Assessing Biocomputational Modelling for Transforming Clinical Guidelines of Osteoporosis Management

Karl Stroetmann*
Rainer Thiel*, Marco Viceconti**

*empirica, Bonn, Germany & **Istituto Ortopedico Rizzoli, Bologna, Italy

www.vphop.eu/
Outline

1. Background
   a) European Virtual Physiological Human Initiative
   b) VPHOP project

2. Objectives and methodological challenges

3. Socio-economic assessment framework:
   a) Approach
   b) Indicator development
   c) Operationalisation

4. First results and conclusions
The European Virtual Physiological Human (VPH)

VPH constitutes effort towards Multi-scale patient-specific models for

- *Personalised* healthcare solutions
- Early diagnostics & *predictive* medicine
- Beyond reductionism – Towards an integrative understanding of diseases across several biological levels

**Vision**

- Framework to enable the investigation of human organs and the human body as a single complex system
- Integrated computer models of the mechanical, physical and biochemical functions of a living human body
Osteoporotic Virtual Physiological Human Project (VPHOP)

• EU funded, 2008-2012, to create a patient-specific hypermodel for predicting, with **ICT-based tools** for **modelling and simulation** of human physiology, the absolute **risk of bone fracture**

• **P2 medicine for osteoporosis;** directly interrelated with improved clinical outcomes as well as the transformation of prognosis and treatment of a chronic disease

• EU FP7 project requirement: assessment and evaluation approaches must be convincingly self-administered:
  • Results will be validated not only technically
  • impact assessed on **organisational, economic and societal issues** including clinical practice
VPHOP hypermodel

Tissue-level model

Bone Remodelling

Cell-level model

Constitutive Equation

Organ-level model

Boundary Conditions

Body-level model

Constituent-level model

Failure Criterion
A new challenge: Assessing the value of VPH computer models

- Radical departure from current type of medical technology
  - Not only an ‘intervention’: the technology has the potential to revolutionise diagnosis & treatment
  - It predicts. Other than decision-support systems, it generates new knowledge from raw data
- Complex ICT technology integrating a multitude of health technologies
Specific methodological challenges

- **Conventional** health technology assessment (HTA) methods **not sufficient** for VPH technologies

- **Impact** on clinical decision making and practice may be **far reaching** (organisational, management, cultural - disruptive)

- Purpose of the assessment is extended to **RTD policymaking**, i.e. decisions made during the development of the technology itself

- *Integrative assessment cycle:* all perspectives must become involved over the **entire life cycle** of the technology, from its design to large scale clinical deployment
VPH Technology Readiness Levels

<table>
<thead>
<tr>
<th>Technology Readiness Level</th>
<th>Description</th>
<th>Development Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRL 1.</td>
<td>Basic principles</td>
<td>Basic research</td>
</tr>
<tr>
<td>TRL 2.</td>
<td>Concept and hypotheses formulated</td>
<td></td>
</tr>
<tr>
<td>TRL 3.</td>
<td>Critical function and/or proof-of-concept</td>
<td></td>
</tr>
<tr>
<td>TRL 4.</td>
<td>Sub-Model design in lab</td>
<td></td>
</tr>
<tr>
<td>TRL 5.</td>
<td>Sub-Model parameterisation/configuration in lab</td>
<td>Experimental verification + validation (inherent accuracy)</td>
</tr>
<tr>
<td>TRL 6.</td>
<td>Sub-Model validation in lab</td>
<td></td>
</tr>
<tr>
<td>TRL 6a.</td>
<td>Multiscale integration validated in lab</td>
<td></td>
</tr>
<tr>
<td>TRL 7.</td>
<td>Prototype demonstration (using patient data)</td>
<td>Pre-clinical verification + validation</td>
</tr>
<tr>
<td>TRL 7a.</td>
<td>Hypermodel prototype demonstration (using patient data)</td>
<td>Clinical validation + assessment (clinical accuracy)</td>
</tr>
<tr>
<td>TRL 8.</td>
<td>Prototype demonstration in clinical environment</td>
<td></td>
</tr>
<tr>
<td>TRL 8a.</td>
<td>Hypermodel prototype demonstration in clinical environment</td>
<td></td>
</tr>
<tr>
<td>TRL 9.</td>
<td>Hypermodel tested/validated in full clinical trial</td>
<td></td>
</tr>
<tr>
<td>TRL 10.</td>
<td>Decision support system successfully used in clinical environment</td>
<td>Operational</td>
</tr>
</tbody>
</table>

