NHS National Institute for Health Research

Beyond Compliance
Protecting Patients, Supporting Innovation

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

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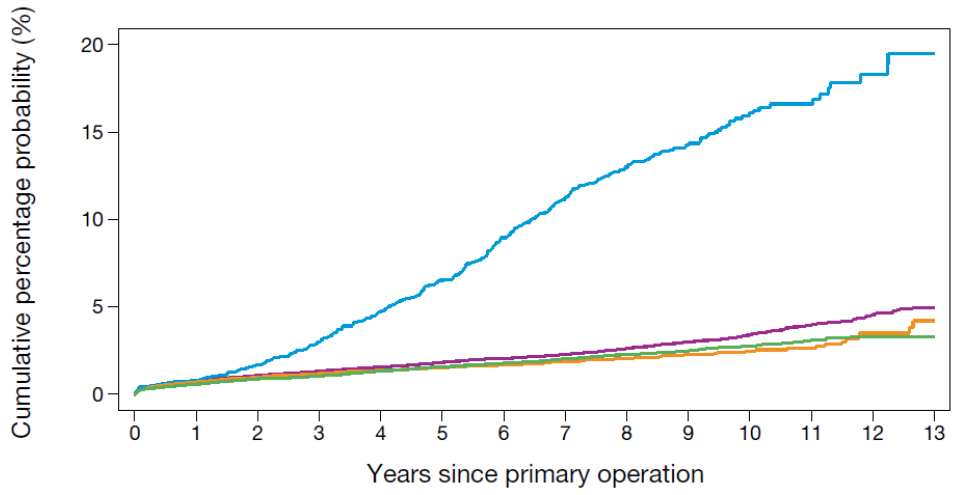
ODEP
Orthopaedic Data Evaluation Panel

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

Comparison of cumulative probability of revision (Kaplan-Meier estimates) for **hybrid** primary hip replacements with different bearing surfaces.



Number at risk

Hybrid MoP	105,619	89,439	75,371	62,342	51,531	41,893	33,194	25,847	19,192	13,474	8,638	5,073	2,424	750
Hybrid MoM	2,188	2,144	2,089	2,023	1,942	1,879	1,763	1,574	1,330	898	525	306	170	65
Hybrid CoP	37,294	27,455	19,594	13,408	9,326	6,920	5,290	3,949	2,817	1,974	1,402	897	487	153
Hybrid CoC	23,206	21,481	19,487	17,298	14,990	12,680	10,391	8,318	6,380	4,661	3,011	1,623	647	149

What we really need?

- Detect disasters
  - Mom
  - Capital 3M
  - Hylamer
  - Charnley Elite
  - Boneloc
- Innovation critical
- Need to identify outliers in 1st 2-3 years

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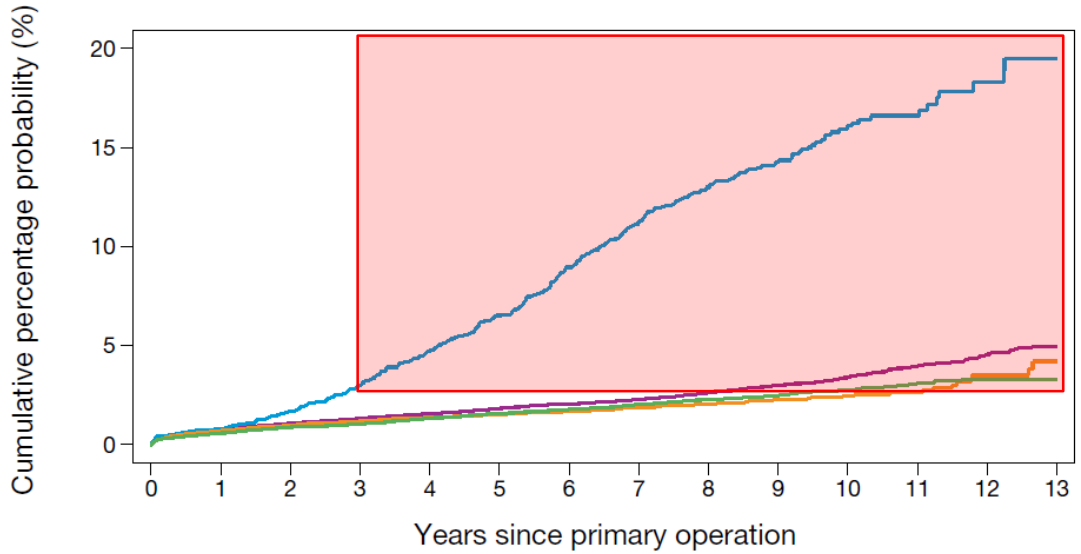

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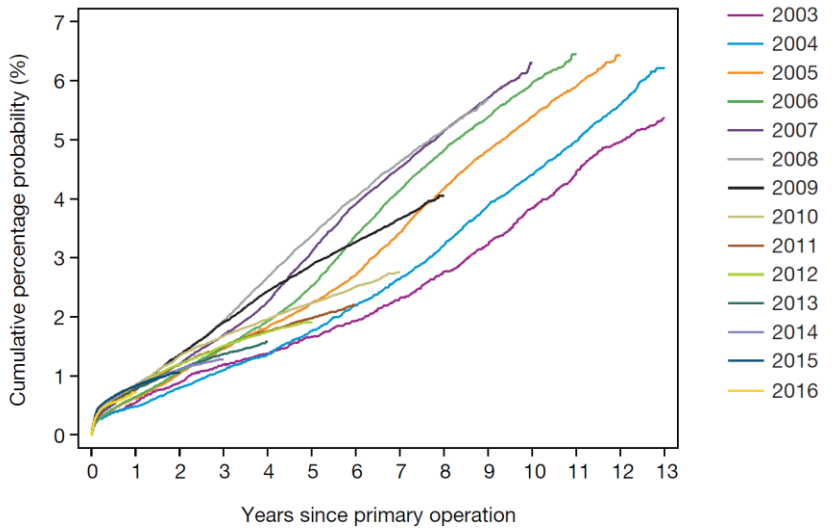
Registry benefits

- 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.

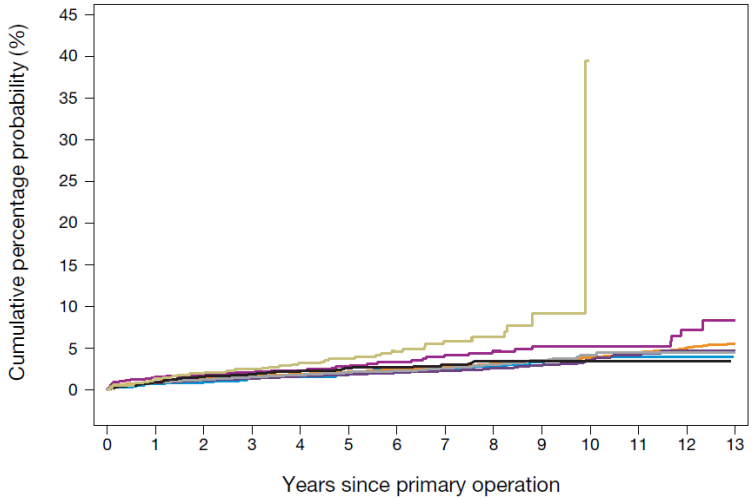
Temporal changes in revision rates after primary hip replacement: Kaplan-Meier estimates of cumulative percentage probability of revision for each year of primary operation.



