Choose certainty.
Add value.

Product Service

Post Market Surveillance

Doz. Dr. Gerold Labek,
LISAVienna 2018-11-06

Disclaimer

This presentation is based on information available as of today and prepared to my best knowledge.

This presentation presents my personal understanding of the medical device requirements in Europe.

Background Gerold Labek and References

- From 1999: Registries and Research

- From 2006: EUPHORIC-Project,
  QoLA Project

- 2011: PIP, ASR
  ➔ EU Commission,

- MDR
- MEDDEV 2.7.1 and others
- IMDRF, Registry working Group, 2 Papers

EU Regulation – Post-Approval

The post-market surveillance system shall be suited to actively and systematically gathering, recording and analysing relevant data on the quality, performance and safety of a device throughout its entire lifetime, and to drawing the necessary conclusions and to determining, implementing and monitoring any preventive and corrective actions..

Why Clinical Data are a Top Issue?

Design | Production | Risk Management | Use of Device | Patients

Health System/Access to Device | ……

Clinical Data provide information on the outcome of the entire treatment chain
➔ „final validation“

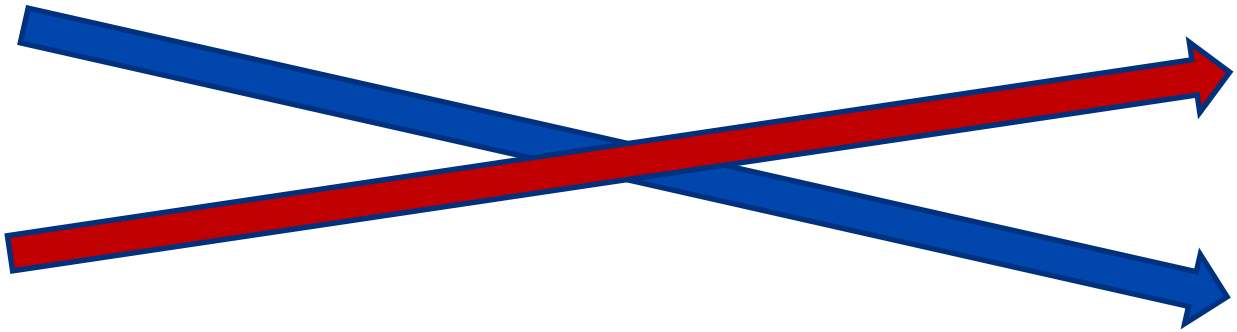
Evaluation of Clinical Data

Confounders

Statistics
(N Patients, Data – Nominal, ordinal. Metric,.)

Methodology
(Selection Bias, Documentation Bias,…)

Treatment Outcome
(Users, Patients, Implantation,…)



RCT

Registries

Pharma

Med. Dev.

Follow Up Studies

EU Regulation – Post-Approval

Limited Data → **Big Data**

EU Regulation – Post-Approval

The manufacturers should:

- establish a comprehensive post-market surveillance (PMS) system
- set up under the quality management system
- and based on a PMS plan.

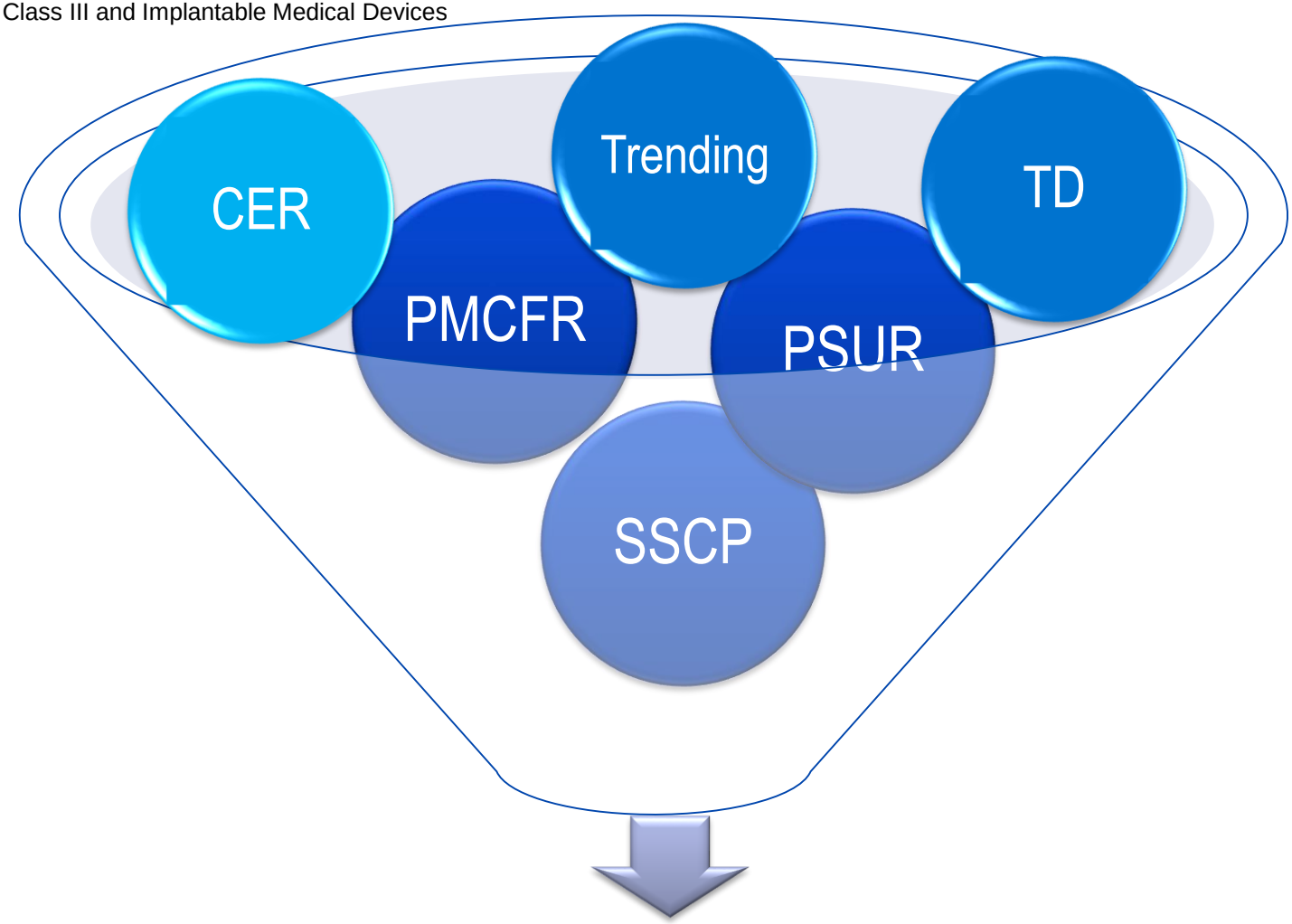
*

Major Elements of the Post-Market Surveillance Requirements

The post-market surveillance system shall be suited to actively and systematically gathering, recording and analyzing relevant data on the quality, performance and safety of a device throughout its entire lifetime, and to drawing the necessary conclusions and to determining, implementing and monitoring any preventive and corrective actions.

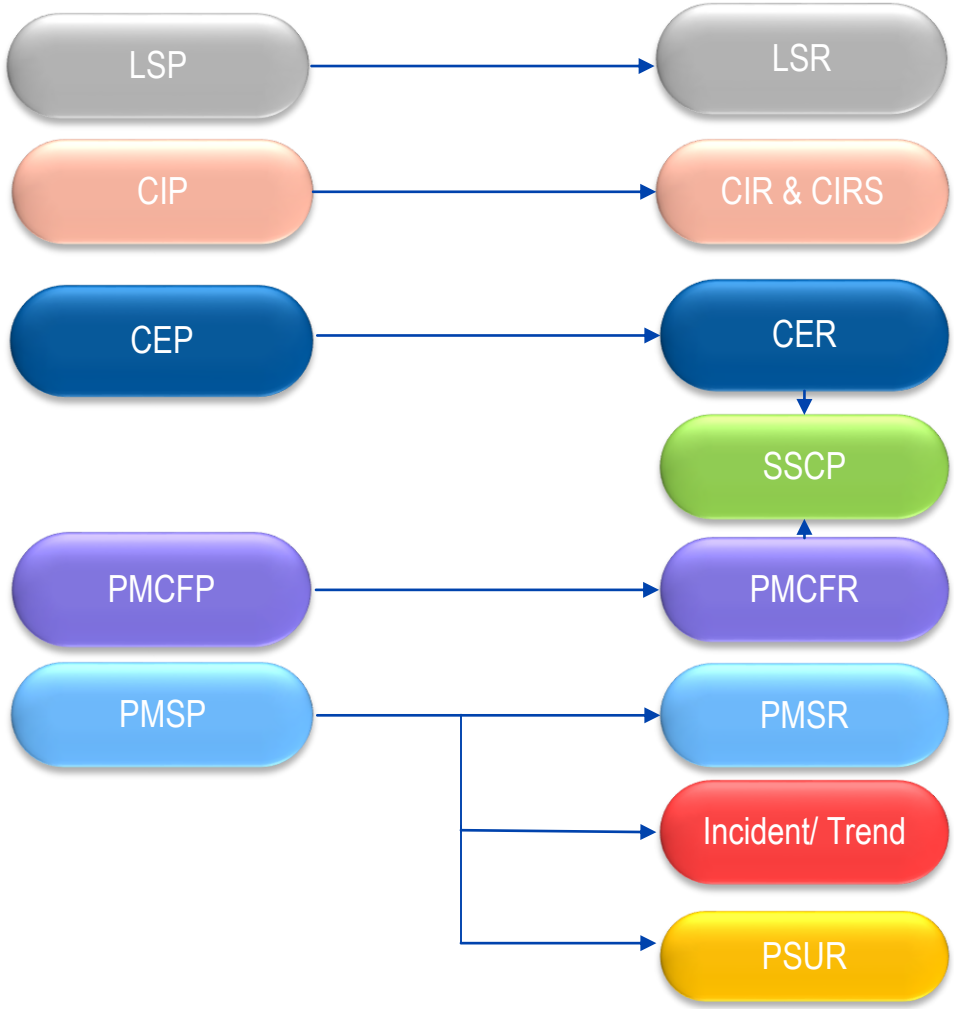
Higher Transparency through Annual Reporting System

Applicable for Class III and Implantable Medical Devices



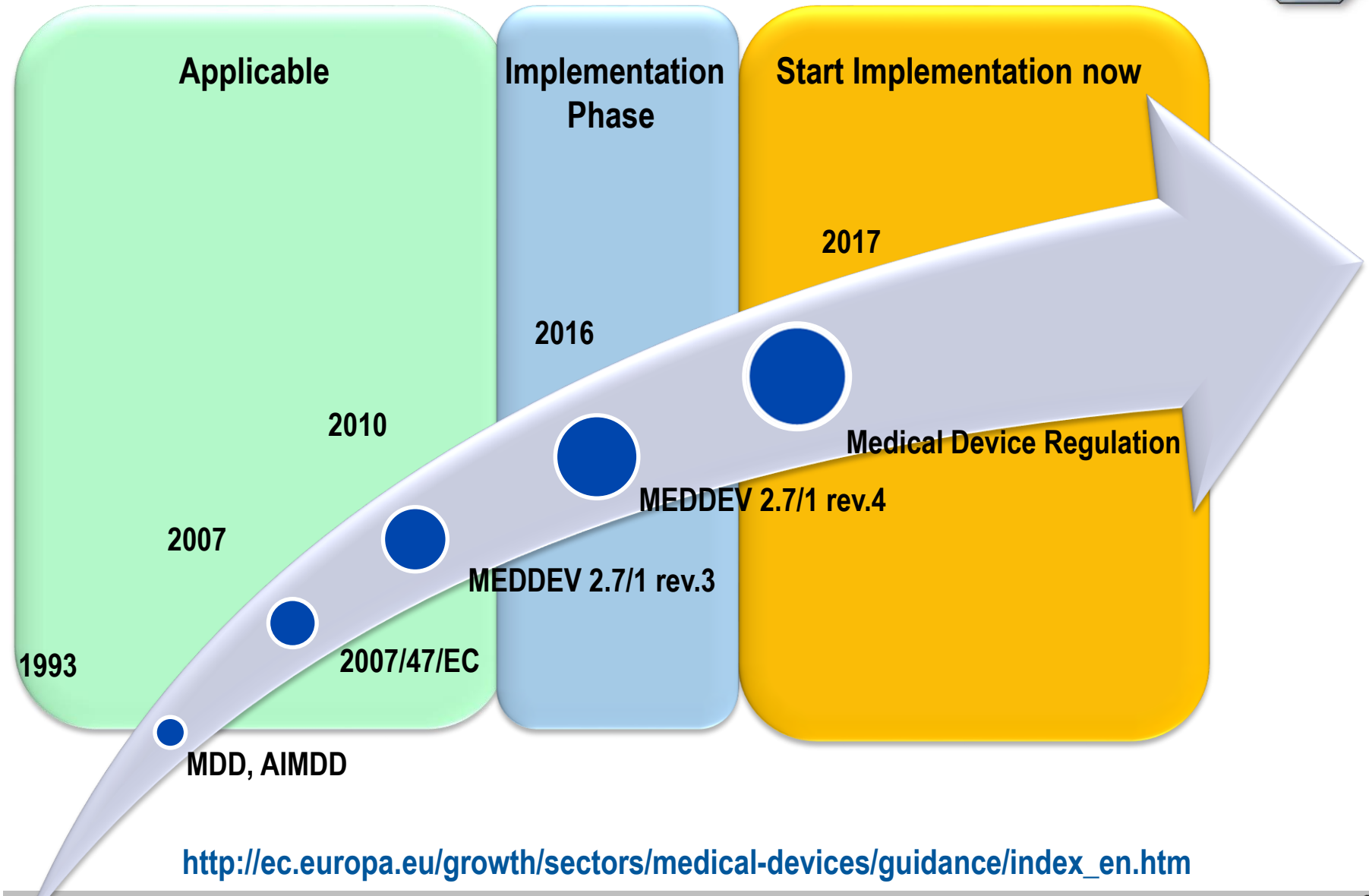
PSUR: Periodic Safety Update Report
CER: Clinical Evaluation Report
TD: Technical Documentation
SSCP: Summary of Safety and Clinical Performance
PMCFR: Post-Market Clinical Follow-Up Evaluation Report

MDR - Clinical Aspects - Processes, Plans (P), Reports (R), Summaries (S)



References in MDR Art. 10, Annex VII, IX, XI, III, XIV
Annex VII, XIV.1
Art. 61, 62-80, 82 Annex XV
Art. 61.11/12 Annex II, XIV, IX
Art. 32 and 61.11
Art. 61.11, Annex III, XIV, IX
Art. 61.11, 84, 85, Annex III, XIV, IX
Art. 87, 88, 89, 92 Annex IX, III
Art. 86, 92 Annex IX, III

Major Regulatory Updates in EU relevant for Clinical Evaluation



http://ec.europa.eu/growth/sectors/medical-devices/guidance/index_en.htm

MEDDEV 2.7.1. rev 4, Appendix 4 Sources of Literature

There are different sources of clinical literature that can be searched for clinical evaluation. A comprehensive search strategy is required, normally involving multiple databases. The search strategy should be documented and justified. Important sources include the following:

• **Scientific literature databases**

- MEDLINE or Pubmed can provide a good starting point for a search. However, with possibly incomplete coverage of European Journals and reduced search features, comprehensiveness may not necessarily be guaranteed.
- Additional databases may need to be used to ensure adequate coverage of devices and therapies in use in Europe, to identify relevant clinical trials and publications of user experience16, and to facilitate searches by device name and manufacturer (e.g. EMBASE/Excerpta Medica, the Cochrane CENTRAL trials register, etc.).
- Information coverage and search features available in scientific databases can change with time. Criteria for selecting adequate databases therefore need to be defined and reevaluated on a regular basis.

• **Internet searches**

MEDDEV 2.7.1. rev 4

MDCG, Common Specifications

Searches provide important data, examples include information on:
- harmonised standards and other standards applicable to the device in question and containing information on clinical performance and clinical safety.
- Field safety corrective actions for the equivalent and/or other devices. These can be found on manufacturer's web sites, internet sites of European Competent authorities, the U.S. Food and Drug Administration (FDA), possibly other sites.
- Implant registry reports.
- Documents available in systematic review databases (e.g. the Cochrane Database of Systematic Reviews, Prospero international prospective register of systematic reviews).
- Expert documents produced by professional medical associations that are important for assessment of current knowledge/ the state of the art, including clinical practice guidelines and consensus statements.
- Meta-analyses and reviews of health technology assessment (HTA) institutes and networks.
- Identification of studies via the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov.

Clinical Data Sources

- Clinical Studies (any kind, systematic search strategy)
- Systematic Reviews
  - Cochrane
  - HTA
  - Metaanalyses
  - Guidelines, Consensus Papers

Clinical Studies

- Implant Registry Reports

Market Experience / Real World Evidence

QoLA Project

- Medical University Innsbruck, Dept. of Orthopaedic Surgery, Austria
- University Kiel, Dept. of Orthopaedic Surgery, Germany
- Hacettepe University, Dept. of Orthopaedic Surgery, Turkey
- University Leiden, Dept. of Orthopaedic Surgery, Nederlands
- Semmelweiss Univ. Budapest, Dept. of Orthopaedic Surgery, Hungary
- Endoklinik, Hamburg, Germany
- Sozialmedizinisches Zentrum Ost, Dept. of Orthopaedic Surgery, Vienna, Austria
- South Danish University, Vejle, Denmark
- Haddassah Univ. Hospital, Jewish University Jerusalem, Israel
- University Martin, Dept. of Orthopaedic Surgery, Martin, Slovakia
- University Pleven, Dept. of Orthopaedic Surgery, Pleven, Bulgaria
- University Hospital Geneva, Dept. of Orthopaedic Surgery, Geneva, Switzerland
- Allgemeines Krankenhaus Linz, Dept. of Orthopaedic Surgery, Linz, Austria
- Istituto Galeazzi, Milano, Italy
- University Arad, Dept. of Orthopaedic Surgery, Arad, Romania
- Medical University Salzburg, Dept. of Orthopaedic Surgery, Salzburg, Austria
- Clinica Foisor de Foc, Bucharest, Romania
- Hospital del Mar, Dept. of Orthopaedic Surgery, Barcelona, Spain
- University Lille, Dept. of Orthopaedic Surgery, Lille, France
- Clinique de l'Yvette, Paris, France
- Dr. Günther Ziernhöld, Bolzano, Italy
- Orthopädisches Physiotherapiezentrum, Graz, Austria
- Johanneum Research, Graz, Austria
- Landeskrankenhaus Klagenfurt, Dept. of Orthopaedic Surgery, Klagenfurt, Austria
- Oberschwabenklinik, Wangen, Germany
- Centro Hospitalar do Nordeste, Macedo de Cavaleiros, Oporto, Portugal
- Hospital Curry Cabral, Lisboa, Portugal
- Centro Hospitalar do Tâmega e Sousa, Penafiel, Portugal

EARO
EUROPEAN ARTHROPLASTY REGISTER
NETWORK

QoLA Project

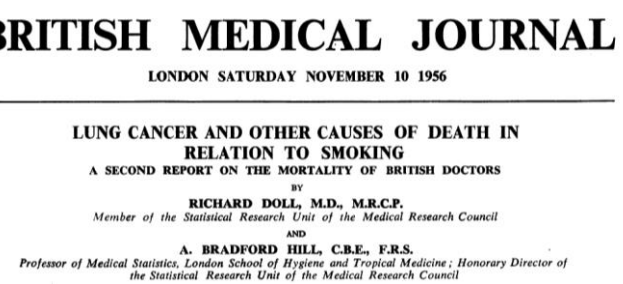
Goal:

- Check validity of clinical studies compared to arthroplasty register data (reference for real world/average patients service)
- Reproducibility of outcome published
- Confounders and Bias Factors
- Systematic Review

Material and Methods

- Medline listed publications on implants with register data

- PTIR – Revisions per 100 observed component years
- 1950-ies: Smoking and Cancer/Cardiovascular side effects
  - Total of years smoking (years at risk) in cohort
  - Incidence of observed endpoints
  - Head to Head comparison ➔ Incidences



BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 10 1956

LUNG CANCER AND OTHER CAUSES OF DEATH IN RELATION TO SMOKING

A SECOND REPORT ON THE MORTALITY OF BRITISH DOCTORS

BY

RICHARD DOLL, M.D., M.R.C.P.

Member of the Statistical Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, C.B.E., F.R.S.

Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council

- Medical Devices: Arthroplasty: Endpoint Revision surgery
  - By definition at risk from day of implantation
  - Linear function
  - Value of 1 = 1% RR @ 1 year, 10% @ 10 years (=NICE Benchmark)

QoLA-Project

- 95 Implant systems with sufficiant data in worldwide registries
  - 74 Systems: Data from clinical studies available
  - 21 Systems (~20%): not a single clinical study with outcome data published

Implant	Manufacturer	
Natural Hip stem	DePuy	
RBK TKA	Global Orthopaedic Tech.	Small company
Option cup	Kinamed	Small company
F2L Multineck	Lima	Small company
Gemini TKA	Link	Small company
SPH-Blind cup	Lima	Small company
Journey TKA	S&N	New
Vanguard TKA	Biomet	New
Maxim TKA	Biomet	
Scan TKA	Biomet	
Citation stem	Stryker	
Scorpio TKA	Stryker	
ABG cup	Stryker	
Unix Uni	Stryker	
Anca-Fit stem	Wright	
Advantim TKA	Wright	
ZCA Uni	Zimmer	
ZUK Uni	Zimmer	New
Securfit-cup	Stryker	
Mitch Resurfacing	Stryker	
Freedom PKR Uni	Stryker	
GRU Uni	Global Orthopaedic Tech.	Small company

EARO
European Arthroplasty Register
NETWORK

Metaanalysis Oxford Uni

- 23 Publications included
- 20 sample based studies
  - 7 by the inventor´s group, Oxford,Nuffield
  - 13 independent publications
- 3 publications based on National Arthroplasty Register datasets (2x SF, 1x S)
- 3 Annual Reports (S, SF, AUS)

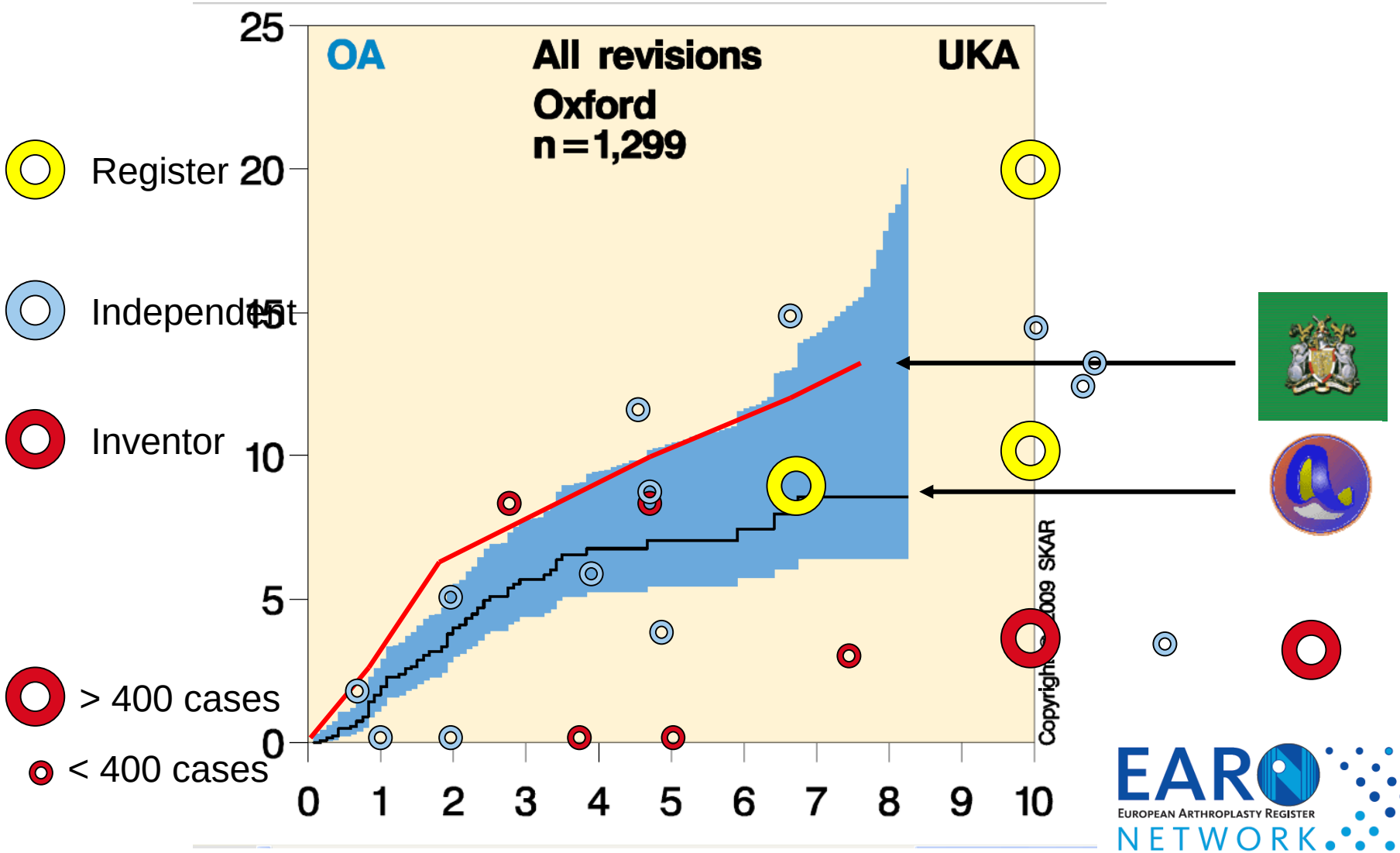
Acta Orthopaedica 2011; 82 (2): 131–135 131

Outcome and reproducibility of data concerning the Oxford unicompartmental knee arthroplasty

A structured literature review including arthroplasty registry data

Gerold Labek, Kathrin Sekyra, Wolfram Pawelka, Wolfgang Janda, and Bernd Stöckl

Metaanalysis Oxford Uni



Metanalyses Oxford Uni

	Number	FUP	Revision Rate [%]	Number primaries	Number Revisions	Observed component years	Revisions per 100 observed component years	CI	Factor Difference to Register
Inventor studies	7	9,64	4,30	**1559**	67	15029	**0,45**	0,35-0,57	**4,40**
Independnt clinical studies	13	4,99	6,09	**1445**	88	7205	**1,22**	0,99-1,50	**1,61**
Total clinical studies	20	7,40	5,16	3004	155	22234	**0,70**	0,60-0,82	**2,82**
Register Journal publications	3	9,04	14,51	**1951**	283	17638	**1,60**	1,43-1,80	
Registers Annual Reports	3	3,51	6,88	**11985**	825	42037	**1,96**	1,83-2,10	

One-third of knee replacement patients are candidates for a mobile bearing UKA, surgeon says

"At least one in three knees that require knee replacement are appropriate for a unicompartmental knee replacement," and would meet all recommended indications and contraindications for it, Murray said at the Knee Society Specialty Day Meeting during the 2010 Annual Meeting of the American Academy of Orthopaedic Surgeons, here.

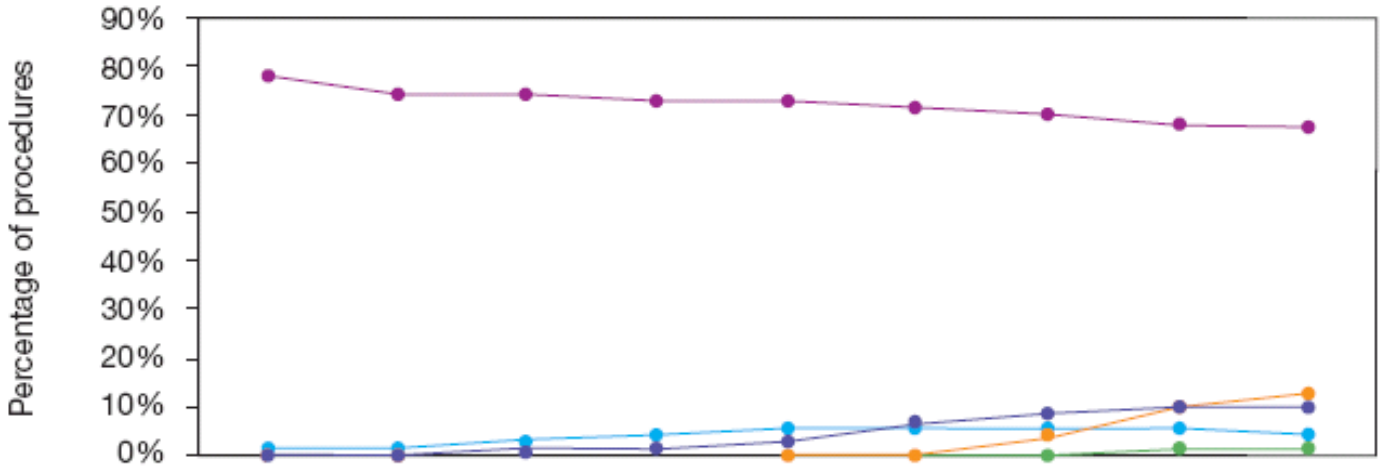
"Two-thirds of our patients are not ideal and have some of these contraindications, yet there is no difference in the outcome between those who have contraindications and those who do not."


Orthopaedicstoday
EUROPE
Surgeons look to hip tribology to provide better clinical results with THA, new bearing surfaces
Mobile bearing UKA appropriate for one-third of knee replacement patients, surgeon says

Metaanalysis Oxford Uni

Figure 2.25

Top five unicondylar knee brands, trends 2003 to 2011.



Year	2003	2004	2005	2006	2007	2008	2009	2010	2011
Number of components used	2,226	4,256	5,428	5,740	6,640	7,069	7,146	7,407	6,811

Oxford Partial Knee — AMC/Uniglide — Sigma HP — Triathlon Uni — Zimmer Uni

Summary Literature worldwide

Implant	Factor Difference Outcome in Registers and comprehensive publications in peer reviewed journals	Factor Difference Inventor Outcome and Register Outcome	Inventor Bias	Inventor Bias leading to Bias in aggregated Assessment	Region of Origin
Citation stem	Not a single revision published	n.a.	n.a.	n.a.	
Contemporary cup	Not a single revision published	n.a.	n.a.	n.a.	
SecurFit cup	Not a single revision published	n.a.	n.a.	n.a.	USA
Summit stem	Not a single revision published	n.a.	n.a.	n.a.	USA
Versys stem	Not a single revision published	n.a.	n.a.	n.a.	USA
Securfit stem	Not a single revision published	n.a.	n.a.	n.a.	USA
Pinnacle cup	Not a single revision published	Not a single revision published	Only inventor studies published		USA
Vitalock cup	Not a single revision published	n.a.	n.a.	n.a.	USA
Epoch stem	Not a single revision published	n.a.	n.a.	n.a.	USA
Preservation Uni	Not a single revision published	n.a.	n.a.	n.a.	USA
Securfit cup	Not a single revision published	n.a.	n.a.	n.a.	USA
Optetrak TKA	41,10	Not a single revision published	Yes	Yes	USA
Pappas-Büchel TAA	10,15	14,29	Yes	Yes	USA
Profemur Z stem	9,72	n.a.	n.a.	n.a.	USA
C-stem	8,69	n.a.	n.a.	n.a.	USA,D,GB
Corail stem	7,78	5,24	Yes	Yes	USA
CPT stem	7,33	n.a.	n.a.	n.a.	USA
Synergy	6,79	n.a.	n.a.	n.a.	USA
Charnley cup	5,28	n.a.	n.a.	n.a.	GB
Trilogy	4,36	n.a.	n.a.	n.a.	USA
AGC	4,01	4,15	Yes	Yes	USA
Genesis II	3,86	3,70	Yes	Yes	US, Can
Fitmore cup	3,22	n.a.	n.a.	n.a.	EU
Recap Resurfacing	3,17	n.a.	n.a.	n.a.	
Accolade Trident	3,17	n.a.	n.a.	n.a.	U
Natural hip stem	3,13	n.a.	n.a.	n.a.	U
Taperloc	2,90	10,81	Yes	Yes	U

Summary Literature worldwide

Repicci Uni	2,89	n.a.	n.a.	n.a.	USA
Bicontact	2,80	2,11	No	No	EU
Oxford Uni	2,71	4,37	Yes	Yes	GB
Link Uni	2,65	11,4	Yes	No	EU
Allofit cup	2,34	1,32	No	No	EU
Avon	2,18	2,17	No	No	GB
Charnley stem	2,17	n.a.	n.a.	n.a.	GB
Spotorno CLS cup	2,11	9,05	Yes	No	EU
Cormet Resurfacing	2,1	n.a.	n.a.	n.a.	EU
Definition stem	1,95	n.a.	n.a.	n.a.	
Hintegra	1,94	1,94	No	n.a.	EU
Alloclassic	1,84	0,87	No	No	EU
Duracon TKA	1,71	1,48	No	No	USA
Durom Resurfacing	1,71	n.a.	n.a.	n.a.	USA
Duracon Uni	1,59	n.a.	n.a.	n.a.	USA
STAR	1,56	4,63	Yes	Yes	EU
Harris-Galante-Pfanne	1,53	2,22	No	No	USA
ABG I cup	1,50	n.a.	n.a.	n.a.	USA
Allgeretto Uni	1,45	n.a.	n.a.	n.a.	EU
LCS	1,46	1,17	No	No	USA
NexGen	1,45	n.a.	n.a.	n.a.	USA
MG Uni	1,44	5,20	Yes	No	USA
Conserve Plus	1,43	1,47	No	No	USA
Advance TKA	1,41	n.a.	n.a.	n.a.	USA
Profix	1,39	n.a.	n.a.	n.a.	USA
BHR	1,33	4,33	Yes	No	

Summary Literature worldwide

Triathlon TKA	1,29	n.a.	n.a.	n.a.	USA
PFC Uni	1,26	n.a.	n.a.	n.a.	USA
AML cementless stem	1,22	4,74	Yes	No	USA
Duraloc	1,21	n.a.	n.a.	n.a.	USA
Romanus cup	1,15	n.a.	n.a.	n.a.	
Natural Knee	1,12	1,07	No	No	USA
ASR	1,06	n.a.	n.a.	n.a.	USA
Agility	1,02	2,43	No	No	USA
SPII	0,99	n.a.	n.a.	n.a.	EU
Spotorno	0,98	1,84	No	No	EU
Eius Uni	0,89	n.a.	n.a.	n.a.	
Kinemax TKA	0,83	2,75	No	No	USA
PFC	0,70	0,64	No	No	USA
Müller Schaft zem	0,70	0,59	No	No	EU
Exeter stem	0,66	n.a.	n.a.	n.a.	EU
RM cup	0,62	n.a.	n.a.	n.a.	EU
Lubinus-cup	0,58	n.a.	n.a.	n.a.	EU
ABG Stem	0,27	n.a.	n.a.	n.a.	USA
Durom THA	0,25	n.a.	n.a.	n.a.	

Literature USA

Implant	Factor Difference Outcome in Registers and comprehensive publications in peer reviewed journals	Factor Difference Inventor Outcome and Register Outcome	Inventor Bias	Inventor Bias leading to Bias in aggregated Assessment	Region of Origin
SecurFit cup	Not a single revision published	n.a.	n.a.	n.a.	USA
Summit stem	Not a single revision published	n.a.	n.a.	n.a.	USA
Versys stem	Not a single revision published	n.a.	n.a.	n.a.	USA
Securfit stem	Not a single revision published	n.a.	n.a.	n.a.	USA
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Vitalock cup	Not a single revision published	n.a.	n.a.	n.a.	USA
Epoch stem	Not a single revision published	n.a.	n.a.	n.a.	USA
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Literature USA

Repicci Uni	2,89	n.a.	n.a.	n.a.	USA
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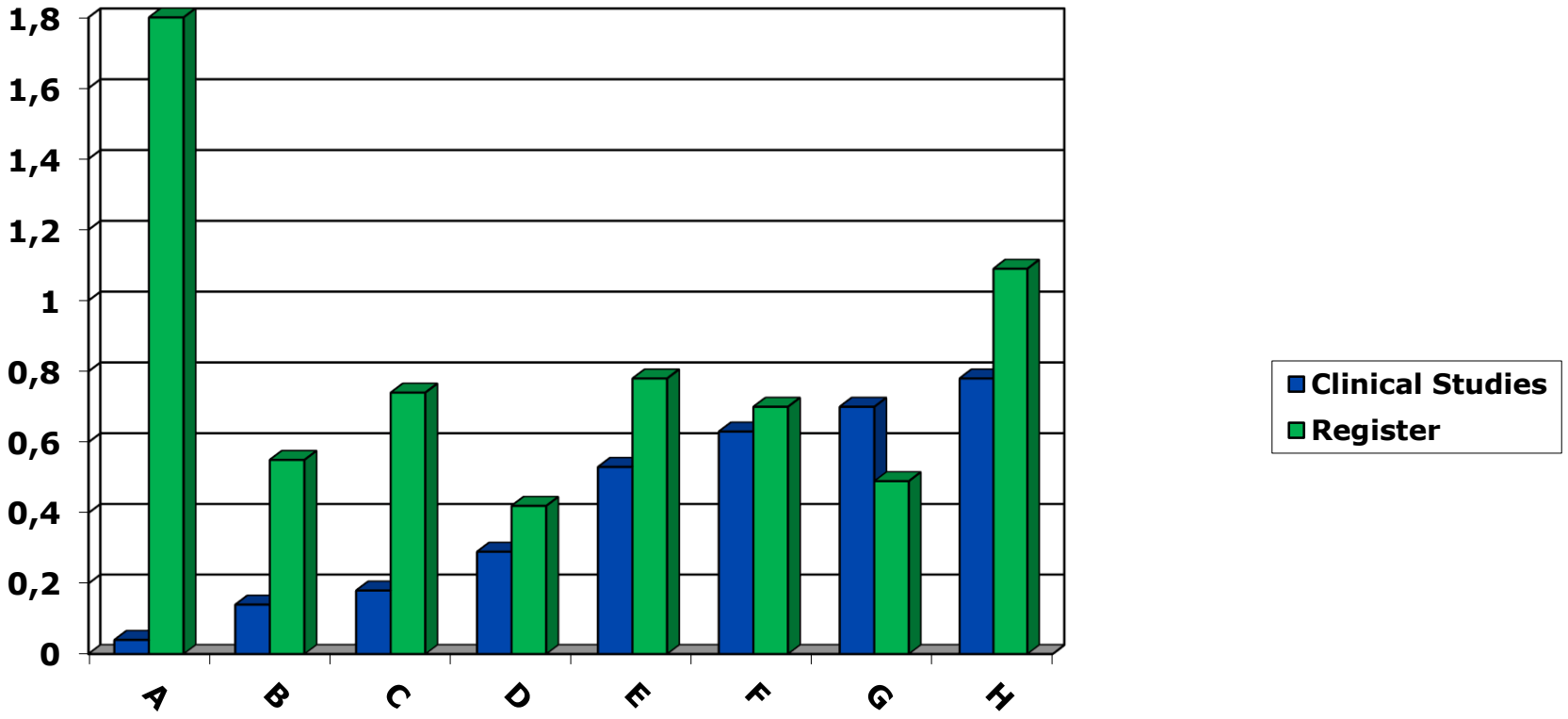
ABG I cup	1,50	n.a.	n.a.	n.a.	USA
LCS	1,46	1,17	No	No	USA
NexGen	1,45	n.a.	n.a.	n.a.	USA
MG Uni	1,44	5,20	No	No	USA
Conserve Plus	1,43	1,47	No	No	USA
Advance TKA	1,41	n.a.	n.a.	n.a.	USA
Profix	1,39	n.a.	n.a.	n.a.	USA
Triathlon TKA	1,29	n.a.	n.a.	n.a.	USA
PFC Uni	1,26	n.a.	n.a.	n.a.	USA
AML cementless stem	1,22	4,74	Yes	No	USA
Duraloc	1,21	n.a.	n.a.	n.a.	USA
Natural Knee	1,12	1,07	No	No	USA
ASR	1,06	n.a.	n.a.	n.a.	USA
Agility	1,02	2,43	No	No	USA
Kinemax TKA	0,83	2,75	No	No	USA
PFC	0,70	0,64	No	No	USA
Durom THA	0,25	n.a.	n.a.	n.a.	USA