- There was no HTA framework for VPH technology...
- Comprehensive overview of the technologies’ maturity at any given time
- Formative assessment framework
## Grid of indicators

### VPH technology assessment

<table>
<thead>
<tr>
<th>Development Phase</th>
<th>Capability</th>
<th>Accuracy</th>
<th>Efficacy</th>
<th>Impact Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic research</td>
<td>Verification, validation</td>
<td>Prediction uncertainty</td>
<td>Estimated accuracy-efficacy function</td>
<td>Projected cost/time based on simulation</td>
</tr>
<tr>
<td>Experimental verification &amp; validation (inherent accuracy)</td>
<td>RMS, ROC, AUC</td>
<td>FP/FN accuracy-efficacy function</td>
<td>Projected cost/time/risk based on actual use on prototype</td>
<td></td>
</tr>
<tr>
<td>Pre-clinical verification &amp; validation</td>
<td>Comparative outcome, QALY</td>
<td></td>
<td>Actual cost/time/risk measured</td>
<td></td>
</tr>
<tr>
<td>Clinical validation &amp; assessment (clinical accuracy)</td>
<td></td>
<td></td>
<td>Indicators of impact upon patient, provider, payer, etc.</td>
<td></td>
</tr>
<tr>
<td>Operational</td>
<td></td>
<td>Ex-post assessment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Impact focus: clinical management and patient health

- Ultimate VPHOP use case scenario: **transforming clinical guidelines** for osteoporosis management
- Current care pathway as central **comparator** of osteoporosis management with the future VPHOP clinical pathways
- Comparison between accuracy / efficacy, costs of old and new clinical pathways in order to arrive at **socio-economic benefits** (& costs)
- Expected benefits from the increased accuracy rates in risk prediction (formalised as **fractures avoided**) in comparison standard of care clinical pathway
Summary VPHOP clinical pathway(s)

**Step 1 Screening**
- Weight/Height
- Age
- Gender
- Previous fracture
- Family fracture
- History of falls
- Life style (nutrition, physical activity)
- Smoking
- Alcohol abuse
- Corticosteroids
- Rheumatoid arthritis
- Secondary osteoporosis

**Step 2**

4 groups of variables:
- **Biochemical measures**
- **Functional assessment** falls, gait, muscle strength, body composition, Actibelt
- **Prevalent fracture(s)** DXA, X-ray
- **Mineral mass** DXA

**Step 3**

- **High Risk**
  - Tailored intervention
  - Site of intervention
- **Middle Risk** (as available)
  - EOS
  - QCT
  - XperCT
  - HRpQCT
- **Low Risk**
  - Lifestyle modification
- **Lifestyle modification**
  - Reevaluation after 2 years
- **Threshold to be determined**

**Cost effectiveness analysis**

MIE 2011 -- Oslo, Norway, August 28th – 31st, 2011
Incidence rates

- VPHOP pathways designed with respective technology components
- Population simulation was hypothesised
- Equally, algorithm with incidence rates designed for current clinical pathway
### Benefit cost analysis