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

(b.i) **Metal-on-polyethylene uncemented metal shells with polyethylene liners**

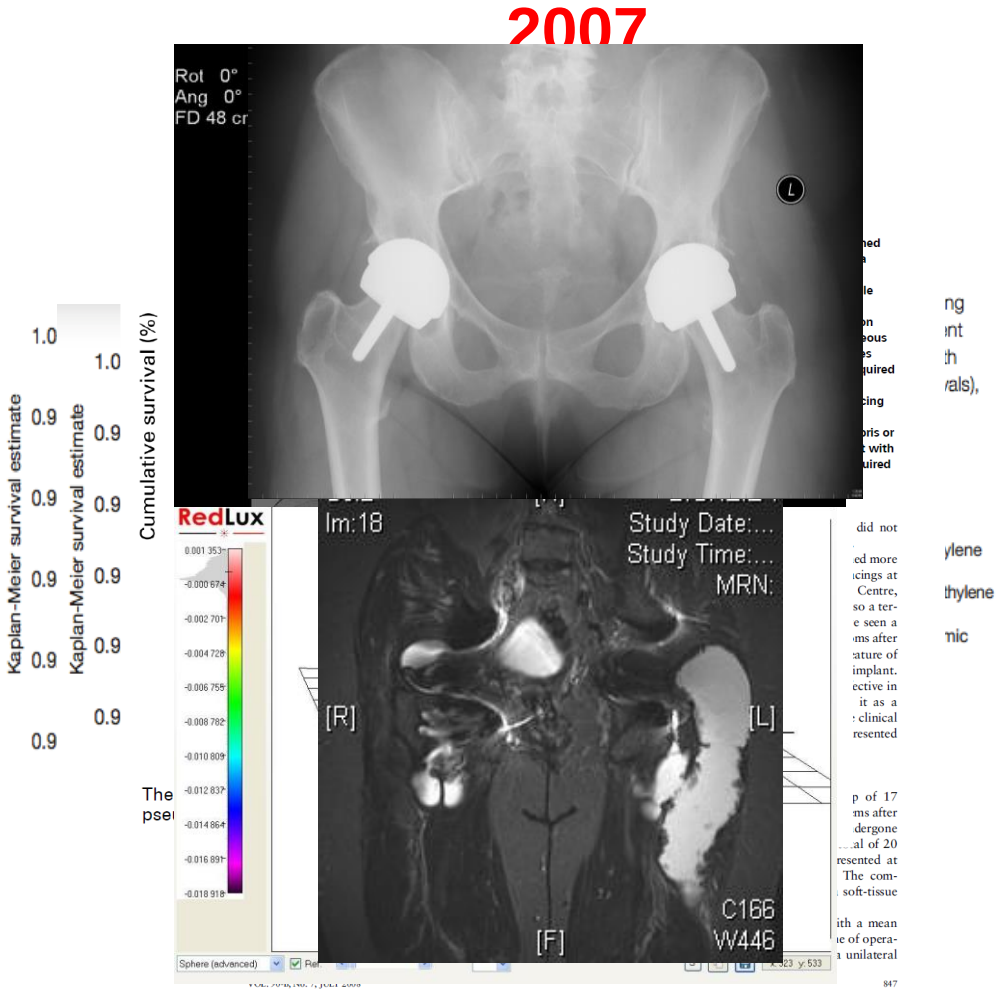


Number at risk

Head size = 22.25mm	1,510	1,217	1,013	850	702	592	501	429	374	322	259	190	113	40
Head size = 26mm	866	827	783	737	682	628	560	483	418	339	255	173	92	22
Head size = 28mm	93,202	85,875	78,663	71,043	63,530	55,633	47,420	39,078	30,829	22,468	15,011	8,954	4,096	1,185
Head size = 32mm	88,377	71,243	56,065	41,871	30,272	21,056	14,036	8,741	4,890	2,485	1,197	458	154	13
Head size = 36mm	47,765	39,734	32,878	26,287	20,283	14,404	9,371	5,346	2,472	1,060	392	134	59	12
Head size = 40mm	3,403	3,255	3,082	2,872	2,624	2,170	1,690	1,174	701	230	16	8	6	0
Head size = 44mm	842	805	773	703	606	488	382	263	155	46	0	0	0	0

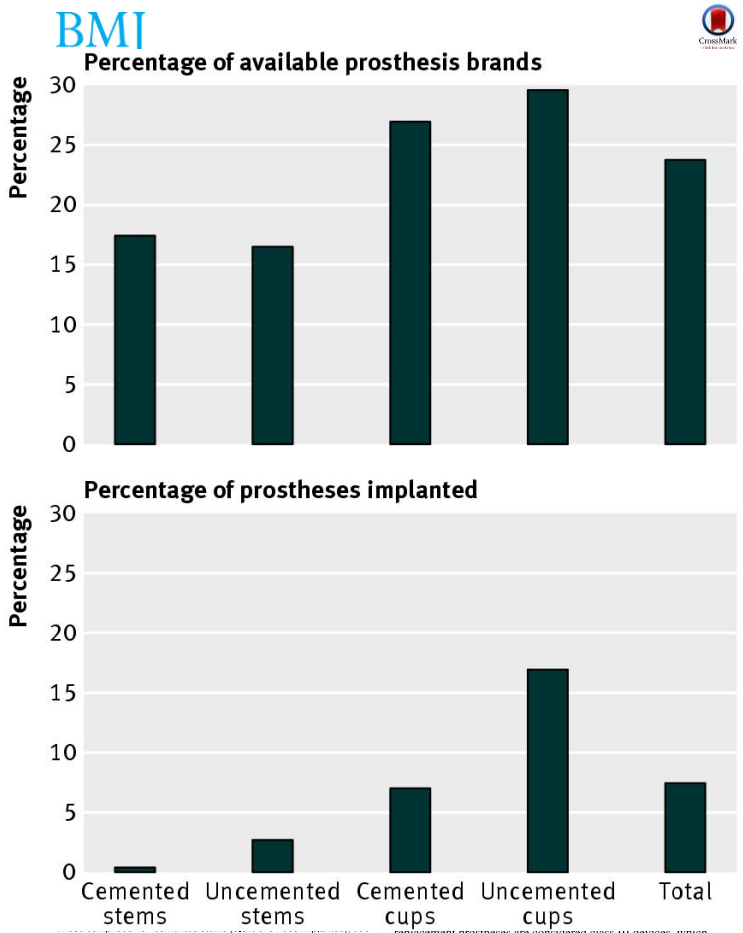
Example

- 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



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



(2,8% of 33 367) uncemented stems, 1732 (7,1% of 24 349) cemented cups, and 7577 (17.1% of 44 222) uncemented cups.