20 Datasets too positive, 1 too negative, 3 borderline,
3 Inventor Bias ➔ 59% not reproducible

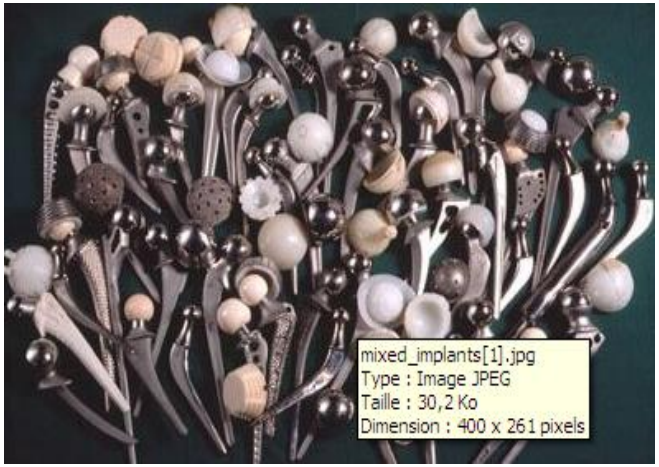
Literature Continental Europe

Implant	Factor Difference Outcome in Registers and comprehensive publications in peer reviewed journals	Factor Difference Inventor Outcome and Register outcome	Inventor Bias	Inventor Bias leading to Bias in aggregated Assessment	Region of Origin
Fitmore cup	3,22	n.a.	n.a.	n.a.	EU
Bicontact	2,80	2,11	No	No	EU
Link Uni	2,65	11,4	Yes	No	EU
Allofit cup	2,34	1,32	No	No	EU
Spotorno CLS cup	2,11	9,05	Yes	No	EU
Cormet Resurfacing	2,1	n.a.	n.a.	n.a.	EU
Hintegra	1,94	1,94	No	n.a.	EU
Alloclassic	1,84	0,87	No	No	EU
STAR	1,56	4,63	Yes	Yes	EU
Allgeretto Uni	1,45	n.a.	n.a.	n.a.	EU
SPII	0,99	n.a.	n.a.	n.a.	EU
Spotorno	0,98	1,84	No	No	EU
Müller Schaft zem	0,70	0,59	No	No	EU
RM cup	0,62	n.a.	n.a.	n.a.	EU
Lubinus-cup	0,58	n.a.	n.a.	n.a.	EU
ABG Stem	0,27	n.a.	n.a.	n.a	EU

Impact on daily decisions



Publications concerning inferior products

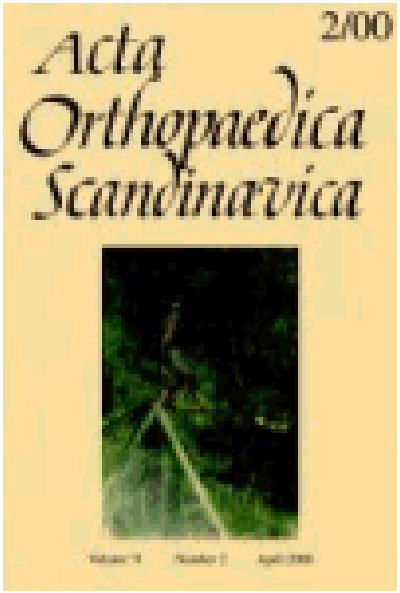


Results

12 Implants identified

- 5 of them: Not a single publication referring to Revision Rate and covering Revisions for any reason
- For 5 out of 12 implants (41%) there are no outcome studies published
- From 3 out of the remaining 7 no problems are published
- In 3 out of 7 Implants some problem could be detected, but on very small numbers.
  Too small for any clear conclusion
- No inventor studies or no revisions published
- In not a single case problems are detectable by clinical sudy review

Confounders in Individual Journals

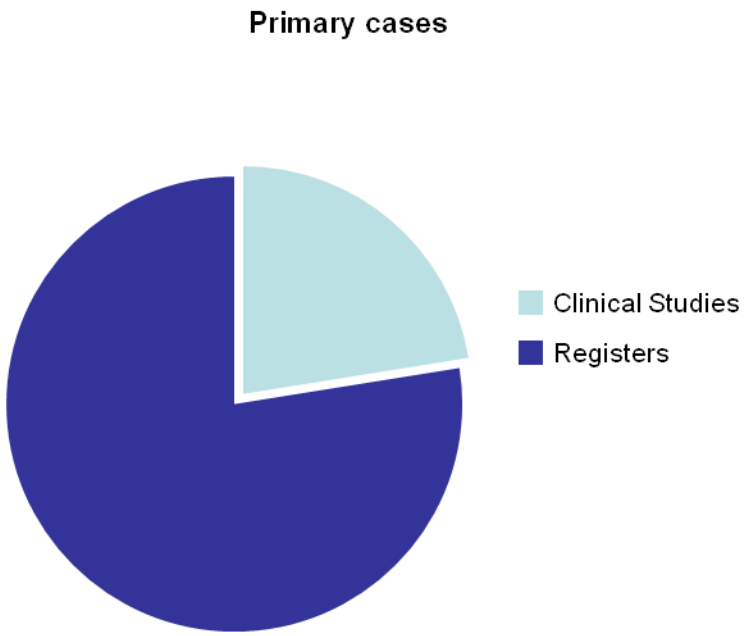


Material and Methods

- All Data concerning Total Knee Arthroplasty from the QoLA-Dataset
  - More exact since no „Mix and Match“ of components like in THA
  - 203 articles
  - About 100,000 primary cases
  - Evaluation focused on
    - Publication of inventors in specific Journals
    - Outcome published
    - Global regions

Published cases concerning TKA

- Clinical studies:
  - 170.938 Primary
  - 6.074 Revisions
- Register:
  - 589.831 Primary
  - 21.995 Revisions
- Ratio:
  - Primaries: 1:3,4
  - Revisions: 1:3,6



Results

- Publications by regions
  - Asia: 8 articles; 842 cases; 0.51 Rp100ocy
  - EU: 82 articles; 31,217 cases; 0.55 Rp100ocy
  - USA: 113 articles; 67,397 cases; 0.35 Rp100ocy

- <u>Publications worldwide:</u>
  - About 2/3 of all cases worldwide are published in US Journals
  - Average outcome published in US Journals is about 1.6 times better than in European or Asian Journals

Results

- Publications according to implant inventor status (Europe)
  - Implants, without identifiable inventor: 17 articles; 2,185 cases; 0.41 Rp100ocy
  - Inventor: 7 articles; 2,342 cases **(=7.5%)**;0.47 Rp100ocy
  - Independent:58 articles; 26,739 cases 0.47 Rp100ocy
  - Total number of cases: 31,266 cases

- Publications according to implant inventor status (USA)
  - Implants, without identifiable inventor: 11 articles; 1,581 cases; 0.28 Rp100ocy
  - Inventor: 31 articles; 36,806 cases **(=54.6%)**0.19 Rp100ocy
  - Independent:70 articles; 29,010 cases; 0.56 Rp100ocy
  - Total number of cases: 67,397 cases

Results

- <u>Publications by US research groups:</u>
  - US Journals:
    81 articles; 62,284 cases; 0.33 Rp100ocy
  - Non-US Journals (EU and Asia)
    9 articles; 4,762 cases; 0.20 Rp100ocy

Results

- Average Outcome published

  – in US Journals is (ratio:3.43; 29%) 0.35 Rp100ocy
  – In European Journals 0.55 Rp110cy
  – In Asian Journals 0.51 Rp100ocy

  – Register benchmark 1.2 Rp100ocy

Results

- 30% of all cases published worldwide are by inventors
- 55% of all cases published in US Journals are by inventors
- 97% of them are published in 2 Journals
  - JOA: 21,261 cases (=58.4%) 0.2 Rp100ocy
  - CORR: 13,978 cases (=38.4%) 0.14 Rp100ocy

  Global Register average benchmark: 1.2 Rp100ocy
- 76% (CORR) and 63% (JOA) of all cases published in these Journals are by inventors

TÜV SÜD Product Service

Choose certainty.
Add value.

Processes

BONELOC CEMENT GUN

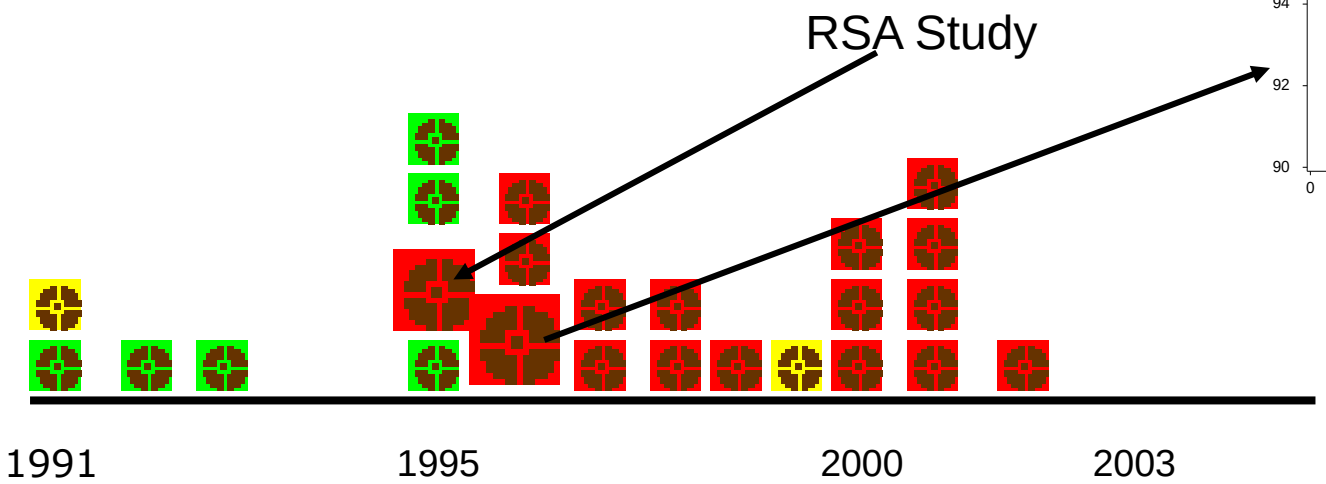
EARO
EUROPEAN ARTHROPLASTY REGISTER
NETWORK

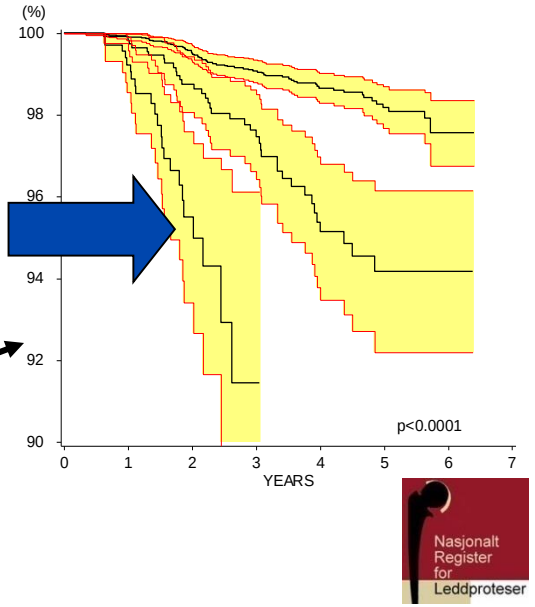
Boneloc

In favour of the product

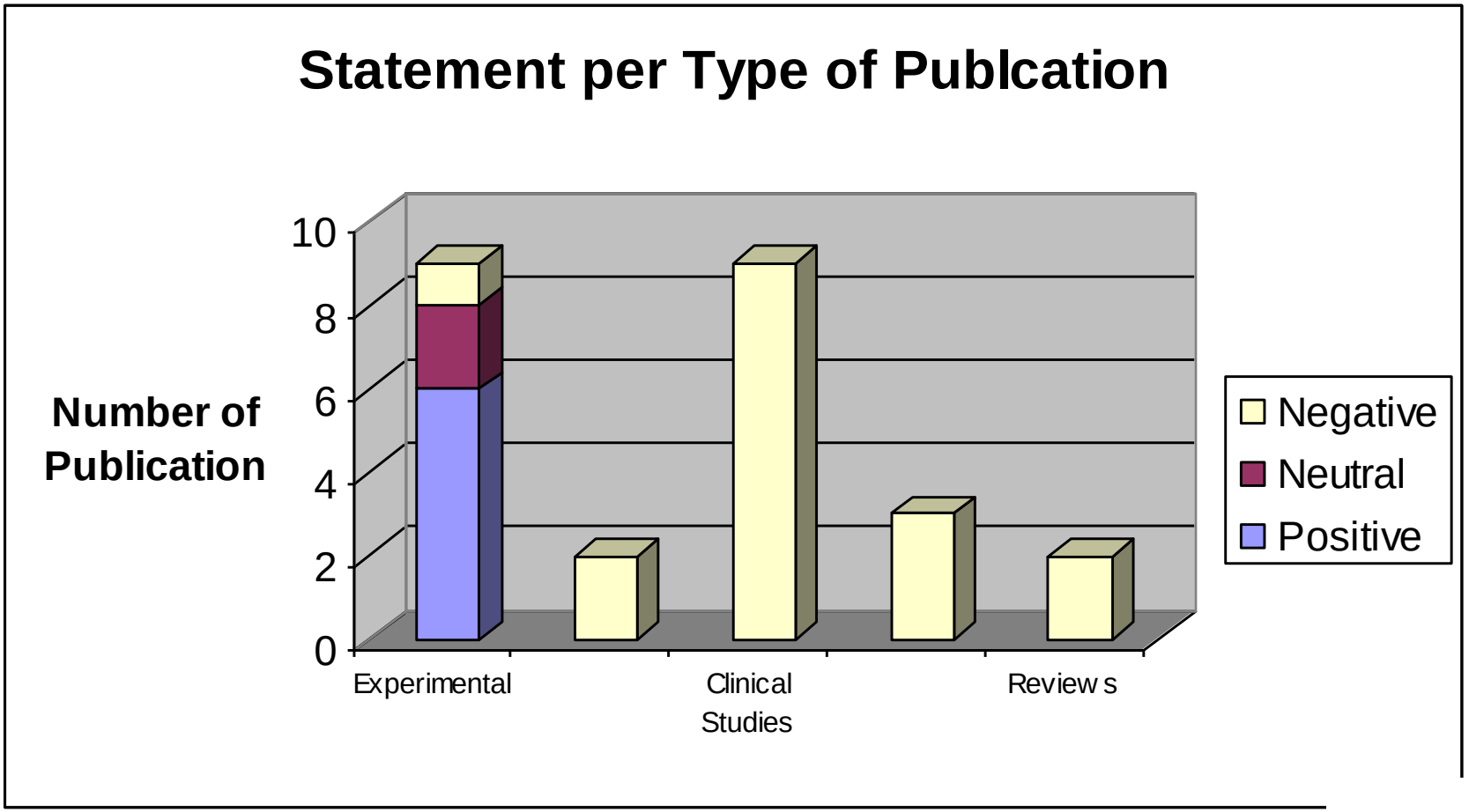
Neutral

Negative towards the product

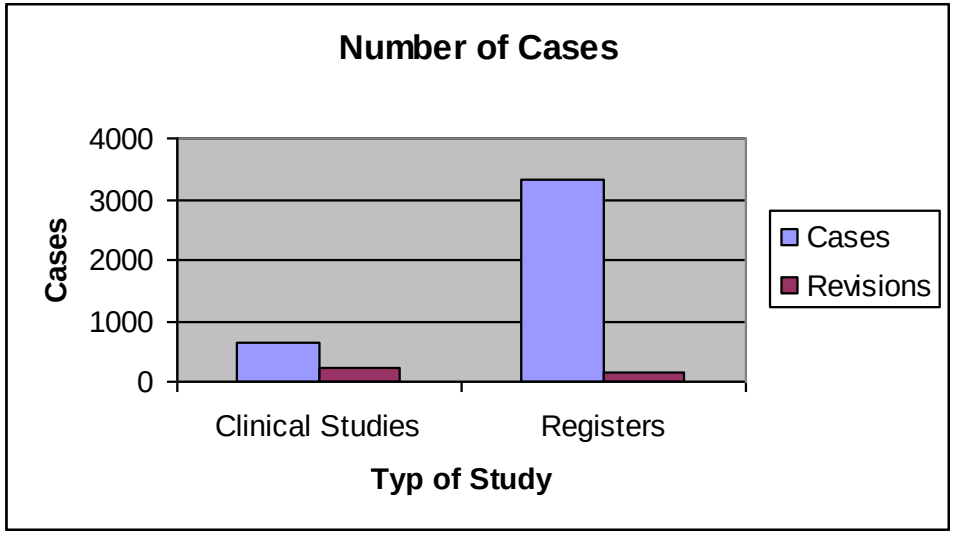




Boneloc


Statement per Type of Publcation
Number of Publication
10
8
6
4
2
0
Experimental
Clinical Studies
Reviews
Negative
Neutral
Positive

Boneloc



- Registers:
  - 3338 cases, 5648 observed component years, 166 revisions
- Clinical Studies:
  - 627 cases, 1091 observed component years, 237 revisions
- Ratio between datasets: **7.38**

Boneloc

- 1991: Boneloc on the Scandinavian market
- 19 Oct 1993: Polymers Reconstructive A/S, (Manufacturer and developer) organises a meeting in Denmark after high revision rates were reported by users. 29 surgeons of 22 (out of 42) Danish orthopaedic departments
  - Mixing device was decided to be responsible and modified afterwards
  - Personal communications of revisions, but positive publications, no overview

Riehmann M. Regulatory measures for implementing new medical device Recalling Boneloc. Dan Med Bull. 2005; 52(1): 11-17

Boneloc

- May 1994: results of evaluations of the Norwegian Arthroplasty Register
- 18 May: Presentation at the
  National orthopaedic society and
  Norwegian Board of Health
- Oct 1994: Publication at the National orthop. congress and the journal of the NBoH
  (Danish Board of Health was subscriber)
- April 1995: Danish Board of Health requests material and data from Norway
- 6 April: Manufacturer stops distribution
  30,694 units were sold in 50 countries

Boneloc

- Between Oct 94 and April 95:
  Finnish and Swedish orthopaedic societies release warnings and request from distributor (Biomet) stop of distribution – which was done

- Market figures from Norway:

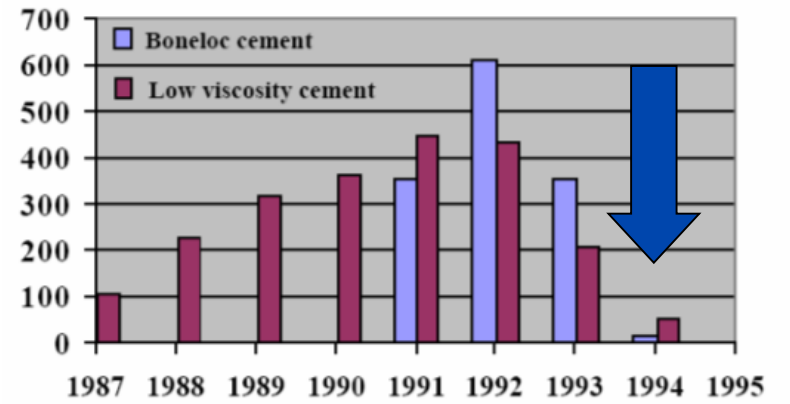


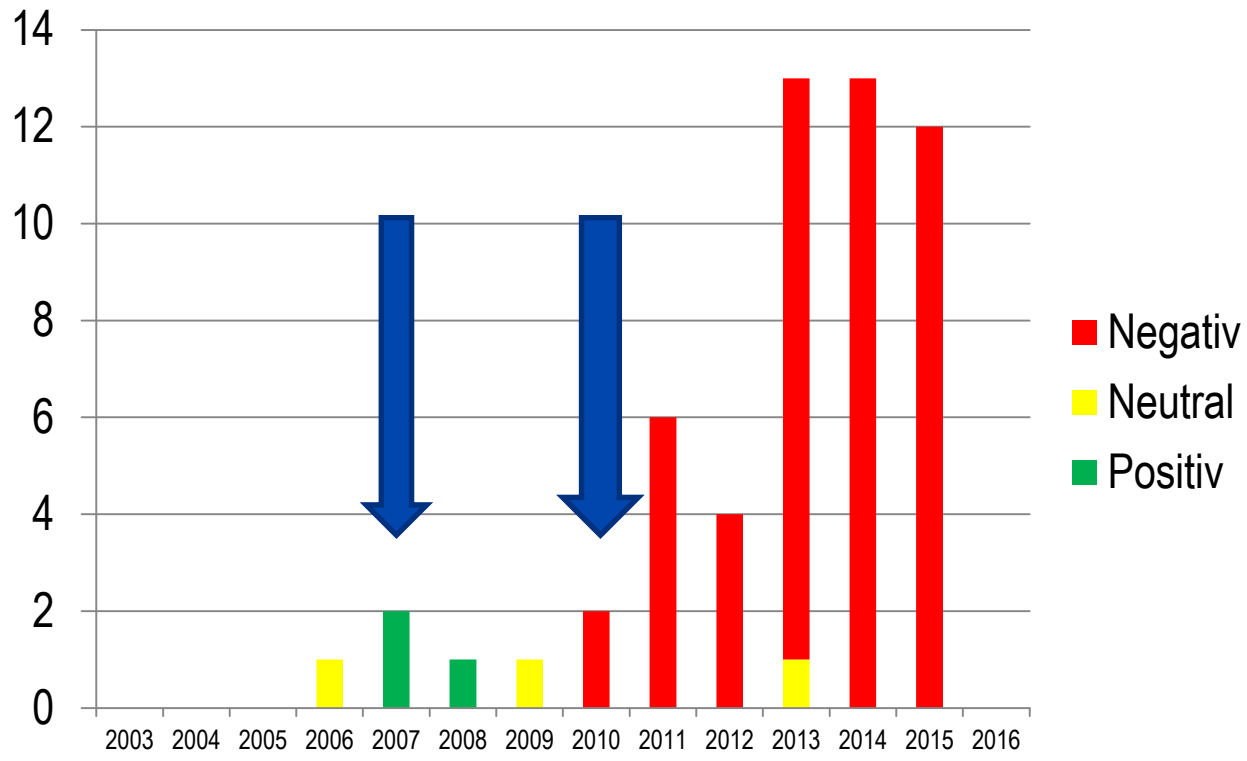
Figure 2: Annual number of hip prostheses with Boneloc or low viscosity cement

