Scientific Evidence and Innovation in the EU

Rob Nelissen

Professor & Chairman Orthopaedics, Leiden University Medical Center

Chairman NORE, a standing committee of EFORT
Disclosures

Institutional Grants
- ZonMW, Dutch Arthritis Foundation, STW, NWO,
- Contract research Stryker, Implantcast, RSACore_LUMC

- Professional Boards:
  - Chairman Dutch Arthroplasty Register (LROI)
  - Chairman Network Orthopaedic Registries of Europe (N.O.R.E.), a standing committee of EFORT
  - President RSA Society
  - Past President Netherlands Orthopaedic Association (NOV -2018)
Innovation Pathway

- Invention
  - In vivo preclinical evaluation
  - IP protection
- Manufacturing Scale Up
- Health economics-Value Proposition
- Commercial Product
- Clinical Trials
  - Regulatory approval

An Uphill Battle: Imagine leading an expedition where every step is more difficult than the last. The journey may seem daunting, but with perseverance and determination, the eventual success is within reach.
• Over 235 million operations are performed worldwide per annum

• Less than 1% of surgical patients are recruited into clinical studies
\[
\frac{\text{Benefit}}{\text{Risk}} > 1
\]
Risk \[ \frac{\text{Risk}}{\text{Benefit}} \] > 1
SIGNAL
Decision based on evidence
Survival Analysis (end-point revision Implant)

Cumulative incidence Revision, females <55 years

Years after primary procedure

Cumulative revision %
Increased Mortality in Metal-on-Metal versus Non-Metal-on-Metal Primary Total Hip Arthroplasty at 10 Years and Longer Follow-Up: A Systematic Review and Meta-Analysis

B. G. Pijls¹*, J. M. T. A. Meessen¹, J. W. Schoones⁴, M. Fiocco²,³, H. J. L. van der Heide¹, A. Sedrakyan⁵,⁶, R. G. H. H. Nelissen¹

### Mortality

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>MOM deaths</th>
<th>non-MOM deaths</th>
<th>FU</th>
<th>Risk Difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pahlage [27]</td>
<td>2013</td>
<td>31</td>
<td>1</td>
<td>28</td>
<td>0.23</td>
</tr>
<tr>
<td>Scholten [18]</td>
<td>2011</td>
<td>39</td>
<td>0</td>
<td>39</td>
<td>0.23</td>
</tr>
<tr>
<td>Jensen [19]</td>
<td>2011</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>0.23</td>
</tr>
<tr>
<td>Grub [10]</td>
<td>2011</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>0.23</td>
</tr>
<tr>
<td>Wexner [23]</td>
<td>2011</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>0.23</td>
</tr>
<tr>
<td>Tuske [35]</td>
<td>2011</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>0.23</td>
</tr>
<tr>
<td>Fu [10]</td>
<td>2011</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>0.23</td>
</tr>
<tr>
<td>Hiliya [34]</td>
<td>2011</td>
<td>25</td>
<td>0</td>
<td>25</td>
<td>0.23</td>
</tr>
<tr>
<td>RE Model for Subgroup</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 5-10 years |       |             |                |    |                         |
|           |      |             |                |    |                         |
| Gulakowski [32] | 2014 | 25          | 0              | 25 | 0.23                    |
| Enderer [29]      | 2014 | 25          | 0              | 25 | 0.23                    |
| Macnab [21]       | 2014 | 37          | 0              | 37 | 0.23                    |
| Eng [12]          | 2014 | 25          | 0              | 25 | 0.23                    |
| Ebbe [37]         | 2014 | 25          | 0              | 25 | 0.23                    |
| Ziegler [38]      | 2014 | 25          | 0              | 25 | 0.23                    |
| NCT01225641 [19] | 2014 | 25          | 0              | 25 | 0.23                    |
| RE Model for Subgroup | | | | | |

| >10 years |       |             |                |    |                         |
|          |      |             |                |    |                         |
| Haddad [33] | 2013 | 11          | 0              | 11 | 0.23                    |
| Casasrodriguez [35] | 2013 | 11          | 0              | 11 | 0.23                    |
| Zijlstra [38] | 2013 | 11          | 0              | 11 | 0.23                    |
| Vougiou [39]  | 2013 | 11          | 0              | 11 | 0.23                    |
| RE model for All Studies | | | | | |

Red box indicates significant difference.
RESEARCH

Appraisal of evidence base for introduction of new implants in hip and knee replacement: a systematic review of five widely used device technologies

Marc J Nieuwenhuijse research fellow ICOR and FDA, R G H H Nelissen professor, J W Schoones information specialist, A Sedrakyan associate professor
1. Gender knee