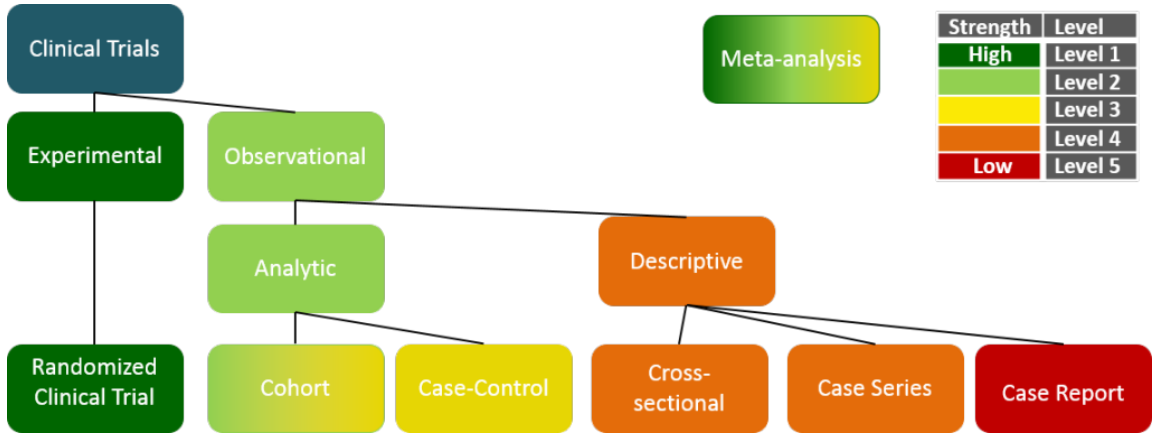
Conclusions This study shows that a considerable proportion of prostheses available to orthopaedic surgeons have no readily available evidence of clinical effectiveness to support their use. Concern exists

replacement prostheses are considered class III devices, which means that the application for approval must include some human clinical investigations,[8] although this need not be new research specific to the device if the manufacturer is claiming similarity to an existing product.

Although no clear list of which class III devices have been cleared for use in the United Kingdom or Europe is available

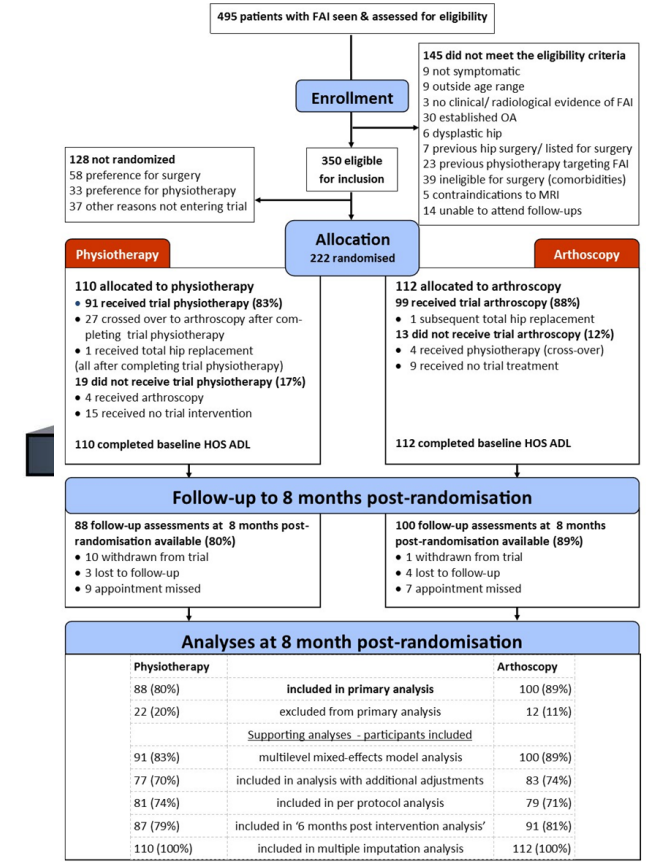
Clinical trials

- 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)



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Solution?

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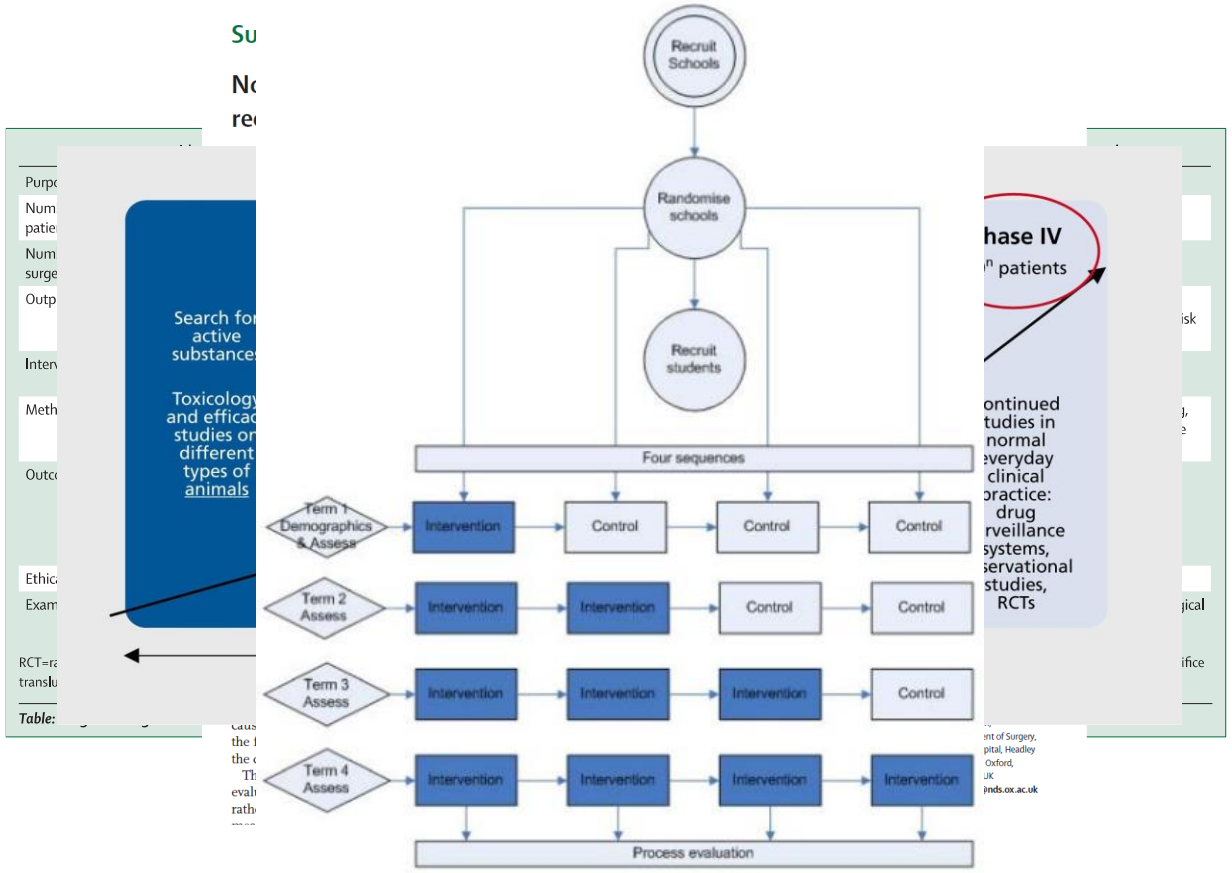
Combined approach

