>
What data are requested?

- impact on morbidity and mortality,
- use and prescription of the medicines,
- impact on quality of life,
- impact on healthcare organization,
- safety
- to be developed: data on economic parameters

All in real life conditions and with a representative cohort of patients treated in France.

Types of questions / objectives

<table>
<thead>
<tr>
<th>Question</th>
<th>%</th>
<th>%</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Conditions of prescription / use</td>
<td>96</td>
<td></td>
<td></td>
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<tr>
<td>Benefit for patients (mortality morbidity QoL)</td>
<td>78</td>
<td>76</td>
<td>12</td>
</tr>
<tr>
<td>Impact on healthcare organisation</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Economic parameters</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Difficulties to be taken into account

- «Cultural» aspects
- Epidemiological challenges
  - Representativeness (Patients, Prescribers)
  - Lost to follow-up
  - Missing data
  - Biases
- Organisational difficulties
  - Studies for multiple products
- Coordination with requests from regulators
  - Coordination with French Medicines Agency

What use of the results?
Influence of ADC on re-appraisal of drugs

<table>
<thead>
<tr>
<th>Influence of ADC on re-appraisal of drugs</th>
<th>Till 2007</th>
<th>Since 2008</th>
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<tbody>
<tr>
<td>Confirmation</td>
<td>57%</td>
<td>73%</td>
</tr>
<tr>
<td>Modification</td>
<td>19%</td>
<td>27%</td>
</tr>
<tr>
<td>Non-informative study</td>
<td>21%</td>
<td>0%</td>
</tr>
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Additional Data Collection: Next steps

- **Lessons to be learned**
  - Detailed analysis of the results of the >150 studies performed in France

- **Impact of the economic evaluation of new drugs and devices**
  - Efficiency now assessed for new drugs and MDs of significant added clinical benefit
  - ADC may be needed to re-assess efficiency some years after launch of the product

- **European context and co-operation**
The role of EUnetHTA
Achievements of the EUnetHTA JA 1
1) The EVIDENT Database

**Description**
The EVIDENT Database enables sharing early information on evidence gaps identified during the production of HTA reports and consequent recommendations / requests for additional data collection.

It also contains information on reimbursement/ coverage and assessment status of promising technologies in Europe.

**Purpose**
To reduce redundancy, promote generation of further evidence and facilitate European collaboration in the domain.

2) Additional Evidence Generation: Selection/prioritization criteria

**Primary criteria: eligibility for ADC?**
1. Did you identify any critical evidence gaps during HTA? (yes, no)
2. Is the research question explicitly defined? (yes, no)
3. Is ADC feasible (especially in terms of timeframe, type of study, population and costs)? (yes, no)
4. Is there a planned/ongoing similar study elsewhere?
   a) Yes, but there is an additional value of performing this one too (yes, no).
   b) No, thus this one is really necessary (yes).
5. Is there an added value of additional data for the subsequent HTA and decision making? (yes, no)

**Secondary criteria: further selection and prioritization**
1. Burden of target disease (mortality, morbidity prevalence, incidence, DALYs, QALYs)
2. Expected benefit of the technology (on the burden of disease/on the management of disease/economical, organisational, social, ethical benefit)
3. Potential of the technology to cover unmet health care needs or to substantially improve the healthcare system compared to existing alternatives
4. Importance of ADC for confirming expected benefit and/or monitoring/optimizing the conditions of use.

One "no" makes the technology not eligible!
EUnetHTA Joint Action 2 (2012-2015)
Planned deliverables

- Recommendations on the implementation of sustainable European network for HTA
- Full Core HTAs
- Pilot rapid assessments
- Methodological guidelines and Templates to support production of core HTA information and rapid assessments
- Guidelines and pilots to improve quality and adequacy of initial and additional evidence generation
- Upgraded and updated application package of HTA Core Model
- Report on yearly training courses on EUnetHTA tools and methodology
- Report on evaluation of project completion including assessment of impact on secondary users of HTA information

EUnetHTA Joint Action 2 (2012-2015)
Planned deliverables

Additional data collection - Deliverables
- Ongoing survey on ADC capacities
- How to best define research question and appropriate methodology (common core protocol)
- Conduct of pilots

Cooperation with EMA and ENCePP
- European Network of Centers of Pharmacoepidemiology and Pharmacovigilance
- How to coordinate request for post-launch data collection (PAES, PASS, HTA requests)
Italian Perspective

Managed Entry Agreements in Italy
Entela Xoxi

Comparing the challenges of comparative effectiveness research in France, Italy and the Netherlands: Current situation and perspectives
November 6th 2013
Public Declaration of transparency/interests*

The view and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to AIFA.