<table>
<thead>
<tr>
<th></th>
<th>Standard of care</th>
<th>VPHOP Diagnosis + Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost [€] or consequence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost per patient</td>
<td>310,80</td>
<td>2.775,19</td>
</tr>
<tr>
<td>Cost per entry cohort of 5000</td>
<td>1.554.000,00</td>
<td>12.072.657,50</td>
</tr>
<tr>
<td>Cost of one fracture</td>
<td>60.000,00</td>
<td>60.000,00</td>
</tr>
<tr>
<td><strong>Misclassification error</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>False Negative</td>
<td>0,50</td>
<td>0,20</td>
</tr>
<tr>
<td><strong>Treatment efficacy (probability to fracture with treatment)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0,50</td>
<td>0,50</td>
</tr>
<tr>
<td><strong>Patients with treatment recomm</strong></td>
<td>2.500,00</td>
<td>2.975,00</td>
</tr>
<tr>
<td><strong>Patients with no treatment recomm</strong></td>
<td>2.500,00</td>
<td>2.025,00</td>
</tr>
<tr>
<td><strong>Fractures per treatment cohort</strong></td>
<td>1.250,00</td>
<td>1.487,50</td>
</tr>
<tr>
<td><strong>No. of misclassified no treatment (false negative = fractures despite no fracture prediction)</strong></td>
<td>1.250,00</td>
<td>405,00</td>
</tr>
<tr>
<td><strong>No. total fractures per entry cohort</strong></td>
<td>2.500,00</td>
<td>1.892,50</td>
</tr>
<tr>
<td><strong>Total cost of actual fracture per cohort</strong></td>
<td>150.000.000,00</td>
<td>113.550.000,00</td>
</tr>
<tr>
<td><strong>Net costs (total cost fractures and diagnosis/prognosis)</strong></td>
<td>151.554.000,00</td>
<td>125.622.657,50</td>
</tr>
<tr>
<td><strong>No. fractures avoided</strong></td>
<td></td>
<td>608</td>
</tr>
<tr>
<td><strong>Cost savings (from fractures avoided)</strong></td>
<td></td>
<td>36.480.000,00</td>
</tr>
</tbody>
</table>

- **Simulated patient cohort** of 5000 with FRAX-based risk profile, adjusted for patient flow
- **Impact on the basis of estimated efficacy**, projected cost
- **Accuracy-efficacy function** obtained with the probabilistic model
Benefit-Cost Ratio: Positive Returns

\[
\text{Cost}_{VPHOP} = \text{Cost per entry cohort}_{VPHOP} - \text{Cost per entry cohort}_{SoC} = 10.446.000 \text{ €}
\]

\[
\text{BCR}_{VPHOP} = \frac{B}{C} = \frac{\text{Cost savings (fractures avoided)}}{\text{Cost}_{VPHOP}} = \frac{36.480.000 \text{ €}}{10.446.000 \text{ €}} = 3.27
\]

Extra costs needed to implement the VPHOP pathways are by far offset through costs savings of the improved fracture risk prognosis.
Conclusion

- Biocomputational modelling/VPH technologies can transform future patient workflows, even replace current clinical management

- Break even with the efficacy and costs of current guidelines (the number of additional fractures needed to prevent) is within realistic reach

- The socio-economic assessment perspective steers the development of concrete clinical scenarios for computer simulation models

- Further research will clearly benefit from a more focused alignment towards routine clinical applications
Thank You!

Further information:

www.vphop.eu/

empirica

Communication & Technology Research

Oxfordstr. 2, 53111 Bonn, Germany

Tel: +49 (2 28) 98 530 -0
Fax: +49 (2 28) 9 85 30 -12

www.empirica.com
Disclaimer

- VPHOP is a project co-funded by the European Commission 7th FRAMEWORK PROGRAMME – their support is gratefully acknowledged.

- The research reported upon in this presentation has either directly or indirectly been supported by the European Commission, Directorate General Information Society and Media, Brussels.

- The results, analyses and conclusions derived there from reflect solely the views of the authors and of the presenter.

- The European Community is not liable for any use that may be made of the information contained therein.