- 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



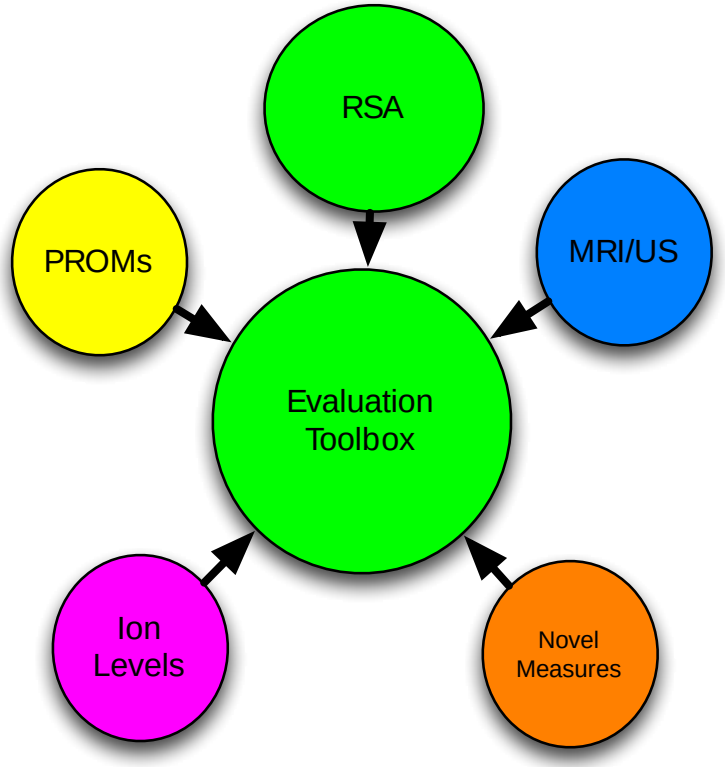
Should reflect CE/benchmarking process

Trials | **Registry**

Pre-entry	3 years	5 years	7 years	10 years
ODEP PRE-ENTRY A*	ODEP 3A*	ODEP 5A*	ODEP 7A*	ODEP 10A*
Product launched under Beyond Compliance	A minimum cohort of 150 hips/knees at the start of the study (consisting of data from beyond the developing centre and from more than 3 centres/surgeons) with a minimum of three years follow up and an actual revision rate of less than 3%. All deaths, loss to follow up, failures and indications for revisions recorded. A maximum of 20% loss to follow-up is permitted.	A minimum cohort of 250 hips/knees at the start of the study (consisting of data from beyond the developing centre and from more than 3 centres/surgeons) with a minimum of five years follow up and an actual revision rate of less than 5%. All deaths, loss to follow up, failures and indications for revisions recorded. A maximum of 20% loss to follow-up is permitted.	A minimum cohort of 350 hips/knees at the start of the study (consisting of data from beyond the developing centre and from more than 3 centres/surgeons) with a minimum of seven years follow up and an actual revision rate of less than 5%. All deaths, loss to follow up, failures and indications for revisions recorded. A maximum of 20% loss to follow-up is permitted.	A minimum cohort of 500 hips/knees at the start of the study (consisting of data from beyond the developing centre and from more than 3 centres/surgeons) with a minimum of ten years follow up and an actual revision rate of less than 5%. All deaths, loss to follow up, failures and indications for revisions recorded. A maximum of 20% loss to follow-up is permitted.
ODEP PRE-ENTRY	ODEP 3A	ODEP 5A	ODEP 7A	ODEP 10A
Products registered with NJR. All primaries and revisions monitored via supplier feedback.	A minimum cohort of 150 hips/knees at the start of the study (consisting of data from beyond the developing centre and from more than 3 centres/surgeons) demonstrating Kaplan - Meier survivorship data of better than or equal to 97% (showing confidence limits on the data with the lower limit of 90%) at the benchmark of three years. A maximum of 20% loss to follow-up is permitted.	A minimum cohort of 250 hips/knees at the start of the study (consisting of data from beyond the developing centre and from more than 3 centres/surgeons) demonstrating Kaplan - Meier survivorship data of better than or equal to 95% (showing confidence limits on the data with the lower limit of 90%) at the benchmark of five years. A maximum of 20% loss to follow-up is permitted.	A minimum cohort of 350 hips/knees at the start of the study (consisting of data from beyond the developing centre and from more than 3 centres/surgeons) demonstrating Kaplan - Meier survivorship data of better than or equal to 93% (showing confidence limits on the data with the lower limit of 90%) at the benchmark of seven years. A maximum of 20% loss to follow-up is permitted.	A minimum cohort of 500 hips/knees at the start of the study (consisting of data from beyond the developing centre and from more than 3 centres/surgeons) demonstrating Kaplan - Meier survivorship data of better than or equal to 90% (showing confidence limits on the data with the lower limit of 90%) at the benchmark of ten years. A maximum of 20% loss to follow-up is permitted.
NOTE: whilst products not currently used within the UK can be awarded an ODEP benchmark, all products must be registered with the UK NJR to receive an ODEP rating	ODEP 3B **minimum 100** Data for a smaller cohort demonstrating less than 3% revision rates at three years, and PTIR or Kaplan-Meier survivorship data of better or equal to 97% (showing confidence limits on the data with the lower limit of 90%). A maximum of 20% loss to follow-up is permitted.	ODEP 5B **minimum 100** Data for a smaller cohort demonstrating less than 5% revision rates at five years, and PTIR or Kaplan-Meier survivorship data of better or equal to 95% (showing confidence limits on the data with the lower limit of 90%). A maximum of 20% loss to follow-up is permitted.	ODEP 7B **minimum 100** Data for a smaller cohort demonstrating less than 7% revision rates at seven years, and PTIR or Kaplan-Meier survivorship data of better than or equal to 93% (showing confidence limits on the data with the lower limit of 90%). A maximum of 20% loss to follow-up is permitted.	ODEP 10B **minimum 100** Data for a smaller cohort demonstrating 10% at ten years, and PTIR or Kaplan-Meier survivorship data of better or equal to 90% (showing confidence limits on the data with the lower limit of 90%). A maximum of 20% 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



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UK
Trial networks in the early stages of implant evaluation

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The NIHR

National Institute for Health Research: integrated health-research system

Early-phase clinical Research

Late-phase clinical Research

NIHR Biomedical Research Centres

NIHR Clinical Research Facilities

Experimental Cancer Medicine Centre

Medtech and In vitro diagnostic Co-operatives (**MICs**).