N.B. < I am not receiving any compensation>

*Entela Xoxi, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (26.01.2012) and published on the Official Journal of 20.03.2012 according to 0044 EMA/513078/2010 on the handling of the conflicts of interest for scientific committee members and experts.

<table>
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<th>Interests in pharmaceutical industry</th>
<th>NO</th>
<th>Currently</th>
<th>Last 2 years</th>
<th>More than 2 years but less than 5 years ago</th>
<th>More than 5 years ago (optional)</th>
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<tbody>
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<tr>
<td>Employment with a company</td>
<td>x</td>
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<tr>
<td>Consultancy for a company</td>
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<tr>
<td>Strategic advisory role for a company</td>
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<tr>
<td>Financial interests</td>
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<td>Ownership of a patient</td>
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<td>Indirect interests:</td>
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<td>Principal investigator</td>
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<td>Investigator</td>
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<tr>
<td>Individual’s Institution/Organization receives a grant or other funding</td>
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</table>

The outline of this talk

1. Italian National Health Service and the pharmaceutical context
2. Pharmaceutical expenditure control
3. AIFA Monitoring Registries
4. Case study: Antidiabetic drugs
5. New Registries
The Italian National Health Service (NHS)

- Provides healthcare to all citizens in equal way
- Primary care and hospital care are free of charge to all patients
- Pharmaceutical care is free of charge for all the most important medicines

Among European countries, in Italy there is:

- A central legislative power which defines licensing, reimbursement and price of medicines for the Italian NHS (AIFA)
- A region’s responsibility for organizing the supply of medicines for healthcare. Regions could influence the market and patient access to medicines.

Balancing innovation and outcomes

To ensure

- Rapid access to new potentially beneficial health technologies
- Obtain best value for money
- Ensure affordability

Healthcare payers are adopting a range of innovative reimbursement approaches called Managed Entry Agreements*.

Some of these agreements link coverage of medical products to:

- The collection of additional evidence
- And/or to measures of health outcomes in the “real world” that is, outside the context of highly controlled clinical trials.
**Instruments**

1. Price-volume agreements
2. Cost sharing (CS)
3. Budget cap
4. Payment by result (PbR)
5. Risk sharing (RS)
6. Success fee (SF)
7. Therapeutic plan
8. ‘AIFA notes’

*According to the HTAi Forum Policy*

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**A range of approaches to Managed Entry: the Italian Experience**

- Refusal
  - Reimbursement (without conditions)
  - Managing budget impact
  - Managing uncertainty relating to clinical benefit and cost-effectiveness
  - Managing utilization to optimize performance

- Non-Outcome based MEAs
  - Monitoring Registers
  - Outcome based MEAs
    - Oncologicals
    - Orphan drugs
    - Antipsoriasis
    - Antidiabetics
    - Cardiovascular
    - Antirheumatics

- Therapeutic plan
  - Payment by Results
  - Risk Sharing

*According to the HTAi Forum Policy*
MEA’s impact

- Can lead to a refusal to reimburse or cover the drug
- More often it lead to restrictions to access to drugs (eg 2nd or 3rd line use, only for some patient groups, etc.)
- Some restrictions are harder to enforce than others, and the implementations of the decisions is automatic
- Sometime the mere intention impacts the use of the drug

Managed Entry Agreements

Web based drug monitoring Registry
Drug-monitoring registry

Physician

Prescriptions

Physician

DB

Dispensing Orders

Pharmacist

DB

Treatment

Disease assessment

Responders (supported by SSN)

Non responders

MEA’s application procedure

Pharmacist

Valid orders

Refund requests

Pharmaceutical Company

YES - NOT

MEA’s rules

DB
Case study
Real life data concerning antidiabetic drugs

✓ A high proportion of patients never reach the clinical target of \( \text{HbA}_1c \leq 7\% \) suggesting the need to better characterize the subset of patients in which these treatments are effective

New therapeutic plans

The new Registries!

✓ Users’ Accreditation
✓ Prescribing centres’ Accreditation
Figures

More than 108,000 treatments

New ... Fabric of Registries
Conclusions

✓ PBRSAs are understandable and logical response to increasing pressure for greater evidence of real-world effectiveness
✓ PBRSAs use performance-linked reimbursement at the patient level
✓ PBRSAs can provide valuable evidence that is potentially a global public good
✓ There are numerous barriers to establishing viable and cost-effective PBRSAs
✓ There is an important gap in the literature of structured ex post evaluation of PBRSAs
✓ Robust evaluation will be important

Open questions

① Is the scheme measuring appropriate outcome?
② Are the cost acceptable?
③ Is the data collecting efficient?
④ Is PBRSA a decision with further evidence?
Thank you!