ASR Hip

- 2003: EU approval by Equivalence route (BHR), no FDA approval
- 2007: MHRA-expert board on Metal and DNA-Changes
- 2008: Haute Autorite de Sante (F): ➔ **no funding** in France
- 2009: „voluntary“ recall in Australia due to Registry
- Designers (T. Schmalzried: 3Mio$, other 500.000$,..)
- April 2010: Langdon (Univ. Hospital of North Tees)➔ high failure rates ➔ MHRA
- Early summer 2010: NJR: 7.5% revision rate ➔ MHRA
- 24.8.2010: ASR Recall

ASR Publications

- 58 Articles with clinical outcome data



Reporting Incidences

	FUP-periode	Revision rate	Primary cases	Revision cases	Observed component years	Revisions per 100 observed component years	CI	factor Difference to Register 2007
immer-Data post marketing surveillance	1,00	0,63	480	3	480,00	0,63	0,21-1,82	3,2
Zimmer ponsored study	4,50	0,00	386	0	1737,00	0,00		
Total market monitoring		0,35	866	3	2217	0,14	0,05-0,4	14,78
Examination immer USA best centres	1	0,6	1300	8	1300,00	0,62	0,31-1,21	3,25
Examination Zimmer USA all centres	1	1,5	1300	20	1300,00	1,54	1,0-2,36	1,3
Australian Arthroplasty Register 2007		2,3	341	8	408	2	0,85-3,86	
2014 Global		8,79	4541	399	33270	1,2	1,09-1,32	

Revision rate increased at the Zimmer-Investigation at a ratio of **11**

Reporting Incidences

- Austria – Recall 2004
- Removal Set
- Incentives by the System

Goals for Clinical Data by MDR + MEDDEV 2.7.1. rev 4

- Checks and Balances needed for a more robust system
- New Data sources required
- Independet data collection
- Different processes for interpretation and publication
- Independet interpretation of clinical data by expert groups
  - Metanalyses
  - Health Technology Assessment
  - Cochrane
- Real World Evidence(RWE) / Registries / Big Data

Lessons Learnt

- Many basic presumptions used for decision making based on clinical data are not correct as the database is subject of confounders
  - Users (health care providers)
  - Risk management and evaluations (manufacturers)
  - Regulators (assessment)
- ➔ incidents not identified ➔ public offenses, legal actions

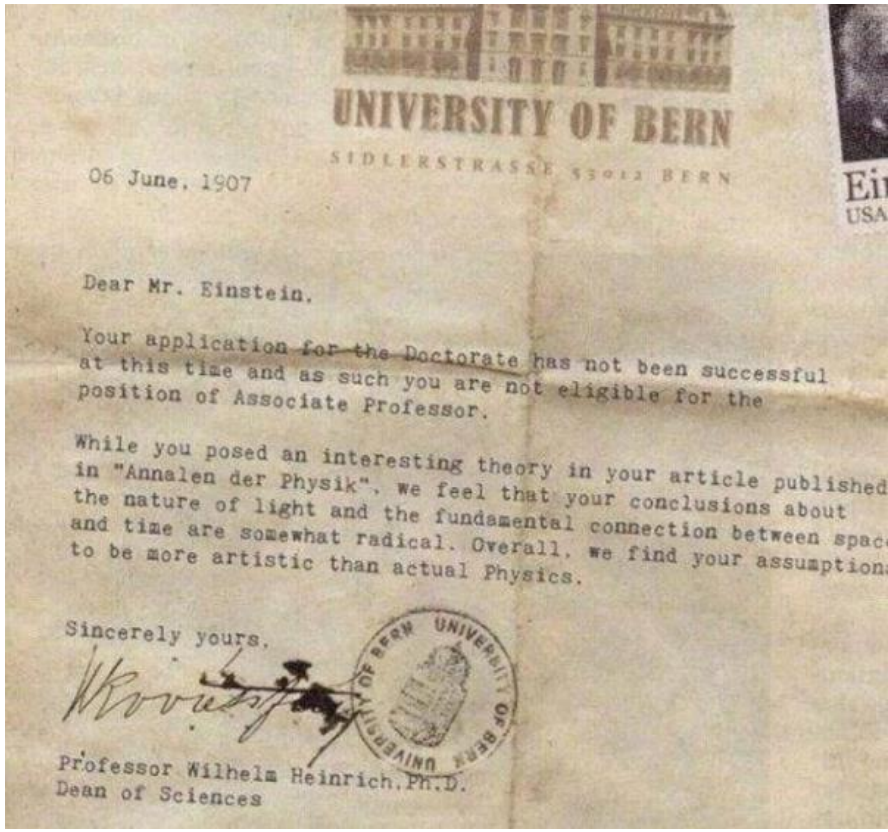
TÜVRheinland®
Genau. Richtig.

- Not exclusively due to wrong processes or personal incompetence
- Bias and structural problems in studies and research processes

- Internal limitations in research processes
- Intransparency
- ➔ Bias, controlled by interest groups

Lessons Learnt

- Journal publications are no proper predictor for problems
- Publications follow a trend
- Often a small number of author groups
  ➔ not representative
  ➔ may be wrong by chance or not
- **How to get ahead to this process and be able to react in time?**



UNIVERSITY OF BERN

SIDLERSTRASSE 5 3012 BERN

06 June, 1907

Dear Mr. Einstein,

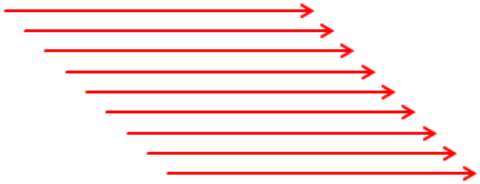
Your application for the Doctorate has not been successful at this time and as such you are not eligible for the position of Associate Professor.

While you posed an interesting theory in your article published in "Annalen der Physik", we feel that your conclusions about the nature of light and the fundamental connection between space and time are somewhat radical. Overall, we find your assumptions to be more artistic than actual Physics.

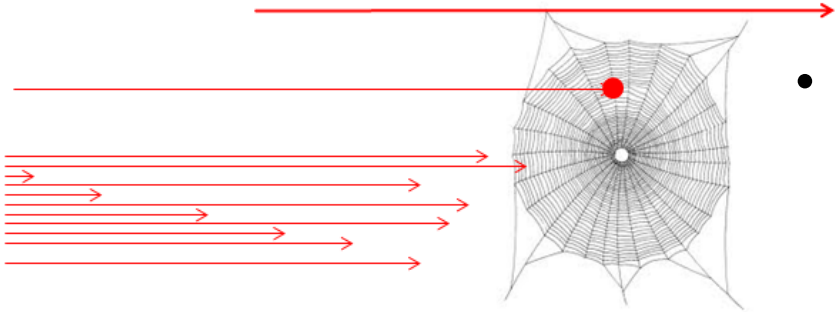
Sincerely yours,

Professor Wilhelm Heinrich, Ph.D.
Dean of Sciences

RWE and Clinical Studies



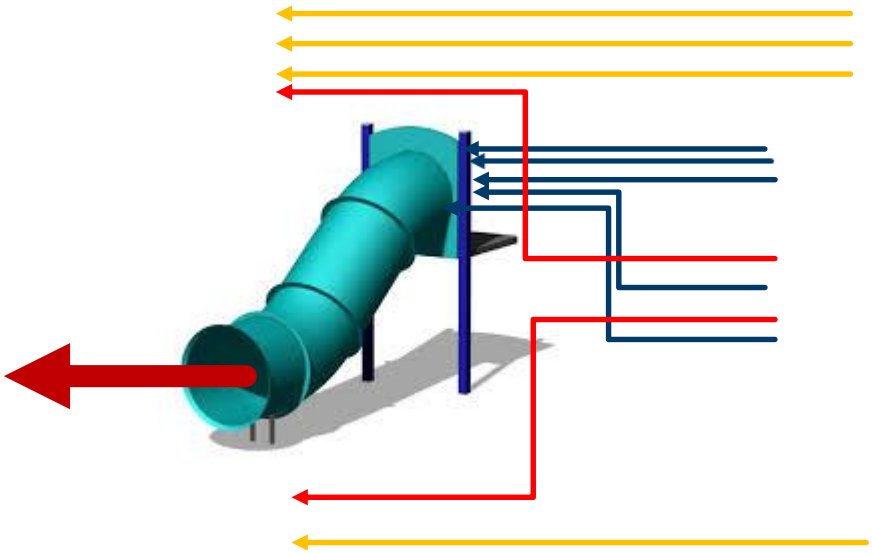
- Clinical Studies:
  - Sample Based (i.e. limited data, inclusion criteria)
  - Verfication of a Theses (Causality)
    - ➔ Bias
    - ➔ Known Risks



- Registies (Real World Evidence)
  - Large numbers (transferable?)
  - Identifcation of Correlation
    - ➔ Misinterpretation
    - ➔ Unknown Risks

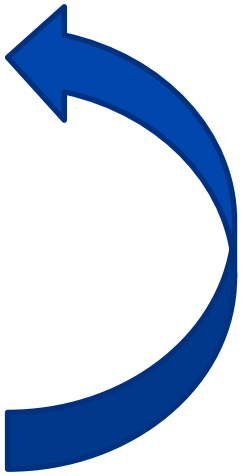
Metaanalyses, Cochrane,…

- Metaanayses:
  - Selection Criteria??
  - Methodology appropriate for Medical Devices?
  - Verfication of a Theses by Metanalysis (Causality)
    - ➔ Bias
    - ➔ Known Topics



Scientific Standards

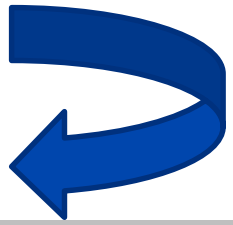
- Data acquisition (Study protocol, RCT, prospective, retrospective,…)
- Evaluation
- Conclusions
- Prepare Publication ➔ Journal submission



Transparency

- Journal:
  - Check IRB, COI
  - Peer review
- Publication in a Journal following a defined process
- Scientific Debate, Rating,

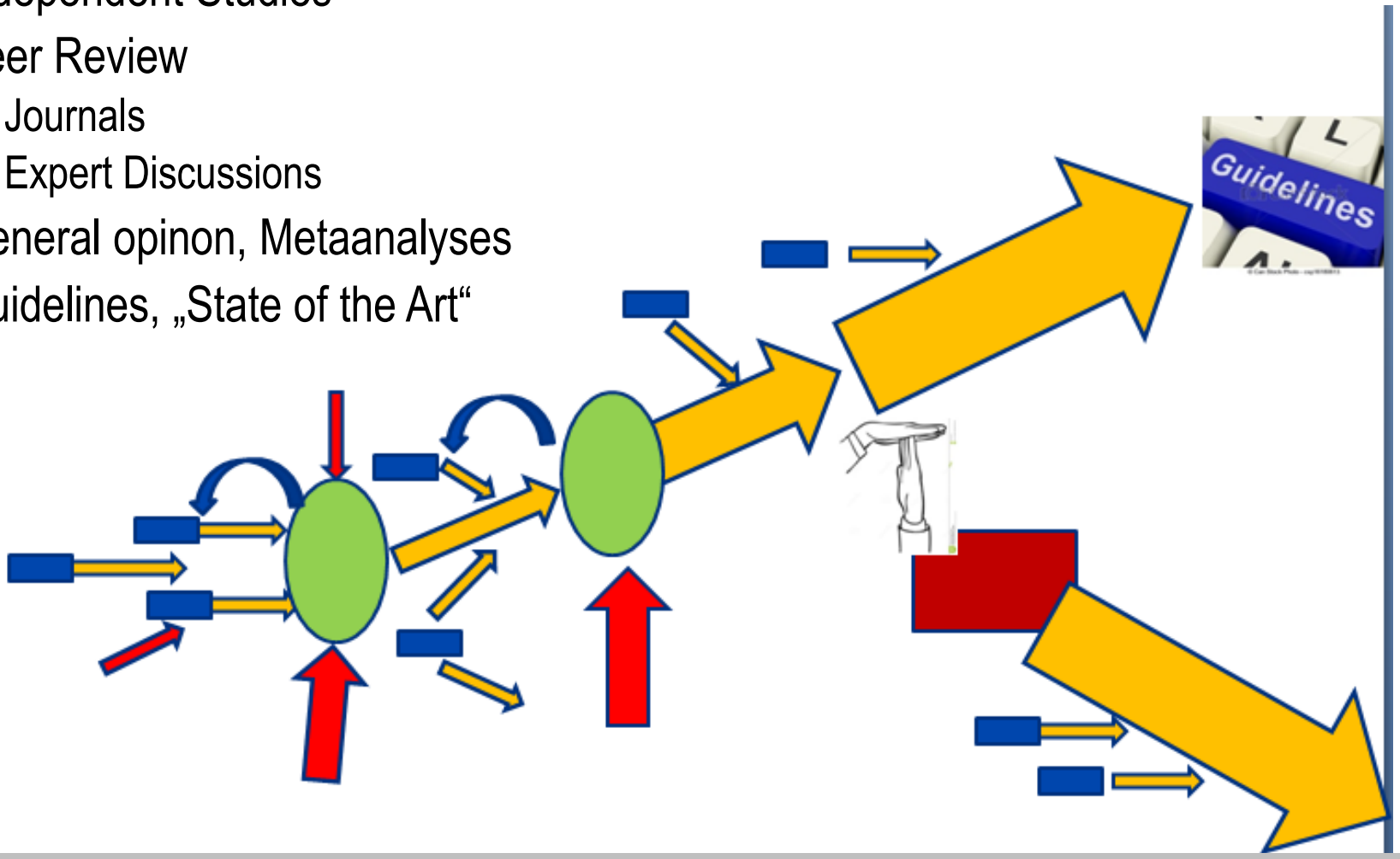
  ➔ Evidence



Selection,
prevent manipulation

Scientific Standards

- Open for everyone ➔ Study
- Independent Studies
- Peer Review
  - Journals
  - Expert Discussions
- General opinon, Metaanalyses
- Guidelines, „State of the Art“



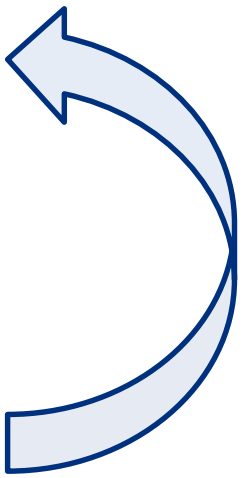
Scientific Standards RWE-Data

- Data acquisition (Study protocol, RCT, prospective, retrospective,…)
- Evaluation
- Conclusions
- Prepare Raw Report ➔ Client
  (Register boards, Public Heath Inst.))
- Journal:
  - Check IRB, COI
  - Peer review

- Publication by defined processes,
  undefined processes or keep it confidential

- Scientific Debate, Rating,

  ➔ Evidence



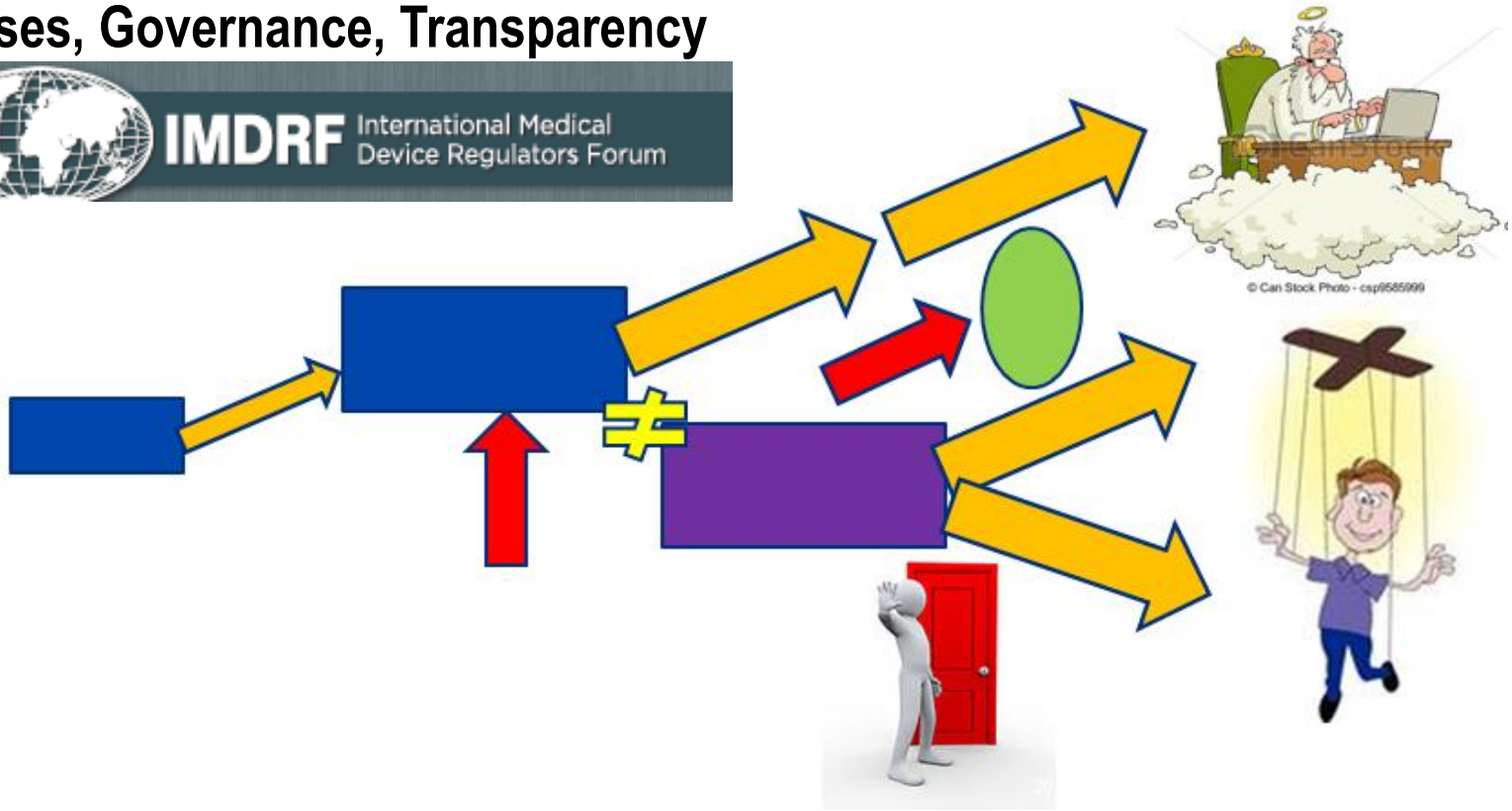
Transparency

How this can work without that??