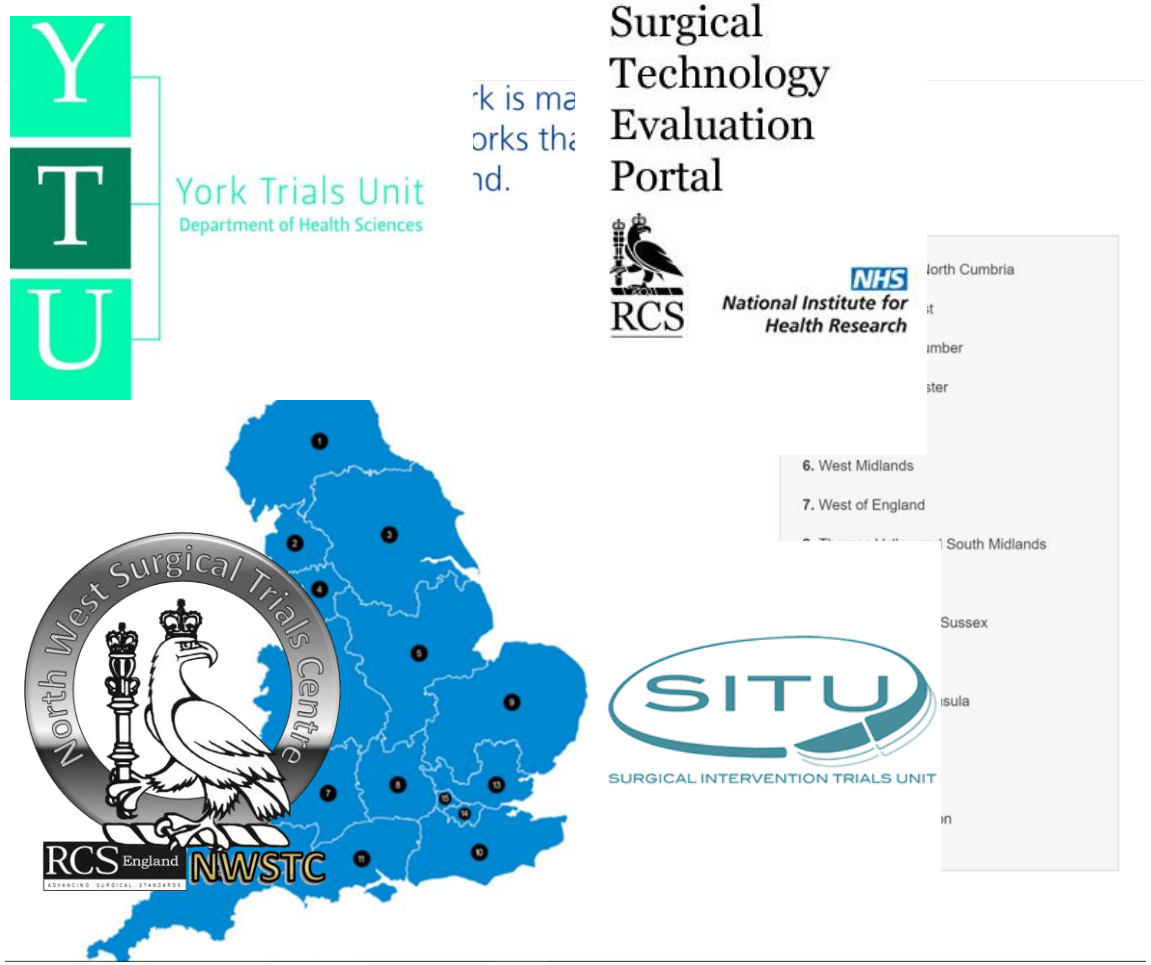
NIHR Clinical Research Network

Collaboration for Leadership in Applied Health Research and Care

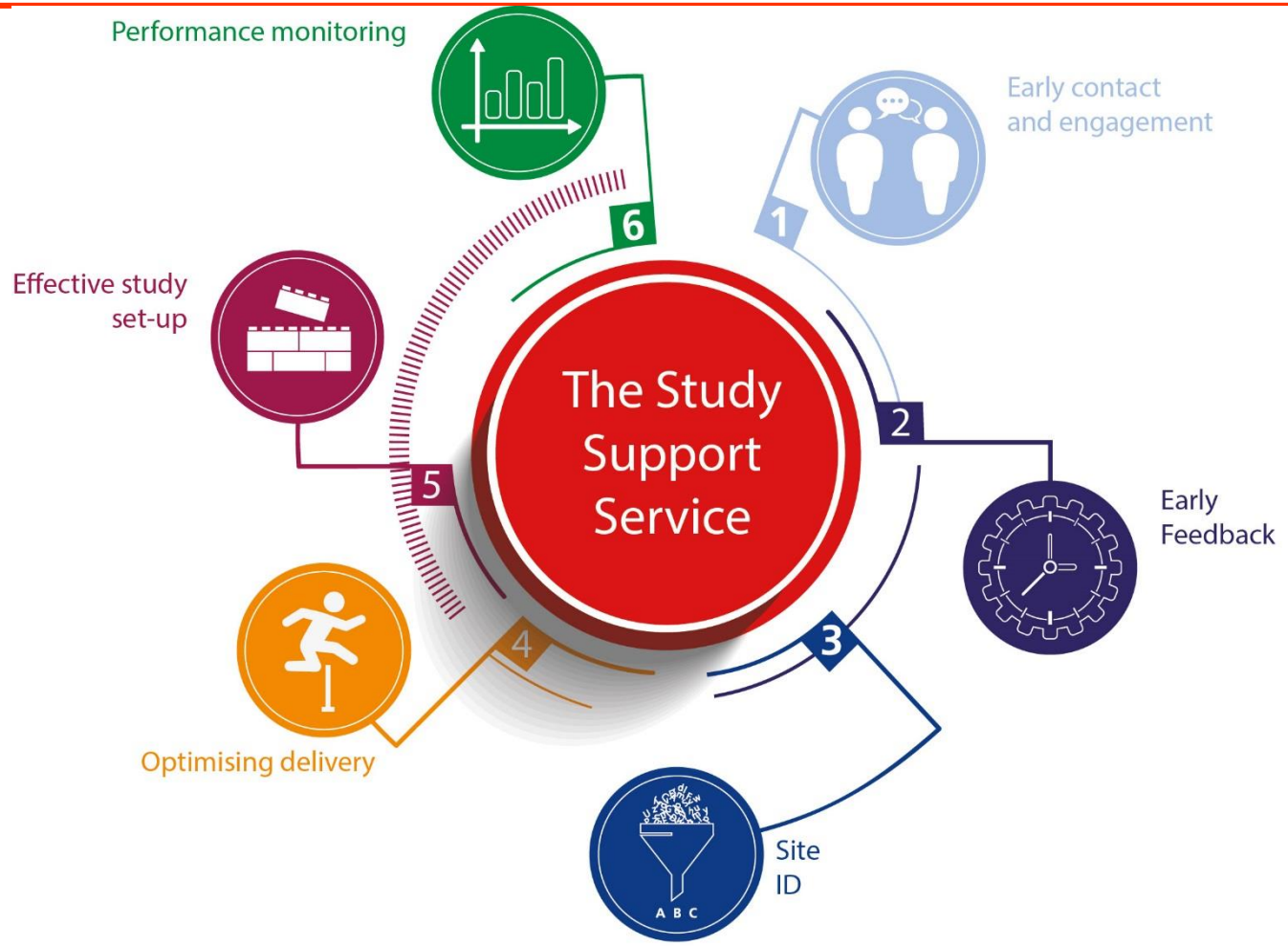
> £1.2 billion p.a. investment in relevant infrastructure to support clinical research at all points in development pipeline

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
729 commercial

666,630+ patients recruited
34,648 commercial

99.9% NHS trusts research active
79% commercial

And since 2006:

1000+ new CDAs signed since 2006

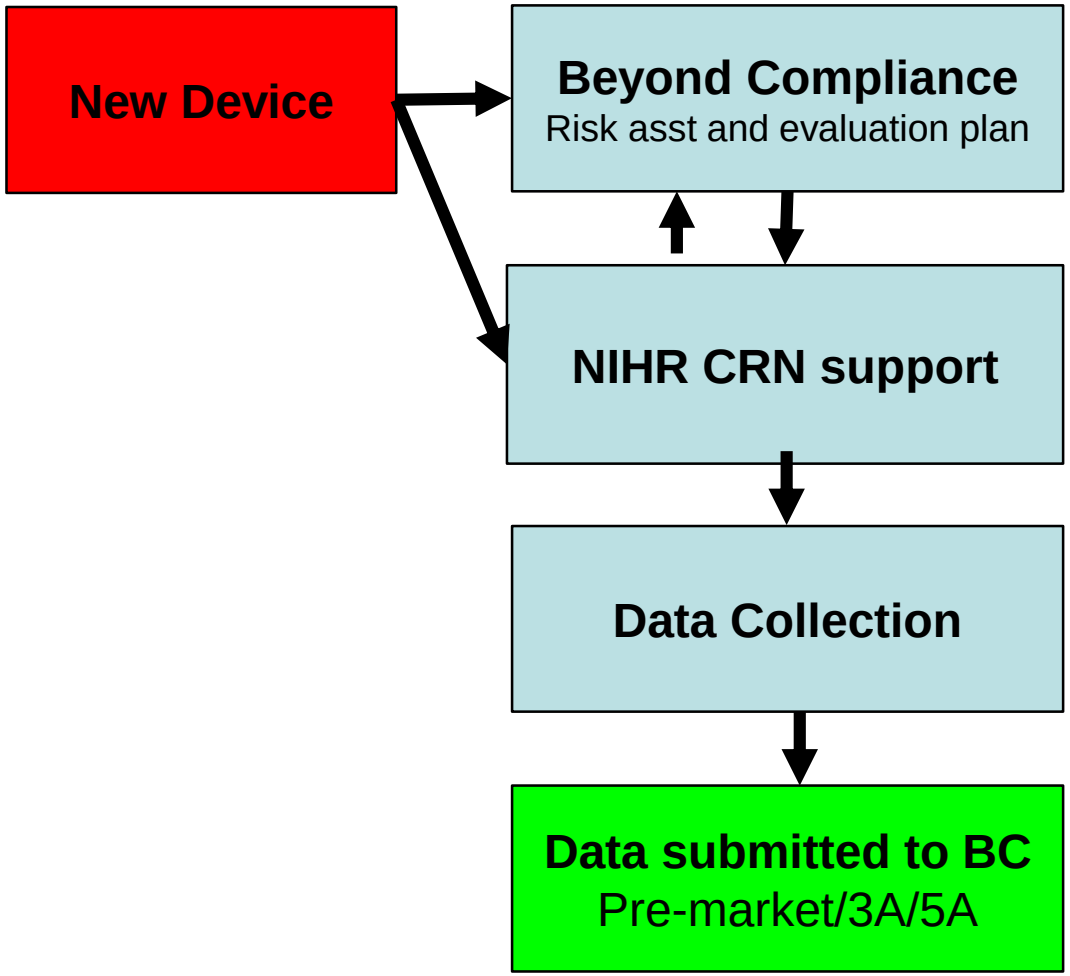
UK Progress-
Linking the NIHR and ODEP/BC
Improving implant monitoring

Aims

- Help industry reduce time taken to submission of early benchmarking data
- Improve the quality of data submitted

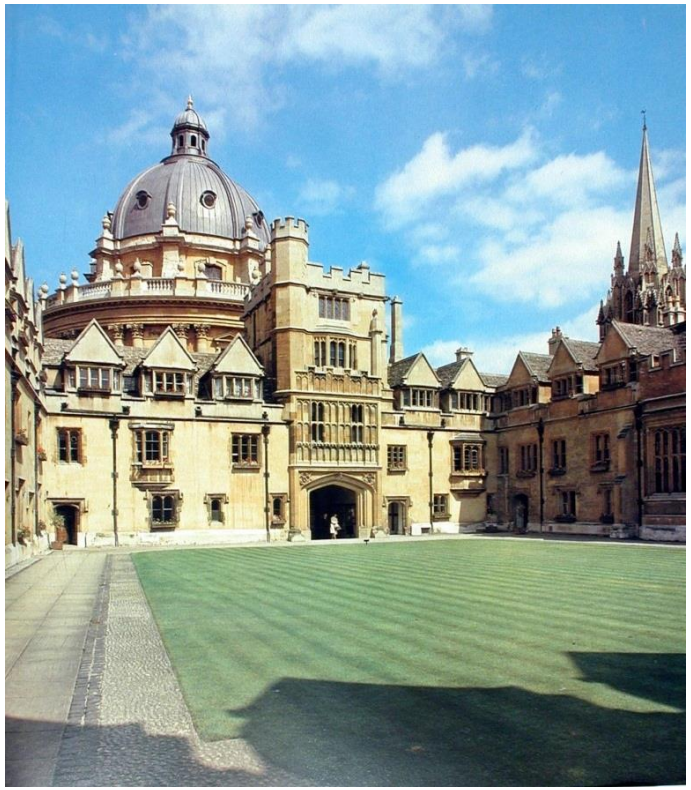
What does it look like?

- 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



Thank you

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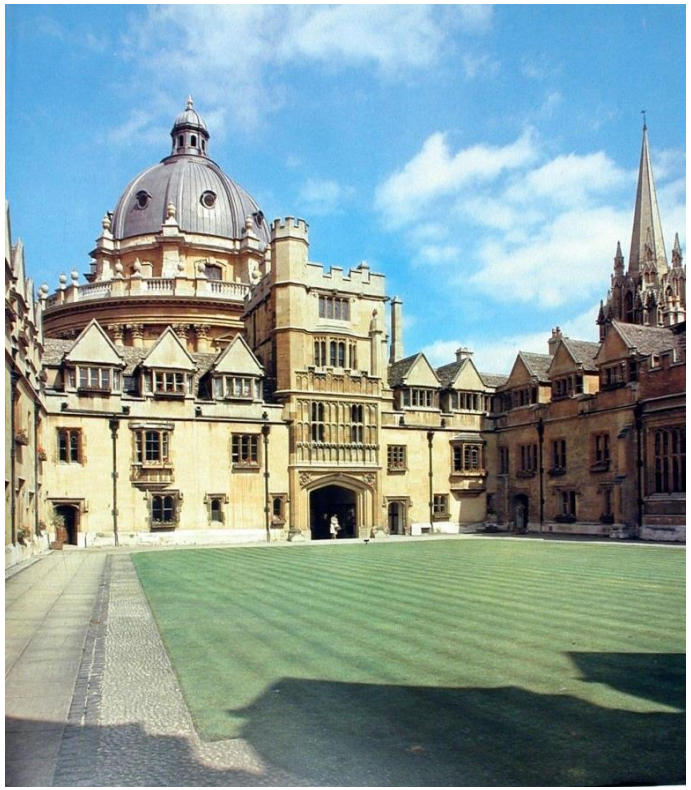

RSA

- 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

Rob G.H.H. Nelissen, MD, PhD, Bart G. Pijls, MD, Johan Kärrholm, MD, PhD, Henrik Malchau, MD, PhD, Marc J. Nieuwenhuijse, MD, and Edward R. Valstar, MSc, PhD

Investigation performed at Leiden University Medical Center, Leiden, The Netherlands

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 roentgen stereophotogrammetric 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-migration 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) could lead to an estimated annual savings of over $400 million to the health-care system.

