Monitoring by registries or do we still need clinical trials?
The Pros and Cons

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What do we want measure

• Implant performance
  ● Long-term differences
  ● Early outliers

• Implant Use

• Audit of practice
  ● Hospital-level
  ● Surgeon level
  ● Economic cost
  ● Mortality
  ● Dislocation rate

• Registries v successful
What we really need?

• Detect disasters
  - Mom
  - Capital 3M
  - Hylamer
  - Charnley Elite
  - Boneloc

• Innovation critical

• Need to identify outliers in 1st 2-3 years
Registry benefits

- Good at collecting limited dataset in large volumes
  - Identify ‘less favourable implants’
- Successes
  - Identifying long-term differences in implant survival
  - Comparing influence of patient factors on outcome
  - Audit of practice/performance
- Linkage to other primary care/PROMS
  - Improves ability to look at patient factors.
Issues with registries

- Reliant on large number of procedures to detect outliers
  - >1000?
  - Fundamentally limited in drawing conclusions with small numbers.
- Do not collect detailed patient-level data
  - No imaging
- Causes of revision hard to ascertain
  - Completed at time of surgery
    - No histo/path report
- Data collection lag? Greater than trials?
- No mechanistic information
- Hard to determine effect of unknown competing factors
Example

- MoM devices
- Registry data
  - First presentation
    - BOOS 2003
      - 12 cases
  - Cohort study 2007
  - Lag of 3-5 years to registry
  - 30-40K implanted before warnings
  - RSA studies did not detect

2007
Isolated issue?

- Registry data comprehensive
  - 5 years onwards
- Historically proportion of THAs without peer-reviewed early evidence high
  - 25% no evidence
  - 17% of those implanted
  - No change over 20 years Carr/Murray 1996
- Paucity in 1st 3-5 yrs of release
- Likely same in TKA

Carr/Murray 1996
Clinical trials

- What do we mean?
- Varying definitions
  - Post market surveillance
  - Cohort studies/case reports
  - RCTs
  - RSA studies
  - Beyond Compliance
  - Safety Reporting
    - MHRA
Clinical Trials

**Advantages**
- Tightly controlled population
  - Inclusion/Excl criteria
- Detailed outcomes
  - Multifactorial
    - PROMs/Imaging/Blood/Functional scores
- Powered for 1 (max 2) outcomes
- Better able to detect unexpected complications
  - Subtle differences
- Rapid results (if well managed)
- Can be Observational but often hypothesis-driven

**Disadvantages**
- Loss to followup- registry much better
- External validity
  - Cohort enrichment
- Trials units uncommon and not setup for ortho trials
- Cost (to do well)
Solution?
Combined approach

• IDEAL Collaboration
• Pharma model
• Early stages
  • Clinical trials
    • 0 to 3 years
    • Small well constructed cohort studies/RCTs
• Later stages
  • Registry
    • 3 yrs+
      • Registry data
• Trials within Registries
  • Cluster Randomisation
  • Adaptive designs
<table>
<thead>
<tr>
<th>Trials</th>
<th>Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-entry</strong></td>
<td><strong>Product launched under Beyond Compliance</strong></td>
</tr>
<tr>
<td></td>
<td>A minimum cohort of 150 hip/knee at the start of the study consisting of data from beyond the development centre and from more than 5 centres/boroughs with a minimum of three years follow-up and an actual retention rate of more than 75%. All deaths, losses to follow-up, failures and non-compliance are counted. A maximum of 25% loss to follow-up is permitted.</td>
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<td>3 years</td>
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<td>CDEP</td>
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<td>10 years</td>
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<td><strong>Registry</strong></td>
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<td><strong>Product registered with NIHR. All primary and preference measured via supplier feedback.</strong></td>
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**NOTE:** While products are currently used with the UK NHS, care can be taken to ensure their use beyond the development centre and from more than 5 centres/boroughs with a minimum of three years follow-up and an actual retention rate of more than 75%. All deaths, losses to follow-up, failures and non-compliance are counted. A maximum of 25% loss to follow-up is permitted.
What does early stage look like

• Combine multiple outcome measures
  • Validated
  • Novel

• Evaluation toolbox
  ● Internationally agreed
  ● Evidence based

• Utilise trials networks
  ● Increase capacity
  ● Speed evaluation

• Quality of data essential
UK
Trial networks in the early stages of implant evaluation
The NIHR
National Institute for Health Research: integrated health-research system

Invention
- Early-phase clinical Research
  - NIHR Biomedical Research Centres
  - NIHR Clinical Research Facilities
  - Experimental Cancer Medicine Centre
  - Medtech and In vitro diagnostic Co-operatives (MICs).