Selection, prevent manipulation

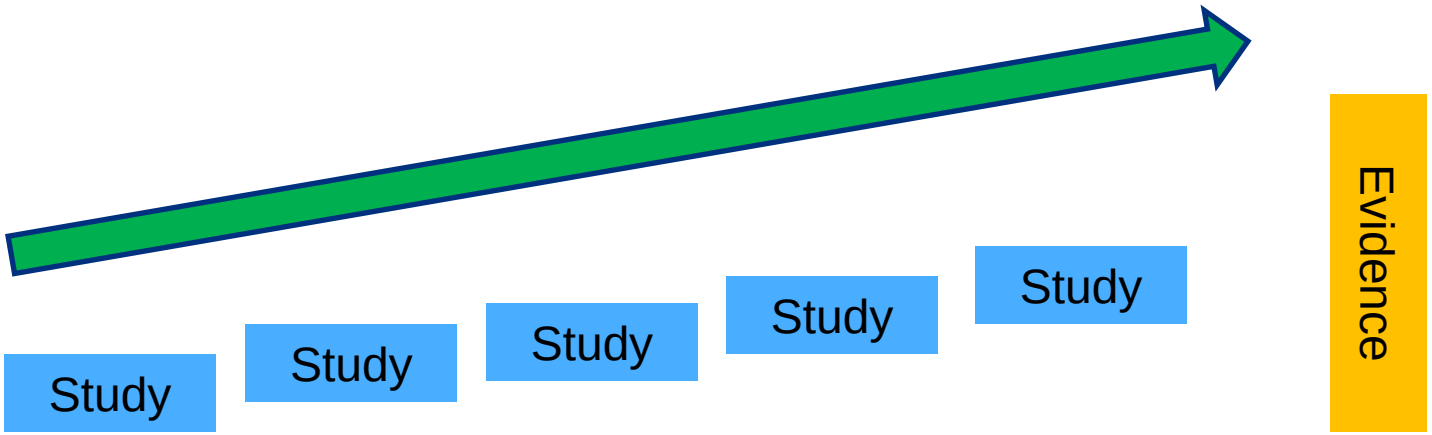
Scientific Standards – RWE Data

- One Big Dataset
- No access, No independent repetition
- Small group of decision makers
- **Processes, Governance, Transparency**



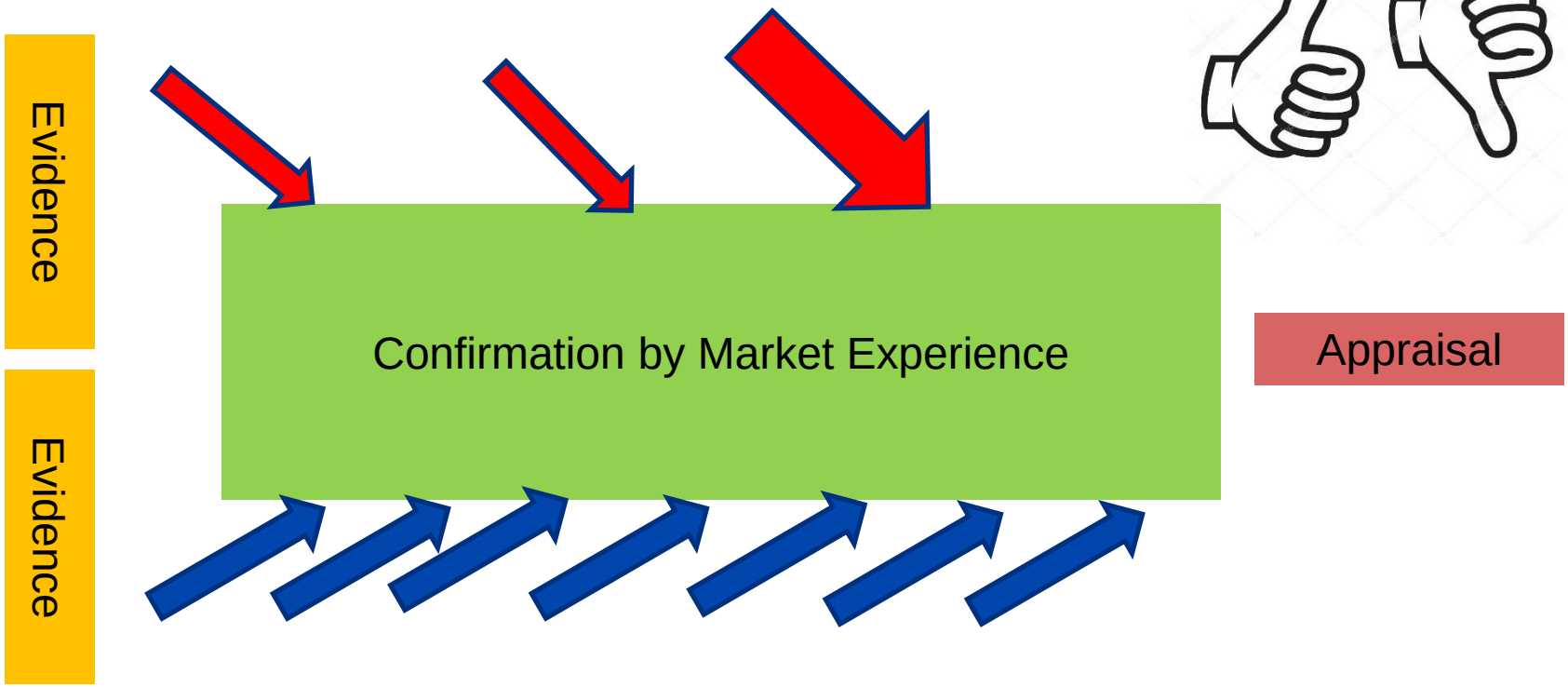
Building Evidence

- Clinical Study
  - Causality
  - Add/change 1 or a few parameters
  - Innovation



Building Evidence

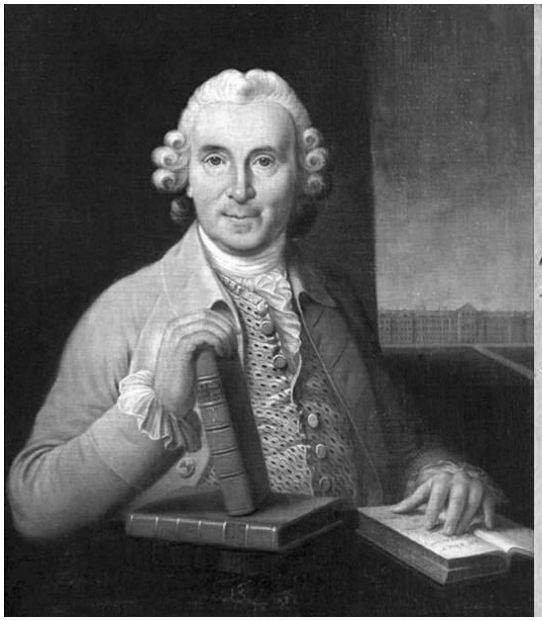
- Registry
  - Correlation
  - Observational
  - Many Impact factors/Confounders
  - Interpretation??

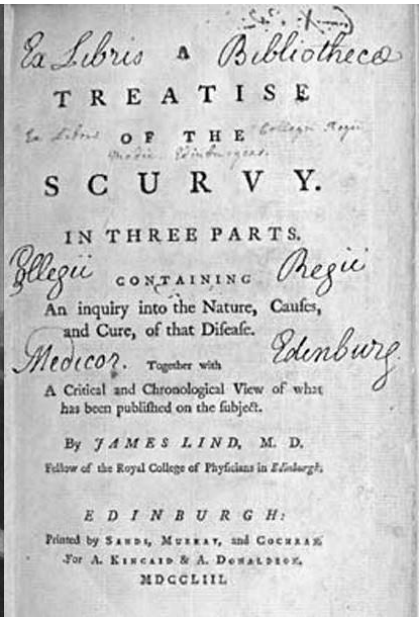


Sources Clinical Data

Milestones in Clinical Data /Research

- 1747: First controlled clinical study
  - 2 groups, 1 received lemon, one not
- Presumed: Scurvy by decay
- Experiments with acidity
- Results/interpretation not in line with Hypothesis
- Charles S. Peirce (1839-1914)
- Randomized experiments (psychology)





Ex Libris A Bibliotheca

TREATISE

OF THE

SCURVY.

IN THREE PARTS.

Collegii CONTAINING Regii

An inquiry into the Nature, Cauſes, and Cure, of that Diſeaſe.

Medicor. Together with Edinburg.

A Critical and Chronological View of what has been publiſhed on the ſubject.

By JAMES LIND, M. D.

Fellow of the Royal College of Phyſicians in Edinburgh.

EDINBURGH:

Printed by SANDS, MURRAY, and COCHRAN;

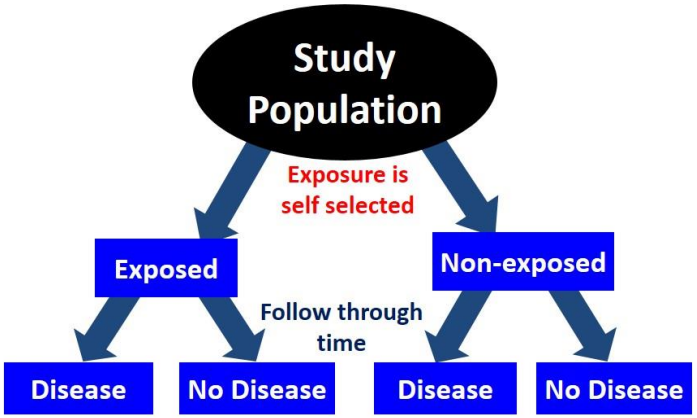
For A. KINCAID & A. DONALDSON.

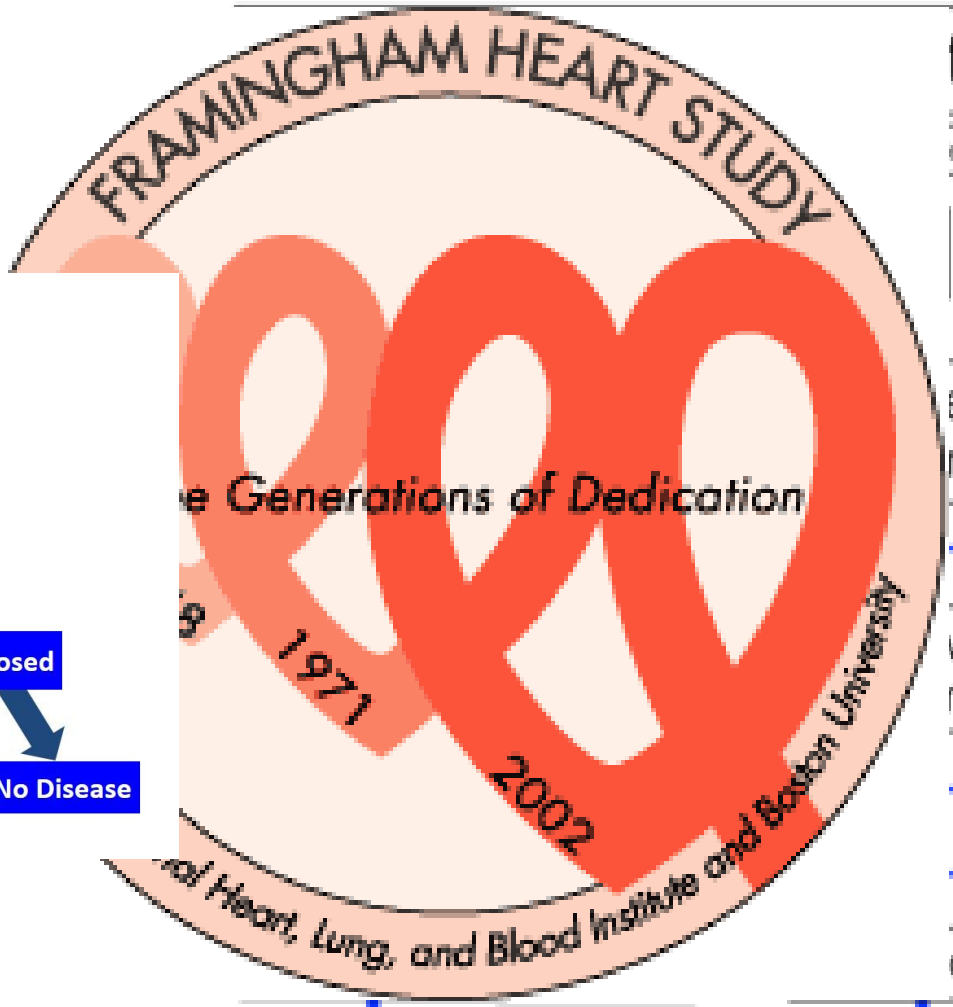
MDCCLIII.

Dr. James Lind (1716-1794)

Milestones in Clinical Data /Research

1948: 1st RCT (Streptc





	Types of Studies			
	Therapeutic Studies—Investigating the Results of Treatment	**Prognostic Studies—Investigating the Effect of a Patient Characteristic on the Outcome of Disease**	**Diagnostic Studies—Investigating a Diagnostic Test**	**Economic and Decision Analyses—Developing an Economic or Decision Model**
Level I	• High-quality randomized controlled trial with statistically significant difference or no statistically significant difference but narrow confidence intervals • Systematic review[2] of Level-I randomized controlled trials (and study results were homogeneous[3])</td>	• High-quality prospective study[4] (all patients were enrolled at the same point in their disease with ≥80% follow-up of enrolled patients) • Systematic review[2] of Level-I studies	• Testing of previously developed diagnostic criteria in series of consecutive patients (with universally applied reference "gold" standard) • Systematic review[2] of Level-I studies	• Sensible costs and alternatives; values obtained from many studies; multiway sensitivity analyses • Systematic review[2] of Level-I studies
Level II	• Lesser-quality randomized controlled trial (e.g., <80% follow-up, no blinding, or improper randomization) • Prospective comparative study[4] [5] • Systematic review[2] of Level-II studies or Level-I studies with inconsistent results	• Retrospective study[6] • Untreated controls from a randomized controlled trial • Lesser-quality prospective study (e.g., patients enrolled at different points in their disease or <80% follow-up) • Systematic review[2] of Level-II studies	• Development of diagnostic criteria on basis of consecutive patients (with universally applied reference "gold" standard) • Systematic review[2] of Level-II studies	• Sensible costs and alternatives; values obtained from limited studies; multiway sensitivity analyses • Systematic review[2] of Level-II studies
Level III	• Case-control study[7] • Retrospective comparative study[6] [5] • Systematic review[2] of Level-III studies	• Case-control study[7]	• Study of nonconsecutive patients (without consistently applied reference "gold" standard) • Systematic review[2] of Level-III studies	• Analyses based on limited alternatives and costs; poor estimates • Systematic review[2] of Level-III studies
Level IV	• Case series[8]	• Case series	• Case-control study • Poor reference standard	• No sensitivity analyses
Level V	• Expert opinion	• Expert opinion	• Expert opinion	• Expert opinion

1. A complete assessment of the quality of individual studies requires critical appraisal of all aspects of the study design.
2. A combination of results from two or more prior studies.
3. Studies provided consistent results.
4. Study was started before the first patient enrolled.
5. Patients treated one way (e.g., with cemented hip arthroplasty) compared with patients treated another way (e
6. Study was started after the first patient enrolled.
7. Patients identified for the study on the basis of their outcome (e.g., failed total hip arthroplasty), called "cases," a
(e.g., had a successful total hip arthroplasty), called "controls."
8. Patients treated one way with no comparison group of patients treated another way.

JBJS The Journal of Bone & Joint Surgery

	Types of Studies			
	Therapeutic Studies—Investigating the Results of Treatment	**Prognostic Studies—Investigating the Effect of a Patient Characteristic on the Outcome of Disease**	**Diagnostic Studies—Investigating a Diagnostic Test**	**Economic and Decision Analyses—Developing an Economic or Decision Model**
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5. Patients treated one way (e.g., with cemented hip arthroplasty) compared with patients treated another way (e.g., with cementless hip arthroplasty) at the same institution.
6. e.g., with cementless hip arthroplasty) at the same institution.
7. Patients identified for the study on the basis of their outcome (e.g., failed total hip arthroplasty), called "cases," are compared with those who did not have the outcome (e.g., had a successful total hip arthroplasty), called "controls."
8. Patients treated one way with no comparison group of patients treated another way.

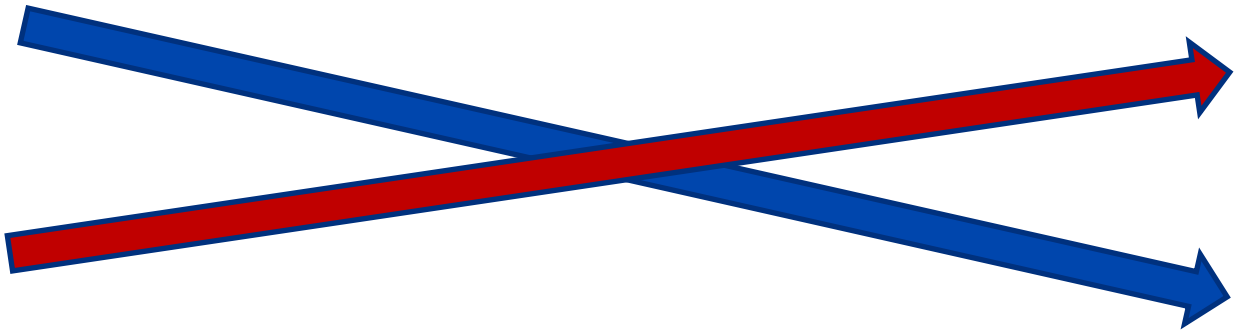
Evaluation of Clinical Data

Confounders

Statistics
(N Patients, Data – Nominal, ordinal. Metric,.)

Methodology
(Selection Bias, Documentation Bias,…)

Treatment Outcome
(Users, Patients, Implantation,…)



RCT

Registries

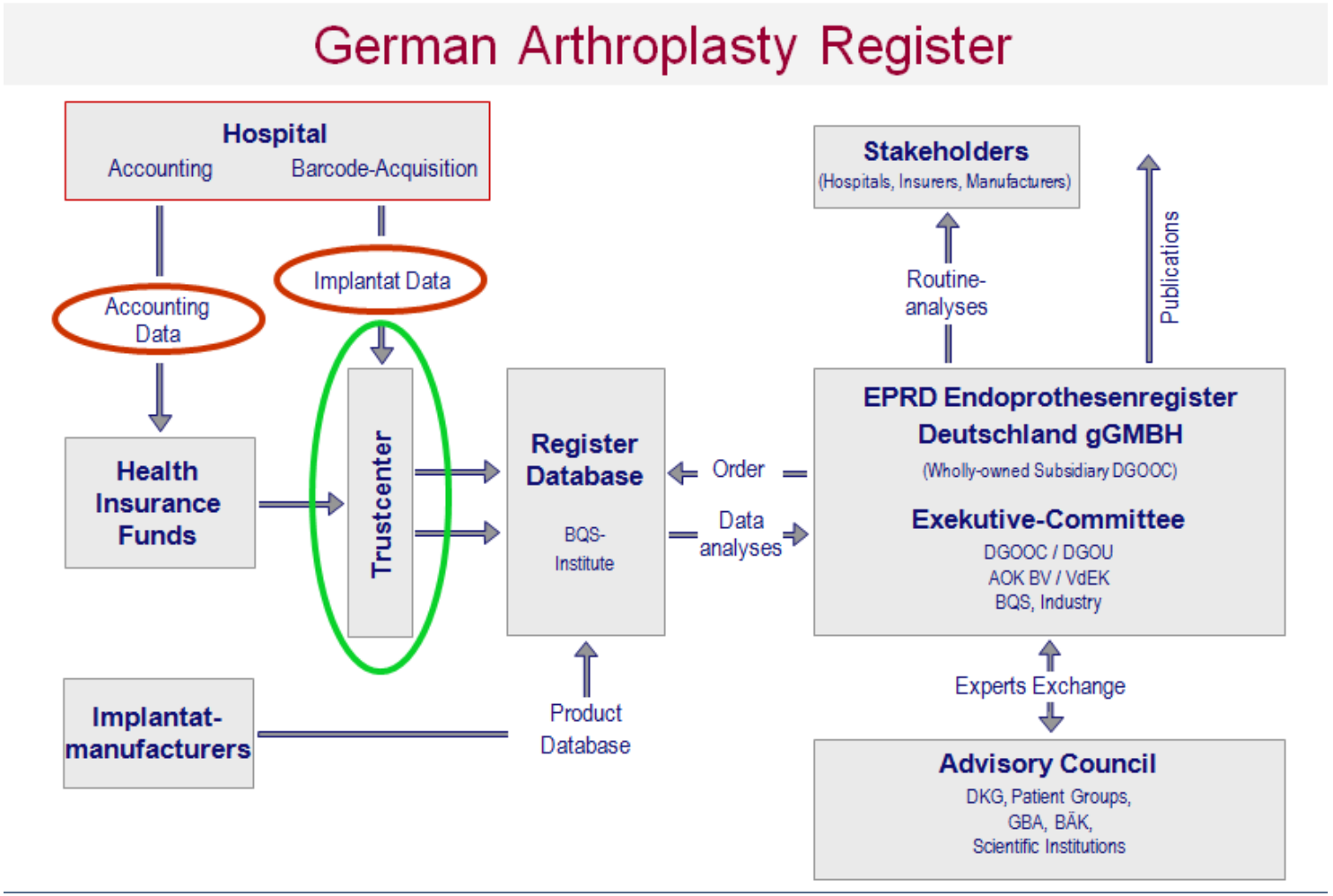
Pharma

Med. Dev.