Conclusion: The phased clinical introduction of new prostheses with two-year RSA results as a qualitative tool could lead to 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.

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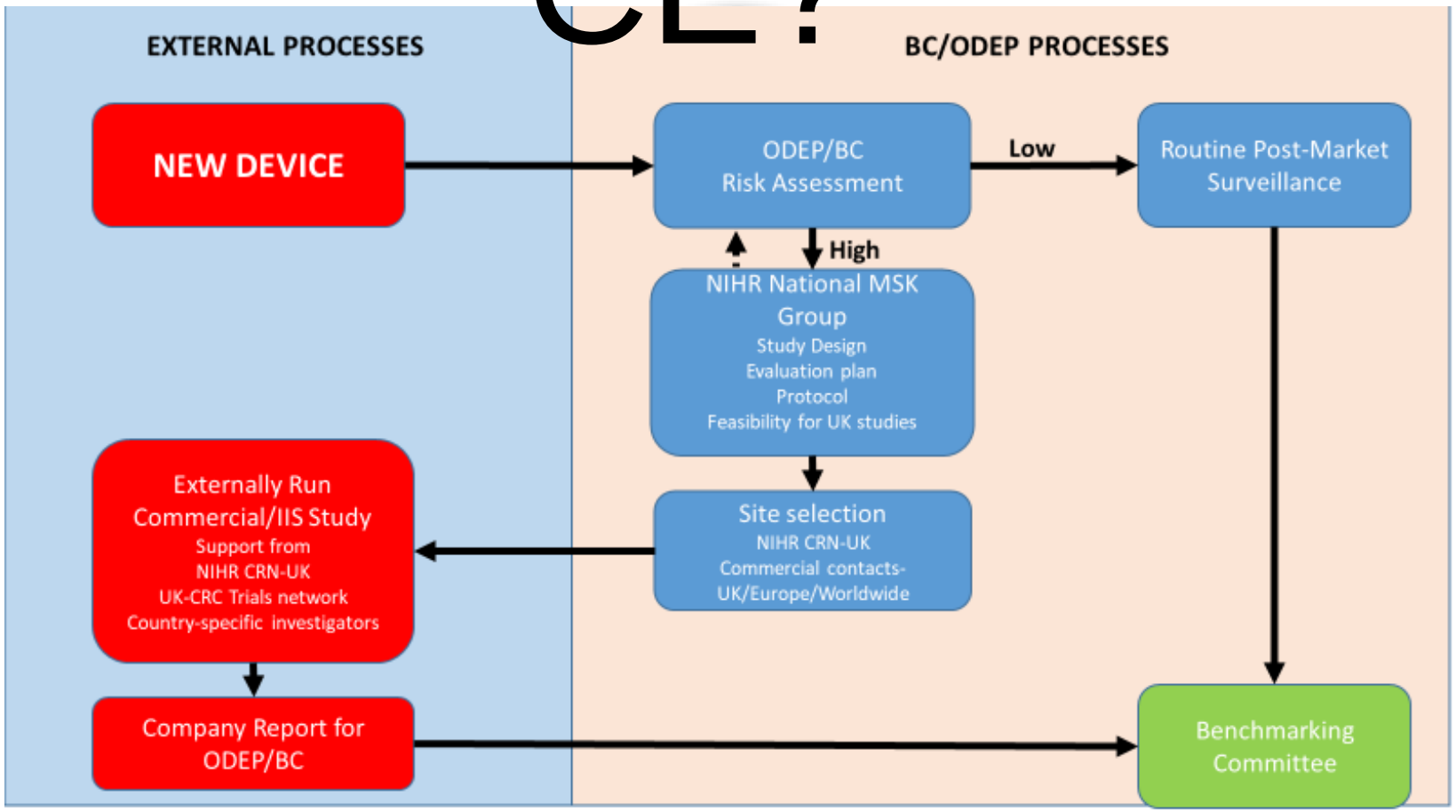
Detailed structure

CE?



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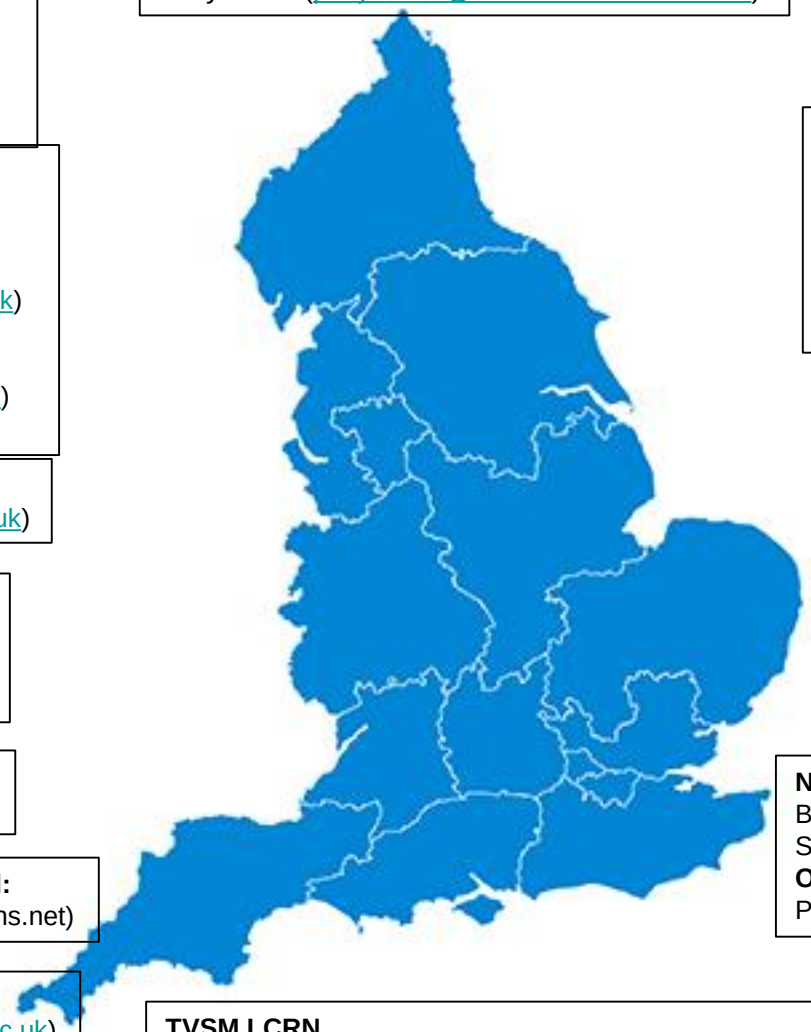

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Stakeholders

- Government bodies
  - NHS Exec
  - NIHR
  - Dept. Trade Ir
  - MHRA
- Manufacturers
- Trials infrastructu
  - NIHR CRN
  - RCS CTUs
- Industry Bodies
  - EUCOMED/A
- Royal Coll.Surg
  - STEP
- Patient Groups

NICRN CLINICAL RESEARCH NETWORK

Orthopaedic Data Evaluation Panel

Corin

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Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