Evaluation
- Late-phase clinical Research

Adoption
- NIHR Clinical Research Network
- Collaboration for Leadership in Applied Health Research and Care

> £1.2 billion p.a. investment in relevant infrastructure to support clinical research at all points in development pipeline.
NIHR CRN

- High quality trials infrastructure
- Including research staff in over 200 hospitals in the UK
  - Nurses/physios/trials expertise
- Enables trials to be delivered quickly
- Can also look at feasibility of trials prior to funding
- Covers all UK
  - All regions of England
  - Sister organisations in Scotland/Wales/NI
- Supported by RCS clinical trials units/STEP
NIHR Services
Financial year 2016/17:

- 2055 new studies
- 666,630+ patients recruited
- 99.9% NHS trusts research active

729 commercial
34,648 commercial
79% commercial

And since 2006:

- 1000+ new CDAs signed since 2006
UK Progress-
Linking the NIHR and ODEP/BC
Improving implant monitoring
Aims

• Help industry reduce time taken to submission of early benchmarking data
• Improve the quality of data submitted
What does it look like?

- Rapid evaluation pipeline
- BC risk assessment/evaluation plan
  - Consensus Group of Surgeons
- Agreed PMS study submitted to NIHR
- NIHR CRN support for
  - Feasibility/Identification of centres
  - Recruitment
  - Trials unit sponsorship (where required)
  - Study design
- Final Approval by BC
- Data submitted at intervals for benchmarking
- Funding models
  - IIS
  - Fully commercial
Conclusions

• Early phase evaluation an issue
• Clinical trials/cohorts essential
• Combined registry/Trials approach
• Need early evaluation Toolbox
Early phase evaluation an issue
Clinical trials/cohorts essential
Combined registry/Trials approach
Need early evaluation Toolbox
RSA

• Advantages
  ● Highly predictive of outcome
  ● Correlates well with registry outcomes
  ● Rapid
  ● Small patient cohorts
    • Low risk
• Disadvantages
  ● Cannot predict unexpected outcomes
    • Soft tissue reactions
    • Sudden mechanical failure
    • Wear in h on h bearings

RSA and Registries: The Quest for Phased Introduction of New Implants

Introduction: Although the overall survival of knee and hip prostheses at ten years averages 90%, recent problems with several hip and knee prostheses have illustrated that the orthopaedic community, industry, and regulators can still further improve patient safety. Given the early predictive properties of noninvasive stereoradiographic analysis (RSA) and the meticulous follow-up of national joint registries, these two methods are ideal tools for such a phased clinical introduction. In this paper, we elaborate on the predictive power of RSA within a two-year follow-up after arthroplasty and its relationship to national joint registries. The association between RSA prosthesis/excision data and registry data is evaluated.

Methods: The five-year rate of revision of RSA-tested total knee replacements was compared with that of non-RSA-tested total knee replacements. Data were extracted from the published results of the national joint registries of Sweden, Australia, and New Zealand.

Results: There was a 22% to 35% reduction in the number of revisions of RSA-tested total knee replacements as compared with non-RSA-tested total knee replacements in the national joint registries. Assuming that the total cost of total knee arthroplasty is $37,000 in the United States, a 22% to 35% reduction in the number of revisions (currently close to 55,000 annually) would lead to an estimated annual savings of over $400 million to the health-care system.

Conclusions: The phased clinical introduction of new prostheses with two-year RSA results as a quasitarget tool could result in better patient care and could reduce the costs associated with revision total knee arthroplasty. Follow-up in registries is necessary to substantiate these results and to improve post-market surveillance.
Detailed structure

**CE?**

**EXTERNAL PROCESSES**

- **NEW DEVICE**
  - Externally Run Commercial/IIS Study
    - Support from NIHR CEN-UK
    - UK-CRC Trials network
    - Country-specific investigators
  - Company Report for ODEP/BC

**BC/ODEP PROCESSES**

- ODEP/BC Risk Assessment
  - High
  - NIHR National MSK Group
    - Study Design
    - Evaluation plan
    - Protocol
    - Feasibility for UK studies
  - Site selection
    - NIHR CRN UK
    - Commercial contacts: UK/Europe/Worldwide
- Routine Post-Market Surveillance
  - Low
  - Benchmarking Committee

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**CE?**

**PRESENTATION TITLE**

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**PRESENTATION LOGO**

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Stakeholders

- Government bodies
  - NHS Exec
  - NIHR
  - Dept. Trade Industry - UKTI
  - MHRA
- Manufacturers
- Trials infrastructure
  - NIHR CRN
  - RCS CTUs
- Industry Bodies
  - EUCOMED/AVAMED/ABHI
- Royal Coll. Surgeons
  - STEP
- Patient Groups
Future Steps

• Accommodate new CE changes
• Consultation process with industry
  ABHI
• International collaboration
• NIHR/BC Industry meeting February 2018
  • Wellcome Institute, London
    • Surgical Devices
    • Pharma
    • Implantable Medicinal Devices
Contacts

- S Glyn-Jones- NIHR National MSK Lead
  - sion.glyn-jones@ndorms.ox.ac.uk
- Vanessa Poustie Cluster D Specialty Lead
  - vanessa.poustie@nihr.ac.uk
What is needed?