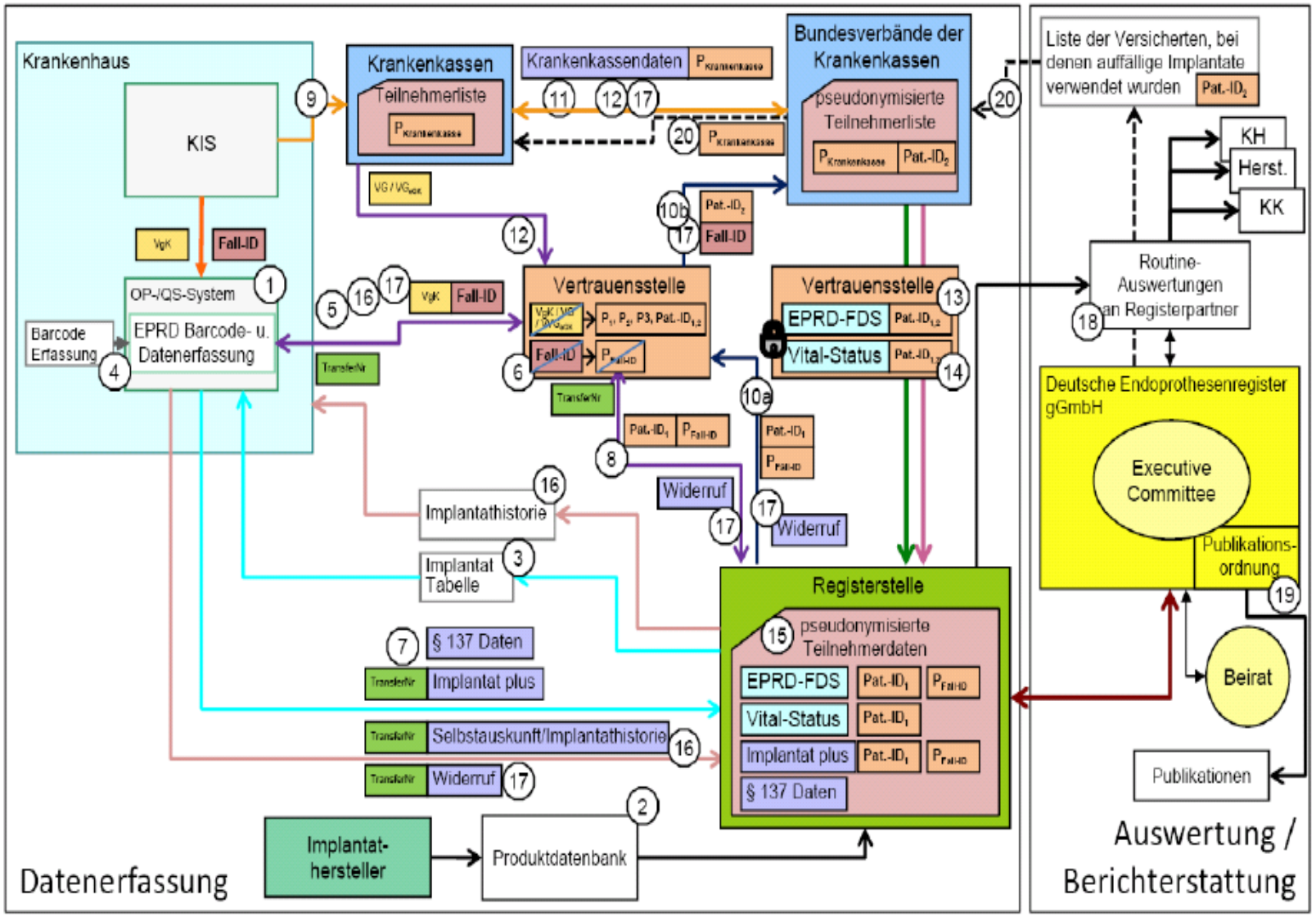
Metaanalyses

Follow Up Studies

Organisation of a Register

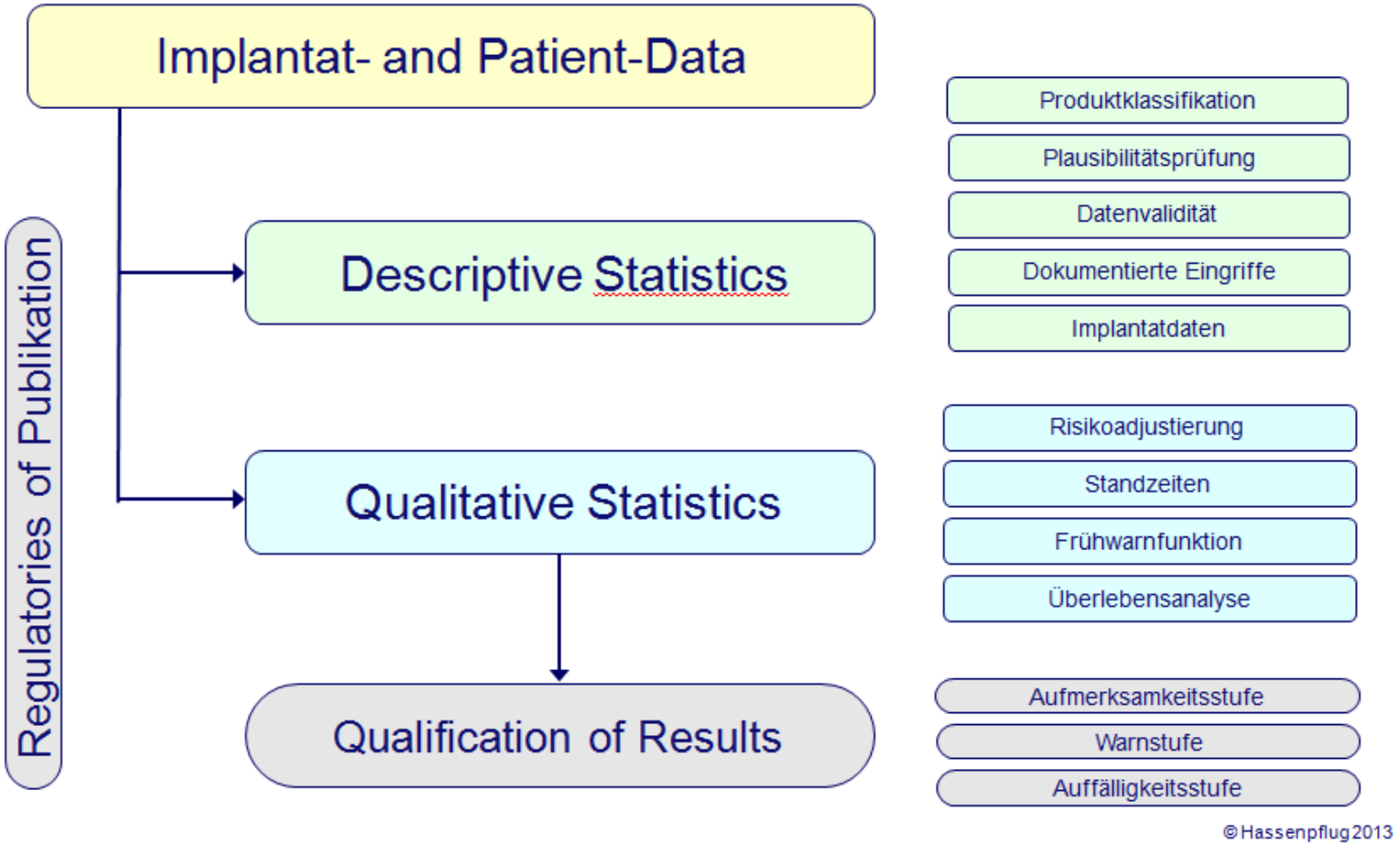


Organisation of a Register

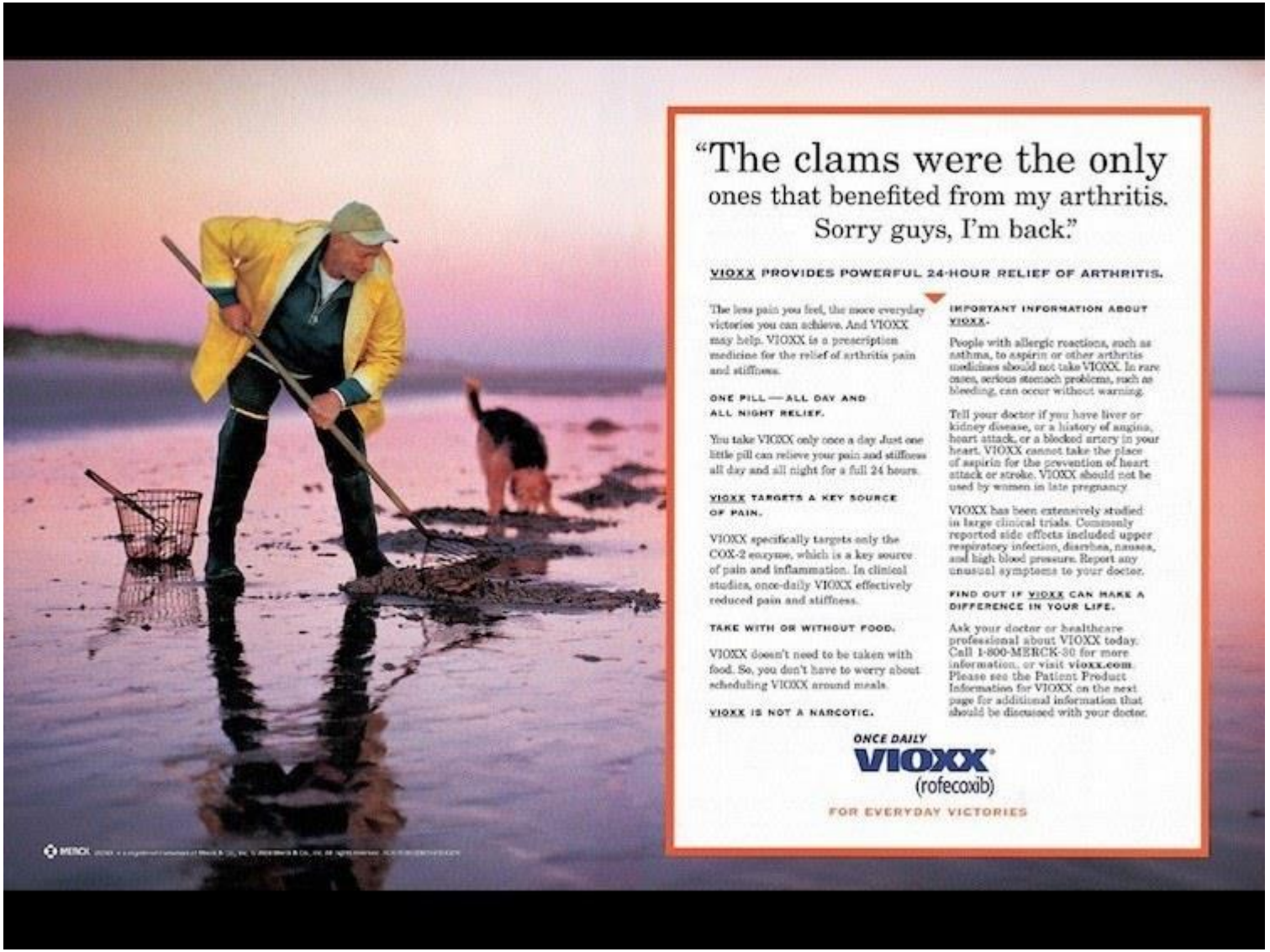


Organisation of a Register

Structure of Evaluation



Recalls based on RWE-Data



Recalls based on RWE-Data

Frankfurter Allgemeine
FAZ.NET

Home | Politik | **Wirtschaft** | Feuilleton | Sport | Gesellschaft

30. Mai 2010 | Reise | Wissen | Auto | Computer | Beruf & Chance | Kunstmarkt | Im

Aktuell › **Wirtschaft**

Vioxx-Skandal

Artikel-Services

Vioxx wohl für bis zu 140.000 Herzinfarkte verantwortlich

Zuerst verboten, nun doch veröffentlicht: Nach einer Studie des stellvertretenden Leiters der amerikanischen Zulassungsbehörde für Arzneimittel ist das Merck-Medikament wohl für bis zu 140.000 Herzinfarkte verantwortlich.

Stellvertretender Leiter der FDA David Graham

25. Januar 2005 Das Schmerzmittel Vioxx ist nach einer Studie seit seiner Markteinführung 1999 in den Vereinigten Staaten wahrscheinlich für bis zu 140.000 teilweise tödliche Herzinfarkte verantwortlich.

Die britische Medizinzeitschrift „The Lancet" veröffentlichte am Dienstag im Internet eine entsprechende Studie von David Graham, dem stellvertretenden Leiter der Abteilung der amerikanischen Zulassungsbehörde für Medikamente FDA (Food and Drug Administration), die Arzneien auf ihre Unbedenklichkeit prüft. Die Untersuchung ist von der FDA allerdings nicht freigegeben worden.

Anzeige

Recalls based on RWE-Data

Recalls based on RWE-Data

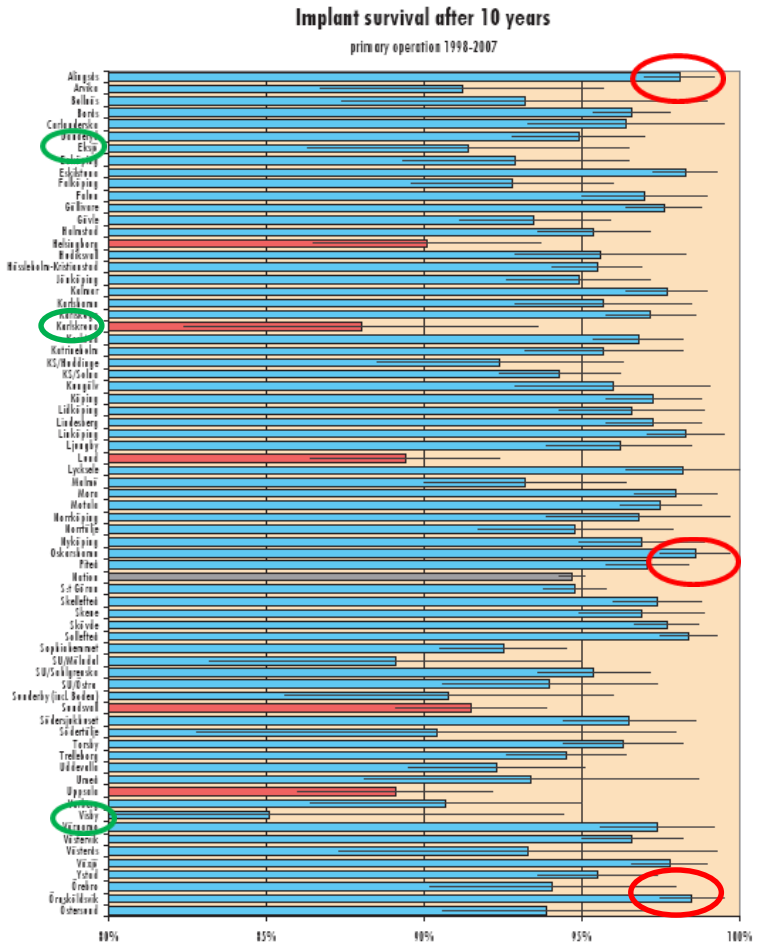
Recalls based on RWE-Data

Interpretation of Register Data
Limitation of Register data

Selection

	S	N	SF	DK	AUS	NZ	GB
AGC	0,94	0,56	0,76	2,39	0,77	0,38	
NexGen	0,37/ 2,71				1,55	1,66	1,27
Oxford Uni	0,86		1,17		0,97		
Duraloc	1,04			1,02	0,86		1,14
PFC	0,91			1,44	1,03	1,02	0,88

Selection

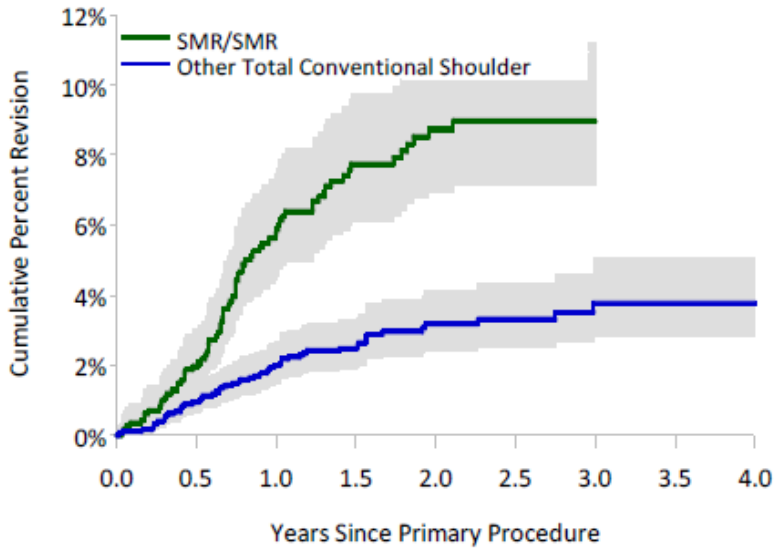


Implant survival after 10 years by department. Grey bar indicates national average. Red bars represent departments whose upper confidence interval is below the national lower competence interval, i.e. departments which with 95% probability have poorer implant survival after 10 years than the average for the country. The primary operations were conducted during the most recent 10-year period.

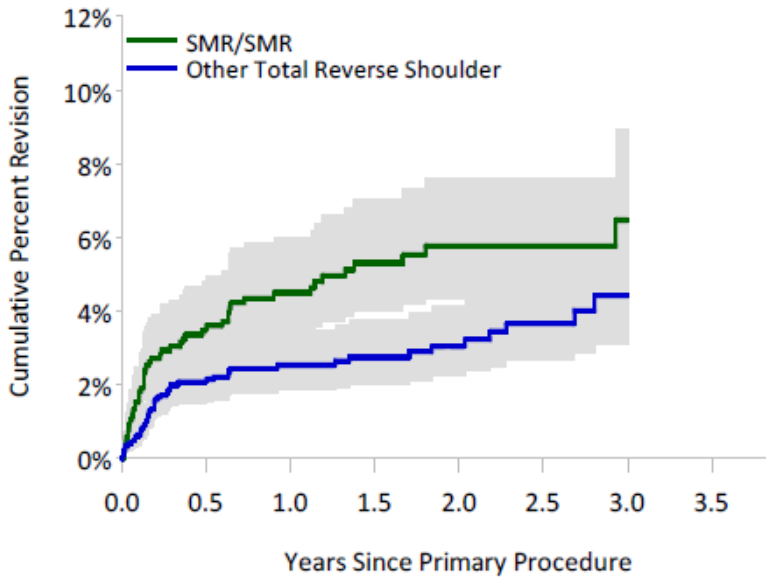
- > 500% Deviation of values on hospital level
- Sweden: best case scenario
  - Registries decrease the deviation
  - Improvement or dissemination of poor performers

Hypothesis

Newly Identified



Re-identified and still used



Hypothesis

Total Conventional

The SMR/SMR prosthesis is newly identified and has been used in 1,170 procedures. It has a three year cumulative percent revision of 9.0% and has a higher rate of revision compared to all other total conventional shoulder prostheses (adj HR=2.72 (1.94, 3.82),p<0.001). Of the 74 revisions, 30 have been revised for instability/dislocation and 24 for rotator cuff insufficiency

Total Reverse

The Registry has re-identified the SMR/SMR total reverse shoulder prostheses combination. The SMR/SMR has been used in 1,055 procedures. It has a three year cumulative percent revision of 6.5% and has a higher risk of revision compared to all other total reverse shoulder prostheses (adj HR=1.73 (1.17, 2.57),p=0.006). Of the 51 revisions, 17 have been revised for loosening and 25 for instability/dislocation.