SIR

abhi
Association of British Healthcare Industries
Innovation in Practice

NHS National Institute for Health Research

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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

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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

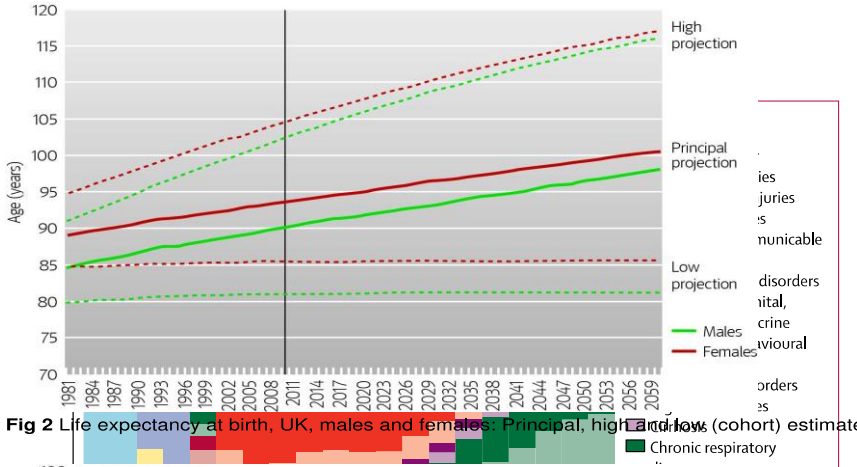


Fig 2 Life expectancy at birth, UK, males and females: Principal, high and low (cohort) estimates[3-5]

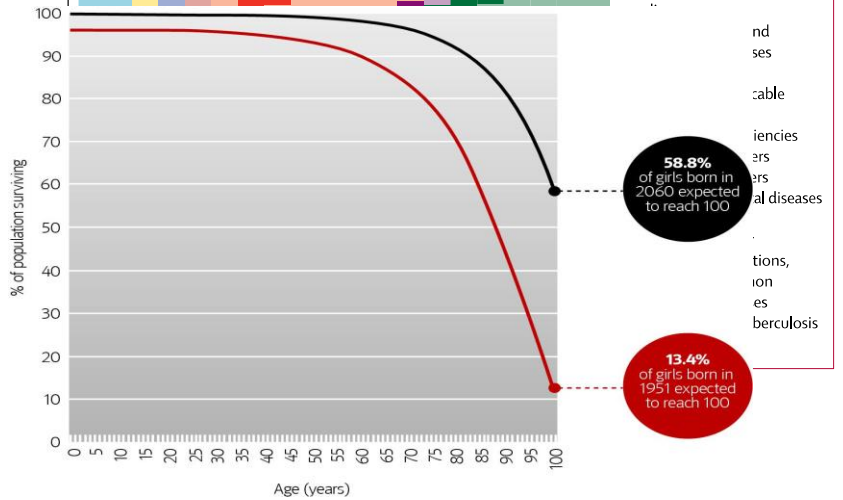
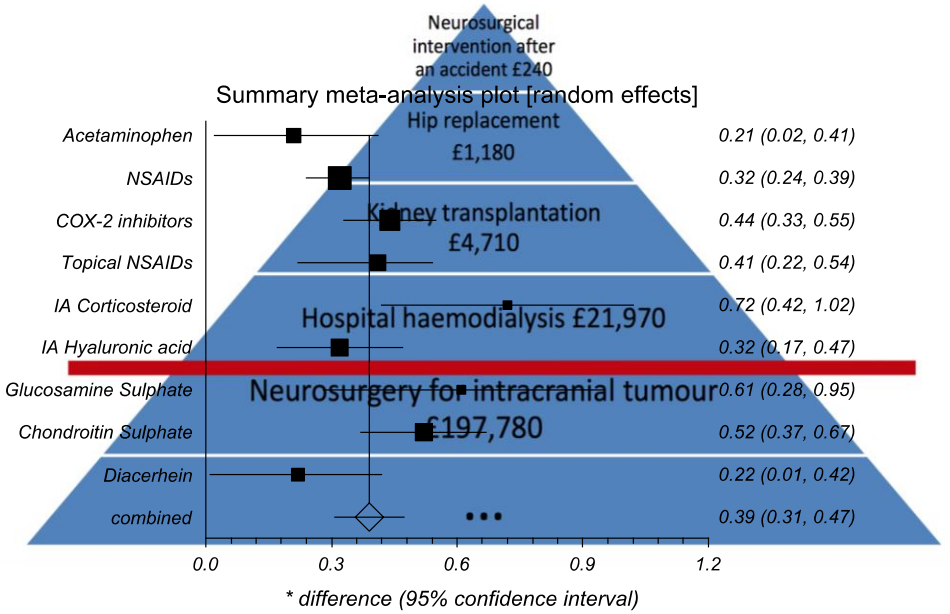


Fig 3 Population survival curves for UK females, 1951-2060[6]

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



ODEP/BC

- Highly successful in benchmarking
- First national benchmarking system
- Now used in 26 healthcare systems worldwide
- Linked to sister organisations
  - Netherlands
  - Germany

UNIVERSITY OF OXFORD

Beyond Compliance
Protecting Patients, Supporting Innovation

NHS National Institute for Health Research

ODEP
Orthopaedic Data Evaluation Panel

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

	1 Idea	2a Development	2b Exploration	3 Assessment	4 Long-term study
Purpose	Proof of concept	Development	Learning	Assessment	Surveillance
Number and types of patients	Single digit; highly selected	Few; selected	Many; may expand to mixed; broadening indication	Many; expanded indications (well defined)	All eligible
Number and types of surgeons	Very few; innovators	Few; innovators and some early adopters	Many; innovators, early adopters, early majority	Many; early majority	All eligible
Output	Description	Description	Measurement; comparison	Comparison; complete information for non-RCT participants	Description; audit, regional variation; quality assurance; risk adjustment
Intervention	Evolving; procedure inception	Evolving; procedure development	Evolving; procedure refinement; community learning	Stable	Stable
Method	Structured case reports	Prospective development studies	Research database; explanatory or feasibility RCT (efficacy trial); diseased based (diagnostic)	RCT with or without additions/ modifications; alternative designs	Registry; routine database (eg, SCOAP, STS, NSQIP); rare-case reports
Outcomes	Proof of concept; technical achievement; disasters; dramatic successes	Mainly safety; technical and procedural success	Safety; clinical outcomes (specific and graded); short-term outcomes; patient-centred (reported) outcomes; feasibility outcomes	Clinical outcomes (specific and graded); middle-term and long-term outcomes; patient-centred (reported) outcomes; cost-effectiveness	Rare events; long-term outcomes; quality assurance
Ethical approval	Sometimes	Yes	Yes	Yes	No
Examples	NOTES video[6]	Tissue engineered vessels[7]	Italian D2 gastrectomy study[8]	Swedish obese patients study[9]	UK national adult cardiac surgical database[10]

RCT=randomised controlled trial. SCOAP=Surgical Clinical Outcomes Assessment Programme. STS=Society of Thoracic Surgeons. NSQIP=National Surgical Quality Improvement Program. NOTES=natural orifice translumenal endoscopic surgery.

Table: **Stages of surgical innovation**

Demographics?

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