• High quality data
  ● Best study design
  ● Trials/stats expertise

• Rapid data collection
  ● Capture data on
    ● Most new patients
    ● In several centres
  ● System for outcomes collection
Burden of OA/JR

- Burden of musculoskeletal disease significant
- US
  - 7% GDP
  - 4% in UK/Europe
- Ageing population
- Joint replacement
  - Finite lifespan
  - Changing demographics

Fig 2: Life expectancy at birth, UK, males and females. Principal, high and low projections (shown by cohort) estimates.

Fig 3: Population survival curves for UK females, 1951-2060.
Cost utility?

- THA one of most effective interventions
  - £1,180 / QALY
- Compare
  - 10 years tx for RA
    - £36,000/QALY
  - Non-operative tx for OA over 10yrs
    - £26K-64K/QALY
- Highly successful in benchmarking
- First national benchmarking system
- Now used in 26 healthcare systems worldwide
- Linked to sister organisations
  - Netherlands
  - Germany
Current Device Evaluation

- **Current system**
  - Registry data
  - Post-market surveillance studies
  - IIS studies

- **Data submitted to BC/ODEP**
  - Late-phase data excellent
  - Early data
    - Poor quality
    - Lag of 3-7 years to benchmark
    - Opportunities for data collection missed

- **NJR cannot detect early failures**
  - Slow to detect outliers
  - Problematic with low vol. implants

- **IDEAL Group**
  - No Phase 2B/3 in device regulation

<table>
<thead>
<tr>
<th>Stages</th>
<th>1: Idea</th>
<th>2a: Development</th>
<th>2b: Exploration</th>
<th>3: Assessment</th>
<th>4: Long-term study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose</td>
<td>Proof of concept</td>
<td>Development; learning</td>
<td>Assessment; development; learning</td>
<td>Assessment</td>
<td>Assessment; development; learning</td>
</tr>
<tr>
<td>Number and type of patients</td>
<td>Single digit, highly selected</td>
<td>Few selected</td>
<td>Many, may expand to mixed; identifying indications</td>
<td>Many, expanded indications (well-identified)</td>
<td>All eligible</td>
</tr>
<tr>
<td>Number and type of surgeons</td>
<td>Very few, innovators</td>
<td>Few, innovators and some early adopters</td>
<td>Many, innovation early adopters, early majority</td>
<td>Many, early majority</td>
<td>All eligible</td>
</tr>
<tr>
<td>Outcome</td>
<td>Description</td>
<td>Description</td>
<td>Measurement; comparison</td>
<td>Comparison, complete information for new IHT participants</td>
<td>Description, audit, regional variation, quality assurance, risk adjustment</td>
</tr>
<tr>
<td>Intervention</td>
<td>Exploring procedure evolution</td>
<td>Exploring procedure development</td>
<td>Exploring procedure evolution; continually learning</td>
<td>Stable</td>
<td>Stable</td>
</tr>
<tr>
<td>Method</td>
<td>Structured case reports</td>
<td>Prospective development studies</td>
<td>Research database, explanatory or feasibility IHT (infancy/baby, demand based; ambiguous)</td>
<td>IHT with one or two added components; alternative design</td>
<td>Registry, routine database (e.g., SGAP-STS, NSQIP); case reports</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Proof of concept; technical achievement; dramatic, dramatic successes</td>
<td>Mostly safety, technical and procedural success</td>
<td>Safety, clinical outcomes (preclinical and clinical), short-term outcomes; patient-centered; reported outcomes; feasibility outcomes</td>
<td>Clinical outcomes specific and gradual; medium-term and long-term outcomes; patient-centered; reported outcomes; cost-effectiveness</td>
<td>Rare events, long-term outcomes, quality assurance</td>
</tr>
<tr>
<td>Ethical approval</td>
<td>Sometimes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* NHTS-2019: NH Upper Limb Registry
* This is an example of a case study

Table: Stages of surgical innovation

[IDEAL Group logo]
Demographics?

- Increase in TKA/THA
- Projections For demand
  - 250% over 20yrs
- Innovation is required
- Introduction new CE marking process