- Majority of revisions due to rotator cuff insufficiancy and dislocation
- Most modular system on the market
  ➔ more complect cases
  ➔ earlier revisions at modular systems (Patella replacement at TKA)
- **case mix!!!!**

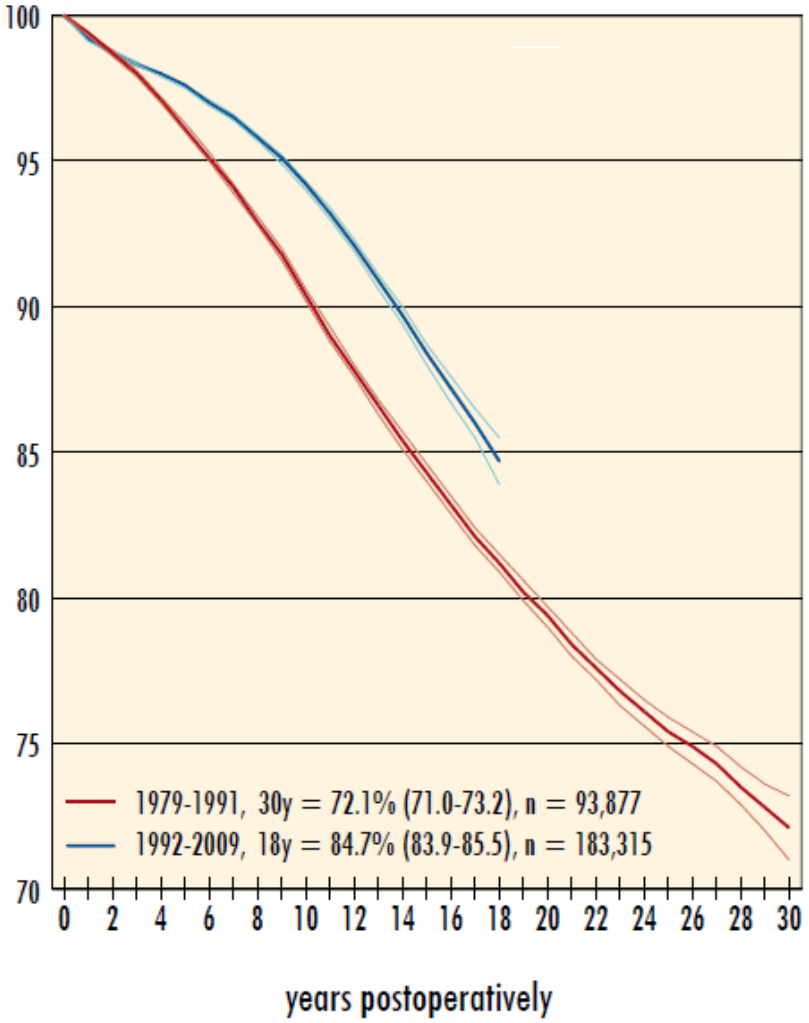
Documentation

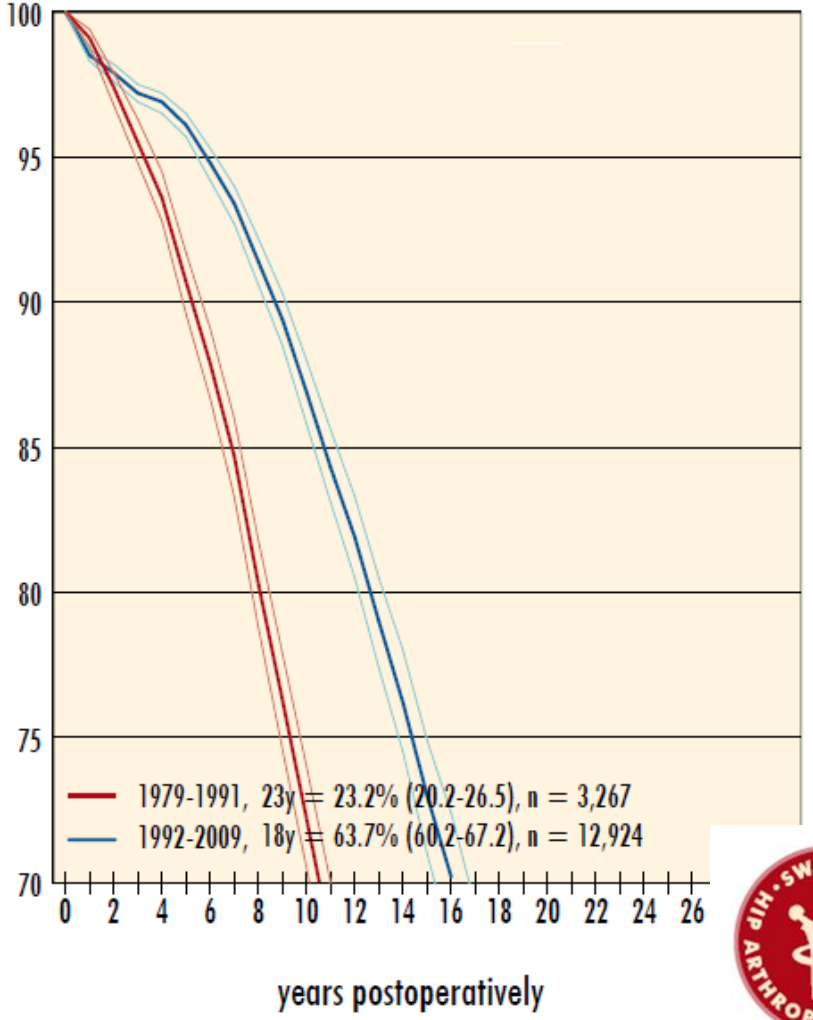
Questionaires and evaluations????
General (legal) background????

Country	Aseptic loosening	instability	technical failures	pain	fracture of inlay	septic loosening/ infection	Periprosthei c Fracture
Sweden	40%	12,50%	11%	6,60%	10%	5%	
Finland	39%	39%	8%		5%	7%	1,70%
Norway	39%	14%	21%	15%	6%	6%	3%
New Zealand	41%			33%		5%	
Australia	41,20%	8,10%	0,70%	3,10%	8,10%	11,50%	3,40%

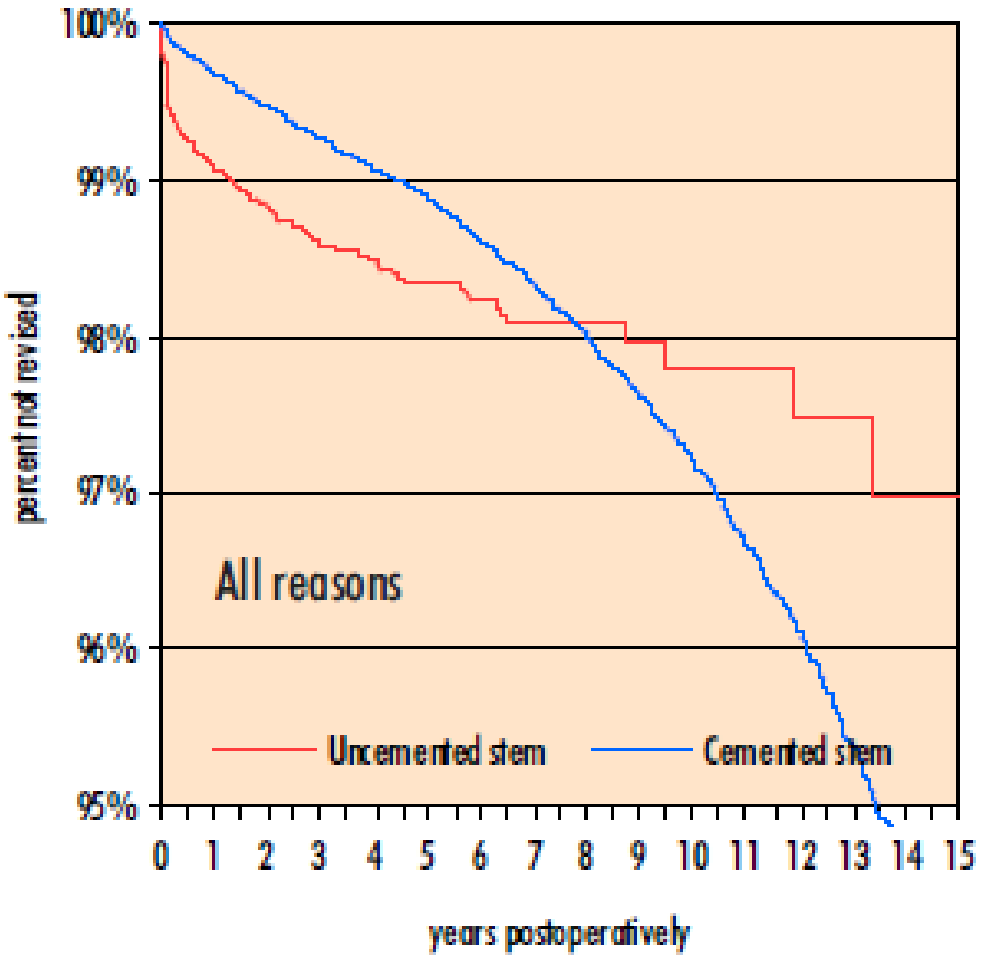
NZ: Not included in the questionair

Evaluation


100
95
90
85
80
75
70
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
1979-1991, 30y = 72.1% (71.0-73.2), n = 93,877
1992-2009, 18y = 84.7% (83.9-85.5), n = 183,315
years postoperatively


100
95
90
85
80
75
70
0 2 4 6 8 10 12 14 16 18 20 22 24 26
1979-1991, 23y = 23.2% (20.2-26.5), n = 3,267
1992-2009, 18y = 63.7% (60.2-67.2), n = 12,924
years postoperatively

Evaluation

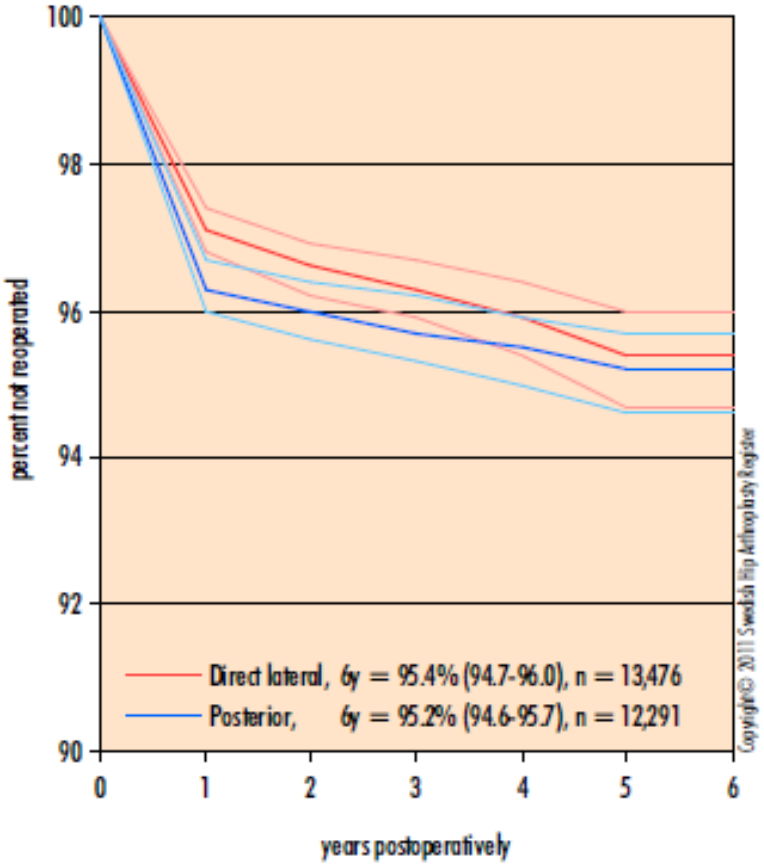


Most popular stems

Learning curves, implant selection (cemented; only the best remaining after years) excluded

Type of approach

2005-2010



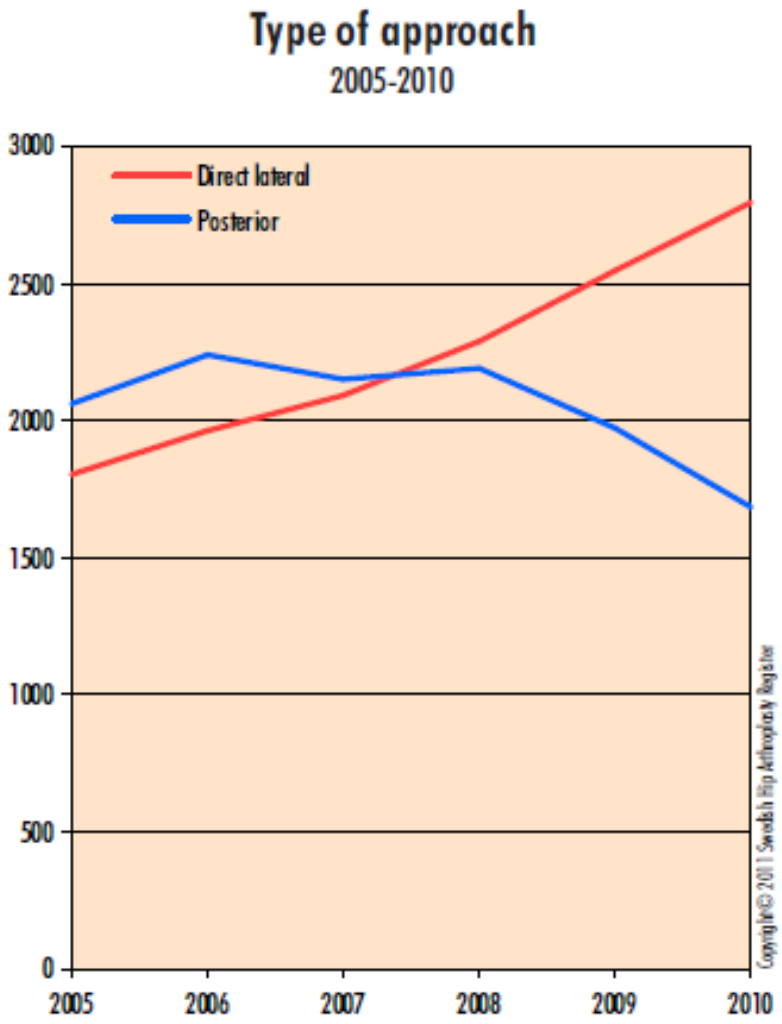

Type of approach
2005-2010
3000
2500
2000
1500
1000
500
0
Direct lateral
Posterior
2005
2006
2007
2008
2009
2010
Copyright© 2011 Swedish Hip Arthroplasty Register

Figure 3.

Operativ adgang ved primæroperationer

Operativ adgang	1995-2008 n	1995-2008 %	2009 n	2009 %	2010 n	2010 %	Total n	Total %
Bagre	75285	88.6	8767	92.3	8556	95.6	92608	89.5
Lateral	6752	7.9	366	3.9	364	4.1	7482	7.2
Minimal invasiv surgery	2383	2.8	309	3.3	8	0.1	2700	2.6
Forreste	320	0.4	26	0.3	13	0.1	359	0.3
Andet	151	0.2	22	0.2	0	0	173	0.2
Missing	70	0.1	6	0.1	2	0.0	78	0.1
Konventionel teknik	20	0.0	0	0	4	0.0	24	0.0
I alt	**84981**	**100.0**	**9496**	**100.0**	**8947**	**100.0**	**103424**	**100.0**

Registries are like an Exit Poll

Tab. 28. Primary THA – surgical approaches

Year	Ante-rior	Antero-lat.	Lateral	Poster.	T-tomy	MIS	Not Identif.
2003	2	815	936	334	0	0	32
2004	13	1 297	1 173	579	0	4	20
2005	20	1 380	894	634	0	24	24
2006	8	1 560	1 314	680	4	9	20
2007	10	1 855	1 544	816	4	11	20
2008	5	2 116	1 434	829	3	2	22
2009	6	2 151	1 745	850	2	1	12
2010	5	2 614	1 434	909	5	2	1

Registries are Exit Polls

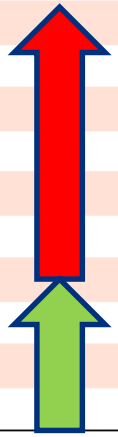
Show the common view of users on a topic ➔ Trend analysis

➔ signals for problems, if yes, interpretation (i.e. related to our topic??)

Computernavigation

Table 32: Primary operations - Total knee prostheses

Year	Yes	No	Missing	Total
2014	417 (8%)	3 868 (78%)	645 (13%)	**4 930**
2013	381 (8%)	3 382 (75%)	722 (16%)	**4 485**
2012	416 (9%)	3 297 (75%)	681 (15%)	**4 394**
2011	442 (11%)	3 175 (78%)	445 (11%)	**4 062**
2010	658 (17%)	3 111 (79%)	185 (5%)	**3 954**
2009	761 (19%)	3 062 (77%)	159 (4%)	**3 982**
2008	741 (21%)	2 641 (75%)	146 (4%)	**3 528**
2007	374 (12%)	2 619 (84%)	119 (4%)	**3 112**
2006	253 (9%)	2 334 (87%)	109 (4%)	**2 696**
2005	185 (7%)	2 332 (84%)	272 (10%)	**2 789**



Nasjonalt Register for Leddproteser

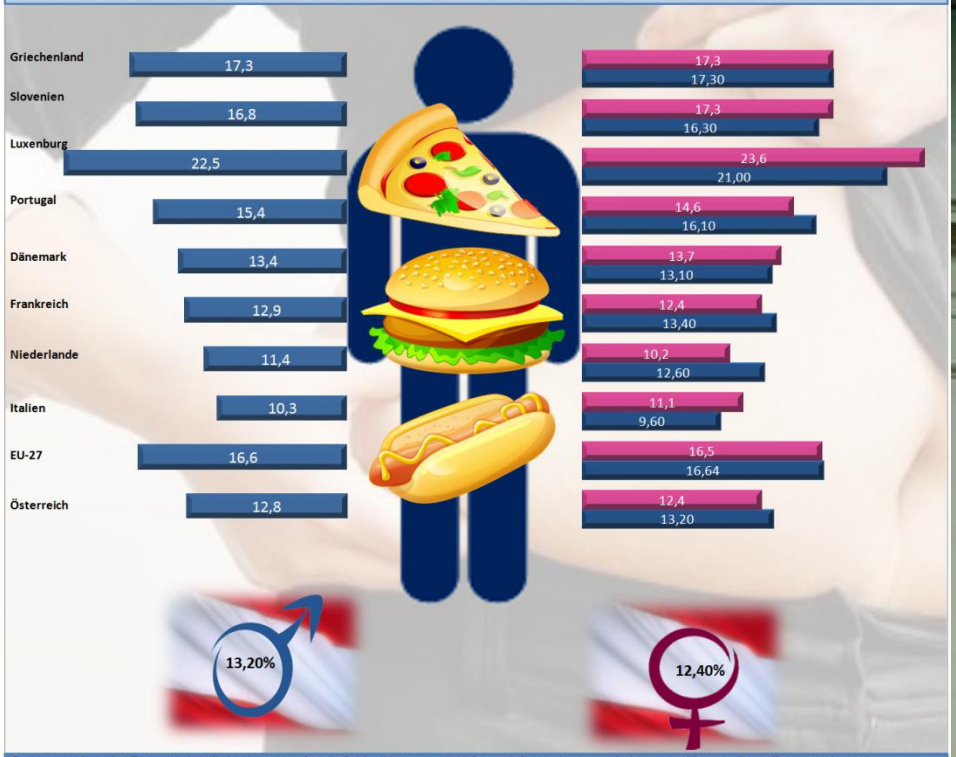
Interpretation of Register Data
Confounders to consider
(Examples)


Lebenserwartung der Männer zum Zeitpunkt ihrer Geburt 2006
Jahre

Österreich – ein Land der Übergewichtigen

ÖSTERREICHISCHE ÄRZTEKAMMER

Die Zahl der übergewichtigen Menschen, insbesondere bereits bei jungen Menschen, ist in Österreich in den vergangenen Jahren deutlich gestiegen. Zwischen 2001 und 2002 waren 11% der Bevölkerung übergewichtig, zwischen 2005 und 2006 14%, im Jahre 2009/10 waren es bereits 15%.