2. High Flex knee

3. Ceramic – ceramic bearing

4. Modular neck

5. Monoblock acetabulum
Summary

Meta analysis 15,384 implants in 13,164 patients

Lower revision

1. Monoblock acetabulum: hazard ratio 0.8 – 1.0

Higher revision

1. modular femoral necks: hazard ratio 1.9
2. ceramic-on-ceramic Hip: hazard ratio 1.0-1.6
3. high flexion knee: hazard ratio 1.0-1.8
Levels of Evidence

- Meta Analyses
- Randomised Controlled Trials
- Cohort Studies
- Case-Control Studies
- Case-Series or Case-Reports
- Editorials and Expert Opinion
The Risk of Small Studies is BIG
Electric Morcellation-related Reoperations After Laparoscopic Myomectomy and Nonmyomectomy Procedures

Presented at the AAGL 41st Global Congress of Minimally Invasive Gynecology, Las Vegas, NV, November 5-9, 2012.

Nigel Pereira, MD, Tommy R. Buchanan, MD, Kayla M. Wishall, MD, Sarah H. Kim, BS, Irene Grias, DO, Scott D. Richard, MD, Carl R. Della Badia, DO

DOI: https://doi.org/10.1016/j.jmig.2014.09.006 | CrossMark

Abstract

Study Objective
To identify, collate, and summarize the most common causes and pathologies of electric morcellation-related reoperations after laparoscopic myomectomy and nonmyomectomy procedures.

Design
A systematic review of published medical literature from January 1990 to February 2014 reporting morcellation-related reoperations after laparoscopic myomectomy.
J&J Begins Settlement of Power Morcellator Cancer Lawsuits

March 30, 2016

Johnson & Johnson is making a move to settle lawsuits filed by women who say the company's surgical devices called power morcellators spread undetected uterine cancer, The Wall Street Journal reported.

As of March 15, 2016, there are about 31 morcellator lawsuits pending in federal court against J&J's Ethicon unit before Judge Kathryn H. Vratil in Kansas, according to the Judicial Panel on Multidistrict Litigation. These cases combined with
Dilemma: Randomised controlled Trial (RCT)

Patients in Your Practice

REAL World Data = Registry data
De LROI is een register voor gewrichtsprothesen (heup, knie, enkel, schouder, elleboog, pols, vinger en duim) die in Nederland geplaatst zijn.

Aantal registraties op dit moment

- Totaal 600.305
- Heup 332.394
- Knie 256.488
- Enkel 495
- Schouder 10.131
- Elleboog 636
- Pols 50
- Vinger/duim 111

Deadline indienen abstracts ISAR congres (IJssel)
Results 7-year revision rate PS vs CR TKA

**men**

- PS Age <60 years
- PS Age 60-69 years
- PS Age 70+ years
- CR Age <60 years
- CR Age 60-69 years
- CR Age 70+ years

**females**

- PS Age <60 years
- PS Age 60-69 years
- PS Age 70+ years
- CR Age <60 years
- CR Age 60-69 years
- CR Age 70+ years

11.6% (95% CI: 10.2-13.3)

6.6% (95% CI: 5.7-7.6)

Too LATE

TKA: Posterior Stabilised vs Cruciate Retaining

n=167,567 TKA
Detection implant failure
Registries slow

Bone resorption (%)

Pain

Follow-up (years)

0 2 4 6 8 10

0 10 20 30 40
RSA measures Implant – Bone fixation

**RSA**: 3D migration

Roentgen Stereophotogrammetric Analysis

- Translation 0.1 mm
- Rotation 0.1°
Revison (%) at 10 yrs and MTPM in similar TKP

Acceptable

At Risk

Unacceptable

> 20,000 TKA metaregression

Pijls, ... Nelissen. Acta Orthop 2012
Early - Mid-term migration TKA (meta analysis n = 2450 TKA)

0-6 months Prognostic Feasible...
Effect RSA:
less performing implant earlier taken off market

22 to 35% reduction in revisions if RSA done
1 revision costs about 30,000€

Nelissen et al JBJS Am, 2011
Decision based on evidence
Evaluation Toolbox New Implants

Preclinical tests

RSA + Co Cr serum + SAE + ..

Surgeon training (e.g. Beyond Compliance)

Post-market Surveillance
Implant Class (e.g. ODEP)
Registries + PROMS + SAE
orthopaedic surgeons

Regulators

Industry
“Don't let your patient become a fashion victim”

Bulstrode BMJ 1993
It is not the strongest of the species that survives, 
nor the most intelligent. 
It is the one that is most adaptable to change. 

Charles Darwin
Evidence:

An Ally for Patients, an Asset for Surgeons