Entela Xoxi

e.xoxi@aifa.gov.it

http://www.agenziafarmaco.gov.it/it/content/registri-farmaci-sottoposti-monitoraggio

Dutch Perspective
Conditional reimbursement in the Netherlands

Caroline M.J. van der Meijden
Dutch Health Care Insurance Board

Comparing the challenges of comparative effectiveness research (CER) in France, Italy and the Netherlands: Current situation and perspectives

ISPOR Dublin, November 6th 2013

CVZ: Dutch Health Care Insurance Board

- Governmental body advising Minister of Health on composition of 'basic health care package'
- Basic health care package: public, mandatory health care insurance
  - Medical aids
  - Medical care (GP’s, medical specialists, etc.)
  - Medicines
    - Extramural (outpatient prescription drugs)
    - Hospital setting
Background

- Since 2006: system of coverage with evidence development (CED) for expensive medicines in hospitals
- Aims: - Appropriate use of care in daily practice
  - Cost-effectiveness with the use of real world data
- Evidence collected in indication-based patient registries (observational data)
- Approximately 5-10 new drugs or indications per year

Topics

- **Process** of CER request and guidance provided
- **Challenges** of CER studies in practice
- **Impact** on the decision making process
- Future changes
- EU collaboration
Process of CER request and guidance provided

T=0

Assessment committee
- Maximum budget impact (>2.5M)
- Therapeutic value
- Proposal Outcome Research
- Estimate Cost-effectiveness

4 years of Coverage with Evidence Development

- Guidance by CVZ:
  - Scientific advice
  - Preliminary meeting on dossier contents
  - Guidelines (e.g. pharmacoeconomic research, cost manual, etc.)
  - Templates

Challenges of CER studies in practice

[Image: Needle in a Haystack cartoon]
Challenges of CER studies in practice

- Extra tasks for health care professionals
- Small sample sizes
- Lack of consistency in data collection and missing data
- Differences in patient characteristics between treatment groups
- QoL measured per health state not for different treatment groups

Impact on the decision making process
Example expensive drug

Assessment committee
- Actual budget impact (>=2.34%)
- Therapeutic value
- Results Outcome Research
- Actual Cost-effectiveness

Appraisal committee
- Necessity
- Effectiveness
- Cost-effectiveness
- Feasibility

Valid
Valid
Insufficient substantiation of appropriate use
" " " " Cost-effectiveness

Continue reimbursement only when a financial arrangement can be accomplished
Price for Performance deal

Advice CVZ
Negotiations at CVZ and Ministry of Health
**Impact on the decision making process**

**Example orphan drug**

T=4

- Assessment committee
  - Actual budget impact (+€2.5M)
  - Therapeutic value
  - Results Outcome Research
  - Actual Cost-effectiveness

- Appraisal committee
  - Necessity
  - Effectiveness
  - Cost-effectiveness
  - Feasibility

√ Heterogeneity -> varying effectiveness
+/- Appropriate use ?? -> dose escalation
+/- ICERs from 0.9 to 15 million Euro/QALY

Several recommendations
- Exclude from insured package; separate funding
- Negotiate better price
- Discuss options of dose-ranging and frequency of dosing
- Research in European context to determine predictive factors
- Independent committee for start/stop criteria

Successful price negotiations

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**Impact on the decision making process**

Expensive drugs from CVZ 2012-2013:

- Often limited therapeutic added value (e.g. 3 months OS extra)
- High annual costs per patient (€ 10.000 to € 84.000)
- High ICERs (€ 74.000 to € 145.000/ QALY)
Future changes

Conditional reimbursement

- Financial arrangements (price reductions, P/V, budget caps)
- Coverage with Evidence Development (CED) with more focus on feasibility

> Will more research decrease ICER uncertainty?
> Will the treatment ever be cost-effective?
> Is the effectiveness limited to subgroups?
> Appropriate care in daily practice?
> Development start- & stop criteria?

Future changes

Risk management

1. Projected total costs
   - $\leq 2.5$ million $\rightarrow$ low risk
   - $> 2.5$ million $\rightarrow$ high risk

2. Claimed relative effectiveness
   - equal therapeutical value $\rightarrow$ mostly low risk
   - added therapeutic value $\rightarrow$ high risk

High risk $\rightarrow$ evaluation by CVZ on budget impact & relative (/cost-)effectiveness
European collaboration

1. European registries for orphan drugs
   to monitor appropriate care and develop start/stop criteria

2. EUnetHTA WP5
   • JA1 was involved with the production of methodologies/guidelines to be used in Rapid REA
   • JA2 is all about putting those methodologies into practice

WP5 Partners
Lead Partner: CVZ
Co-lead partner: LBI
27 Associated Partners
12 Collaborating Partners

BIG thank you to Panelists
Debate time

And of course BIG thank you to audience