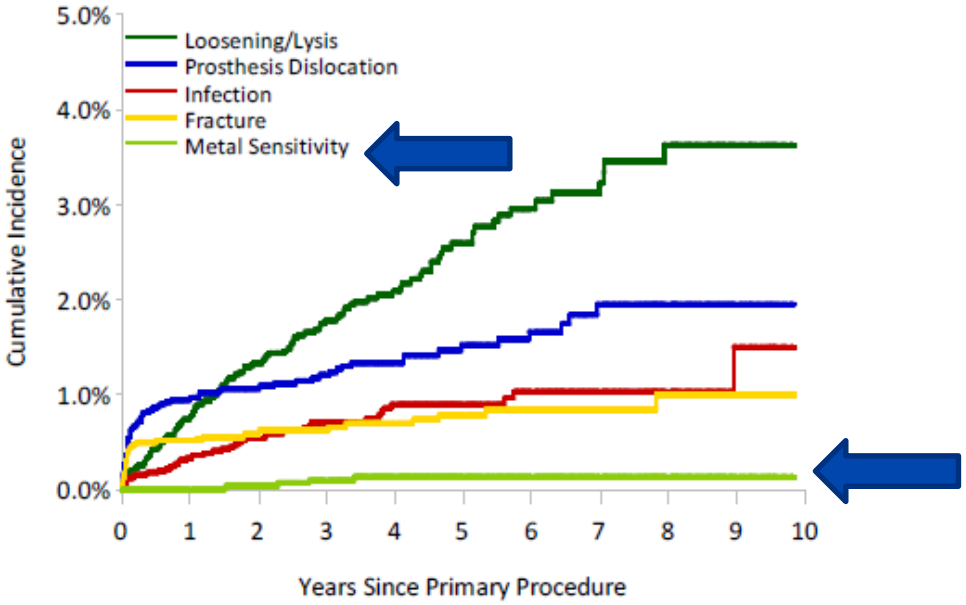
Spitzenreiter in Europa ist Griechenland mit 21% übergewichtigen Menschen, gefolgt von Slowenien, Portugal und Luxemburg sowie Italien. Die wenigsten übergewichtigen Menschen befinden sich mit 8% in den Niederlanden, wo die Zahl zudem rückläufig ist, in Dänemark mit 9%, ebenfalls bei rückläufigen Quoten, sowie in Frankreich bei 10%, ebenfalls bei rückläufiger Tendenz.

Offensichtlich herrschen direkte Zusammenhänge zwischen Vorsorgeinvestitionen, dem Volkseinkommen und Bildungsniveaus. Je ärmer Länder sind, umso stärker ist die Zahl der Übergewichtigen, je ausgewogener die Einkommenssituation, umso geringer die Zahl der Übergewichtigen.

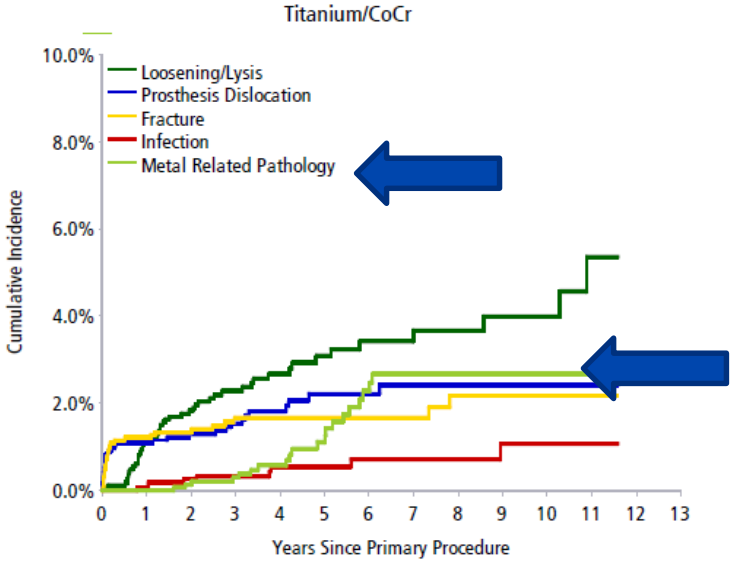
Quelle: "Health at a Glance 2012" © OECD 2012

- Australian Data
  - Changed data/definitions in retrospect during a controversial discussion??

2011



2014



Local-international screening

- MIS compared to conventional approaches ➔ no difference

- One of Major Promotors of MIS
  - Courses
  - > 60 % MIS THA in this region

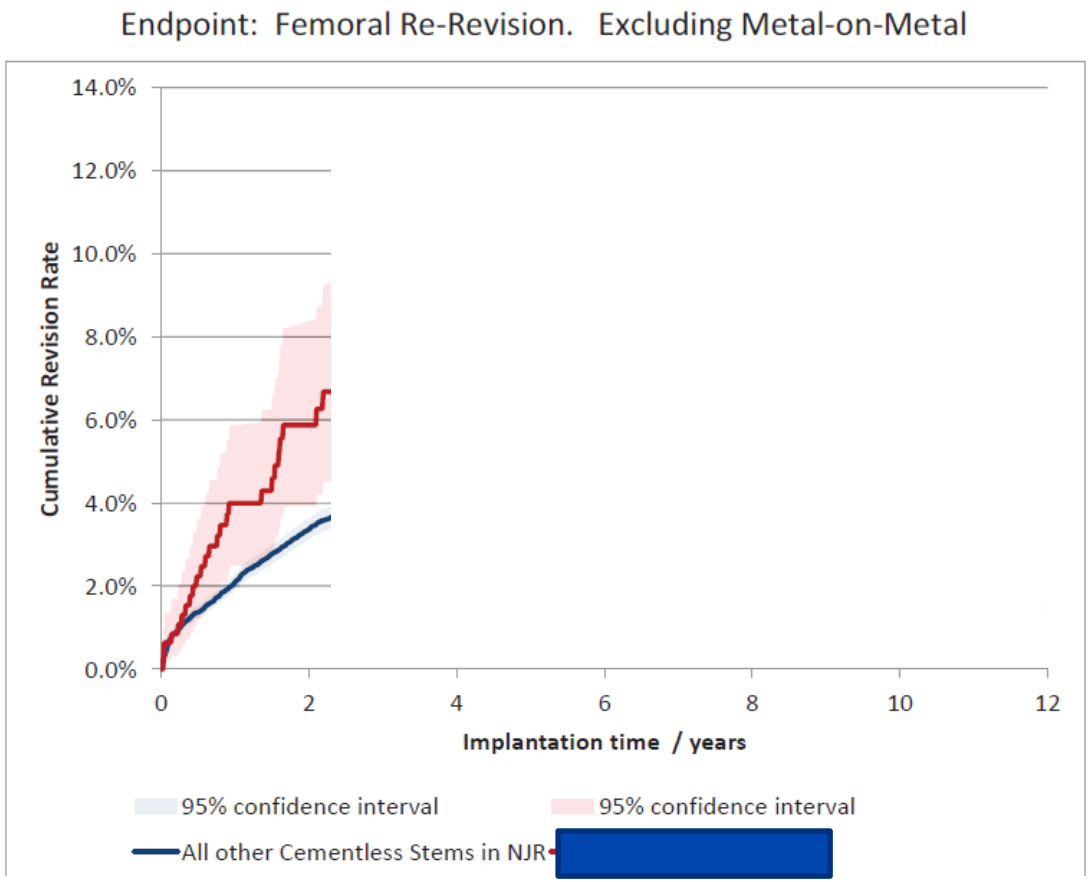
Prothesenregister Tirol

tilak Unternehmen Gesundheit

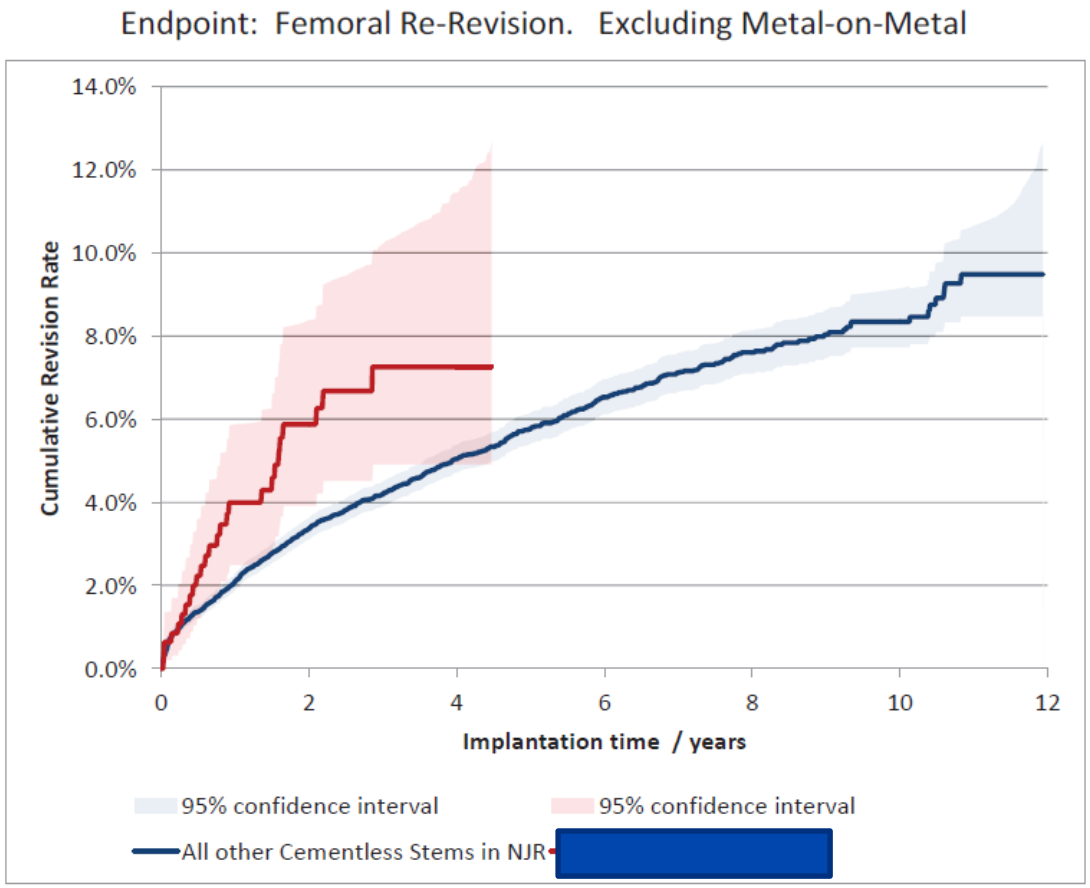
IET Institut für klinische Epidemiologie der TILAK Ges.m.b.H. Zertifiziert nach ISO 9001:2008

Country	Revision rate 1 Year	Revision rate 2 Years	Revision rate 3 Years		Relative Risk Ratio Tirol to reference	Relative Risk Ratio Tirol to reference	Relative Risk Ratio Tirol to reference
Tyrol	1,7	2,4	2,7				
Australia	1,5		2,6		**1,13**		**1,04**
GB	1,07	1,69	2,32		**1,59**	**1,42**	**1,16**
Italy (Emilia Romagna)	1,2	1,9	2,4		**1,42**	**1,26**	**1,13**
NZ	1,04	1,57	2,05		**1,63**	**1,53**	**1,32**
Sweden		1,8				**1,33**	

Time scale


Endpoint: Femoral Re-Revision. Excluding Metal-on-Metal
14.0%
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
Cumulative Revision Rate
0
2
4
6
8
10
12
Implantation time / years
95% confidence interval
95% confidence interval
All other Cementless Stems in NJR

Time scale



Cox Proportional Hazards model for re-revision risk ratio of Lima Revision Stem / All other Cementless Stems in NJR, with endpoint as Femoral re-revision.

Adjustment	Hazard Ratio (95% CI)	*p*- value
Excluding MoM, Unadjusted	1.62 (1.09 - 2.39)	0.016
Excluding MoM. Adjusted for age, gender, year cohort and indications.	1.67 (1.12 - 2.49)	0.012

Case Mix

Reason for Re-Revision	Number of procedures †	Crude Re-Revision Rate		
			All NJR Cementless Stems	All NJR hip replacement
Pain	6	1.27%	1.59%	1.46%
Dislocation / Subluxation	5	1.06%	1.77%	2.03%
Adverse Soft Tissue Reaction	3	0.64%	0.71%	0.49%
Infection	6	1.27%	1.44%	1.69%
Aseptic Loosening - Stem	13	2.76%	1.85%	1.39%
Aseptic Loosening - Socket	6	1.27%	1.51%	1.69%
Periprosthetic Fracture Stem	0	0.00%	0.69%	0.66%
Periprosthetic Fracture Socket	0	0.00%	0.13%	0.14%
Malalignment Stem	0	0.00%	0.23%	0.17%
Malalignment Socket	0	0.00%	0.26%	0.29%
Wear Of Acetabular Component	2	0.42%	0.36%	0.40%
Lysis Stem	1	0.21%	0.37%	0.35%
Lysis Socket	0	0.00%	0.34%	0.42%
Implant Fracture Stem	0	0.00%	0.24%	0.19%
Implant Fracture Socket	1	0.21%	0.08%	0.10%
Dissociation Of Liner	1	0.21%	0.15%	0.16%
Other / reason not recorded	4	0.85%	0.71%	0.50%
Total Re-Revisions	**34**			

Highly modular stem ➔ often used in more compex cases➔ aseptic loosening is explicable ➔confounder

Potential Elements of a Clinical Investigation Plan

Please Note

ANNEX XIV

CLINICAL EVALUATION AND POST-MARKET CLINICAL FOLLOW-UP

PART A

CLINICAL EVALUATION

1. To plan, continuously conduct and document a clinical evaluation, manufacturers shall:

(a) establish and update a clinical evaluation plan, which shall include at least:

— an identification of the general safety and performance requirements that require support from relevant clinical data;

— a specification of the intended purpose of the device;

— a clear specification of intended target groups with clear indications and contra-indications;

— a detailed description of intended clinical benefits to patients with relevant and specified clinical outcome parameters;

MDR, Annex XIV, Part A

- an indicative list and specification of parameters to be used to determine, based on the state of the art in medicine, the acceptability of the benefit-risk ratio for the various indications and for the intended purpose or purposes of the device;
- an indication how benefit-risk issues relating to specific components such as use of pharmaceutical, non-viable animal or human tissues, are to be addressed; and
- a clinical development plan indicating progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations, and a PMCF as referred to in Part B of this Annex with an indication of milestones and a description of potential acceptance criteria;

(b) identify available clinical data relevant to the device and its intended purpose and any gaps in clinical evidence through a systematic scientific literature review;

(c) appraise all relevant clinical data by evaluating their suitability for establishing the safety and performance of the device;

Clinical Data

- Bench- and Lab-Tests
- Clinical Studies (sample based)
  - Focus on a specific topic
  - Premarket / Postmarket
- Interpreted Evidence
  - Metaanalysen, Cochrane,….
  - HTA-Reports
  - Guidelines/Consensus Papers by Research Societies and other Expert Groups
    - Independence???
- Registries / RWE
  - PMS
  - Search for unknown side effects
  - Evidence to allign regulatory documents/processes with reality in patient care
- FUP-Studies, Complaints,….

Trends and General Issues with Registries/Real World Data in Healthcare

Veterans Programme

- Large Data Collection
- Good control on the cohort
  - Stay in the programme
- Motivated patients
- Professional project management
- Representative sample of a special population

Veterans Health Administration
Research & Development
Improving Veterans' Lives — www.research.va.gov

Million Veteran Program:
A Partnership with Veterans

National Children Study

- Goal: 100.000 files

- Data collection from birth to 21
  - Placenta
  - Water
  - Polution/Environment
  - Life Style

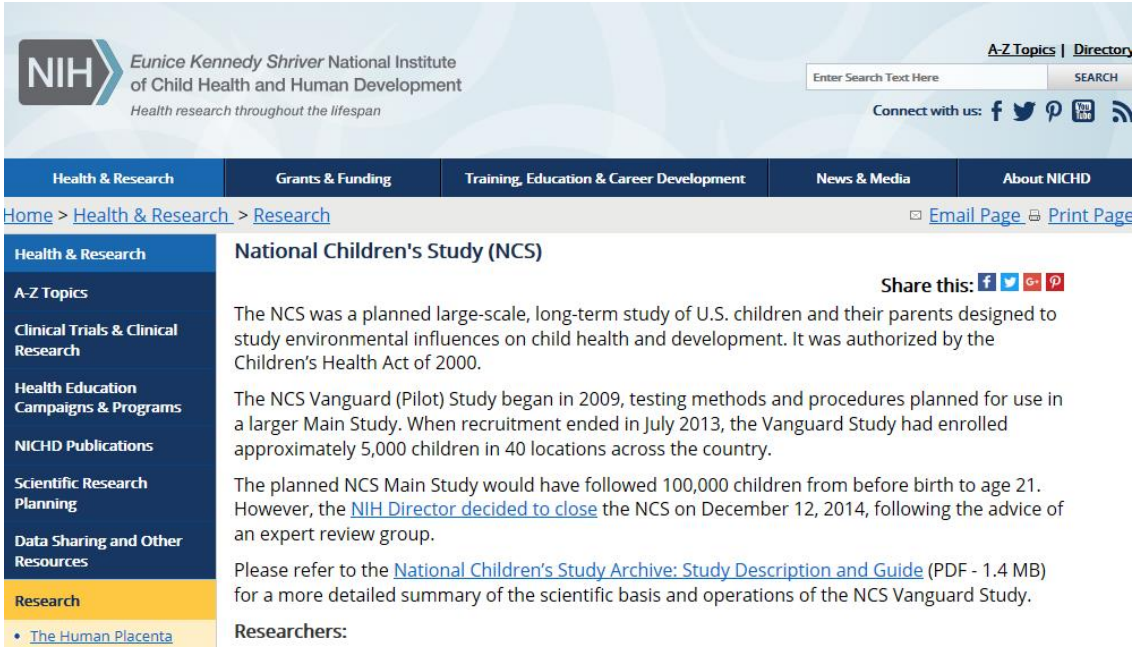
- 14 years
- 1,3 Billions$

- Pilot Study
- 40 centres
- 5000 children

- Abondaned

THE NATIONAL CHILDREN'S STUDY

HEALTH GROWTH ENVIRONMENT



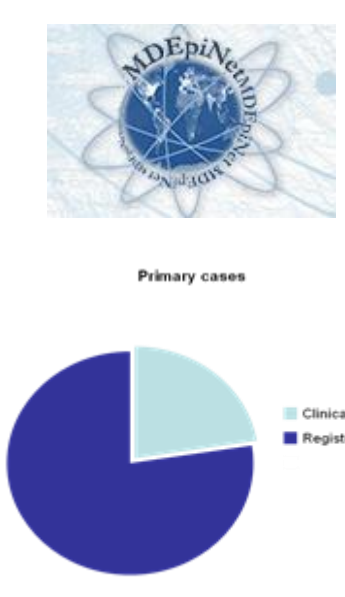
Precision Medicine Initiative

- 1 Million files, US-citicens
- Electronic health records
- Biological samples (blood, hairs,..)
- Gen-marker
- Life style (surverys)
- Mobile sensors and health apps

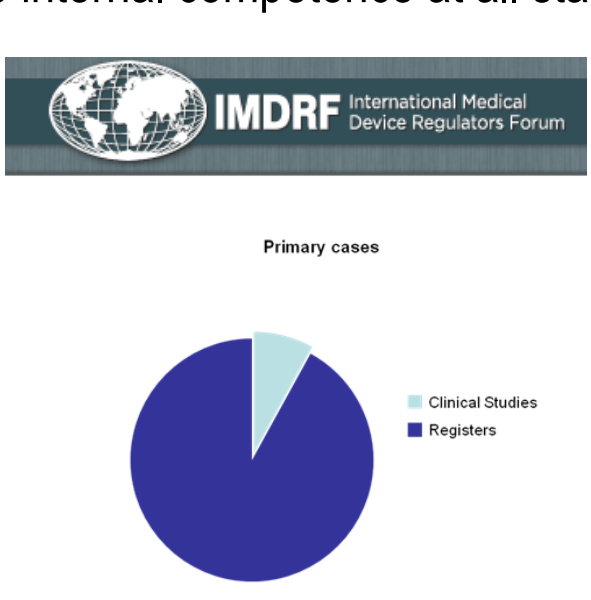
- ➔ corellation between life style and gens to pathologies
- ➔ development of drugs for common pathologies
  - Diabetes
  - Rheumatoid arthritis
  - Alzheimer
  - COPD
  - Parkinson
  - Cancer,…..

Orthopaedics/Knee Arthroplasty

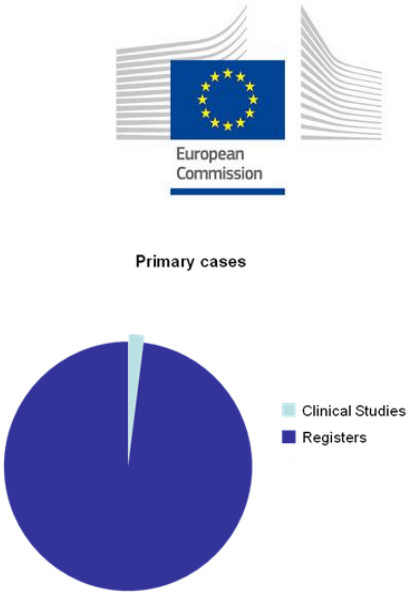
(IT)-Technical and regulatory development will force to consider real world data and build up internal competence at all stakeholders.



2010



2015



2025

Choose certainty.
Add value.

Product Service

We are ahead to fundamental changes ➔ uncertainty, moving targets, processes to be defined