EU Regulatory Affairs – Medical Devices

Wireless technology and e-Health

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Cardiovascular Imaging and Dynamics

Chairman, Committee on Regulatory Affairs
Member, European Commission Working Group on Clinical Investigation & Evaluation
Approval of medical devices in the European Union

A national responsibility but approval gives access to whole EU market

Manufacturer → Competent Authority → NOTIFIED BODY → MARK → Market authorisation

Standards

EU DG GROW

Directives

Guidance

Fraser AG et al, Eur Heart J 2011; 32: 1673-86
CardioMEMS device

Pressure Sensor on Catheter-based Delivery System

Home Electronics
120cm
4.5cm
PA Monitoring Database
Proprietary database for secure storage of patient data

CardioMEMS device
Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial

CHAMPION trial, 550 patients in Class III heart failure

- CE mark in Europe in 2011; no details public

Monitoring of pulmonary artery pressures using a wireless implantable haemodynamic monitoring system (CardioMems) may be considered in symptomatic patients with HF with previous HF hospitalization in order to reduce the risk of recurrent HF hospitalization.

European Society of Cardiology 2016
Heart Failure – Clinical Practice Guidelines

- FDA declined in 2011, approved in 2014;
All documents available on website
Cost-effectiveness of implantable pulmonary artery pressure monitoring in chronic heart failure

In the CHAMPION study, the CardioMEMS device:
• reduced lifetime hospitalizations 2.18 vs. 3.12
• increased quality-adjusted life-years 2.74 vs. 2.46
• cost per QALY $82,301 in patients with HFREF
• cost per QALY $47,768 in patients with HFPEF

In the lower-risk CHARM cohort:
• the device would need to reduce hospitalizations for heart failure by 41% to cost <$100,000 per QALY

Sandhu AT et al, JACC Heart Failure 2016
Council of the European Union

Brussels, 22 February 2017 (OR. en)

10728/16

PHARM 43
SAN 284
MI 478
COMPET 402
CODEC 977

LEGISLATIVE ACTS AND OTHER INSTRUMENTS

Increased engagement of independent scientific, engineering and clinical experts, and medical professional associations, with regulatory governance:

- Clinical evaluation and trials
- Expert panels and reference laboratories
- Scrutiny / Device-specific standards / CTS
- Post-market surveillance
- Transparency of evidence

https://ec.europa.eu/growth/sectors/medical-devices
EU definition of a medical device (2017):
“Any .. software, implant .. intended by the manufacturer to be used, alone or in combination, for .. diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease”

In the case of implantable devices, clinical investigations shall be performed:
“clinical benefit means .. positive impact .. on the health of an individual .. in terms of a meaningful, measurable, patient-relevant clinical outcome”
e-Everything .. everyware

• 51 unique definitions
• eHealth = healthcare practice supported by electronic processes and communication

  Oh H et al, J Med Internet Res 2005;7:e1

• By 2017, 50% of the 3.4 billion smartphone or tablet users worldwide will use mobile health apps
• >160,000 health-related apps available
• 0.5% regulated as medical devices

/www.researchandmarkets.com/reports/2603873/mobile_health_trends_and_figures_20132017

EU voluntary guidance – in preparation

Lifestyle Apps

Where should regulation begin?
Reliability and validity

Software as a medical device
Devices for diagnosis, monitoring, treatment
<table>
<thead>
<tr>
<th></th>
<th>Inform clinical management</th>
<th>Drive clinical management</th>
<th>Diagnose or treat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-serious</strong></td>
<td>1 a</td>
<td>1 c</td>
<td>2 c</td>
</tr>
<tr>
<td><strong>Serious</strong></td>
<td>1 b</td>
<td>2 b</td>
<td>3 b</td>
</tr>
<tr>
<td><strong>Critical</strong></td>
<td>2 a</td>
<td>3 a</td>
<td>4a</td>
</tr>
</tbody>
</table>

**IMDRF**

**Analytical & scientific & Clinical performance / IR**
EU legislation pertinent to eHealth and mHealth

Data protection

Regulation 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data
(to be implemented fully by 2018)

ePrivacy

Directive 2002/58/EC of 12 July 2002 concerning the processing of personal data and the protection of privacy in the electronic communications sector

Consumer rights

### All cause mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events Total</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antonicelli 2008</td>
<td>3</td>
<td>5</td>
<td>2.4%</td>
<td>0.62 [0.16, 2.36]</td>
</tr>
<tr>
<td>Balk 2008</td>
<td>9</td>
<td>101</td>
<td>3.6%</td>
<td>1.26 [0.50, 3.14]</td>
</tr>
<tr>
<td>Capomolla 2004</td>
<td>7</td>
<td>66</td>
<td>3.4%</td>
<td>0.70 [0.24, 2.11]</td>
</tr>
<tr>
<td>Cleland 2005 (Telemon)</td>
<td>20</td>
<td>208</td>
<td>12.8%</td>
<td>0.71 [0.42, 1.18]</td>
</tr>
<tr>
<td>de Lusignan 2001</td>
<td>2</td>
<td>10</td>
<td>1.4%</td>
<td>0.67 [0.14, 3.17]</td>
</tr>
<tr>
<td>Giordano 2009</td>
<td>32</td>
<td>230</td>
<td>15.5%</td>
<td>0.66 [0.39, 1.10]</td>
</tr>
<tr>
<td>Goldberg 2003 (WHARF)</td>
<td>28</td>
<td>142</td>
<td>12.4%</td>
<td>0.44 [0.22, 0.85]</td>
</tr>
<tr>
<td>Kielblock 2007</td>
<td>49</td>
<td>251</td>
<td>33.3%</td>
<td>0.54 [0.37, 0.77]</td>
</tr>
<tr>
<td>Mortara 2009 (Telemon)</td>
<td>17</td>
<td>155</td>
<td>8.3%</td>
<td>0.63 [0.30, 1.29]</td>
</tr>
<tr>
<td>Soran 2008</td>
<td>5</td>
<td>62</td>
<td>4.8%</td>
<td>1.19 [0.34, 4.22]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>147</td>
<td>200</td>
<td>100.0%</td>
<td>0.66 [0.54, 0.81]</td>
</tr>
</tbody>
</table>

Total events: 147 / 200
Heterogeneity: $\chi^2 = 8.84, df = 10 (P = 0.55), I^2 = 0$
Test for overall effect: $Z = 4.07 (P < 0.0001)$

### HF hospitalisation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events Total</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleland 2005 (Telemon)</td>
<td>40</td>
<td>24</td>
<td>14.6%</td>
<td>0.84 [0.55, 1.30]</td>
</tr>
<tr>
<td>Giordano 2009</td>
<td>43</td>
<td>230</td>
<td>33.5%</td>
<td>0.59 [0.42, 0.82]</td>
</tr>
<tr>
<td>Kielblock 2007</td>
<td>71</td>
<td>251</td>
<td>37.7%</td>
<td>0.87 [0.66, 1.13]</td>
</tr>
<tr>
<td>Mortara 2009 (Telemon)</td>
<td>35</td>
<td>195</td>
<td>14.1%</td>
<td>1.03 [0.65, 1.61]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>844</td>
<td>726</td>
<td>100.0%</td>
<td>0.79 [0.67, 0.94]</td>
</tr>
</tbody>
</table>

Total events: 189 / 207
Heterogeneity: $\chi^2 = 4.88, df = 3 (P = 0.18), I^2 = 39$
Test for overall effect: $Z = 2.66 (P = 0.008)$

Assessment of e- and m-tools used in clinical trials

• **eHealth and mHealth ubiquitous**
  ✷ monitoring of clinical status, compliance
  ✷ delivery and optimisation of treatment
  ✷ end-points such as patient-related outcomes

• **new regulatory challenges – unresolved**
  ✷ clinical evaluation under new MD Regulation
  ✷ similar criteria applied as for other devices
  ✷ shared standards e.g. IMDRF for “SaMD”
  ✷ new responsibilities for manufacturers
The symptoms or the sufferings generally considered to be inevitable and incident to the disease are very often not symptoms of the disease at all, but of something quite different – of the want of fresh air, or of light, or of warmth, or of quiet, or of cleanliness, or of punctuality and care in the administration of diet, of each or of all of these.

All hurry or bustle is peculiarly painful to the sick.

Always sit down when a sick person is talking business to you, show no signs of hurry, give complete attention and full consideration if your advice is wanted, and go away the moment the subject is ended.