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To examine how the NHS assesses the potential benefits of new or alternative medical technologies;

The innovation process:

The process of development, validation and adoption of new technologies is recognised as being a lengthy process, and one that does not always meet the intended expectations.

This experience is contributing to the increasing focus on fast tracking the innovation process in healthcare across many healthcare systems.

Innovation in healthcare results from a collaboration between clinicians, scientists, entrepreneurs and commercial organisations - as well as managers and policymakers in healthcare. Defining present standards of care and utilising new technology to redefine products and services will allow new best practices to be implemented and audited across healthcare systems.

In terms of UK adoption of technologies there is currently no method similar to adoption of pharmaceuticals. Whereby, once clinical and cost effectiveness has been demonstrated, there is requirement for commissioners to adopt a technology across the wider NHS. Developing and delivering an effective evidence base, should be seen as a marker of quality for adoption not in the UK, but globally.

This is presenting unique problems whereby expediency in the innovation process, subverting the usual evidence requirements for effectiveness is leading to considerable harms and not realizing the full benefits of new technologies.

This reports highlights the important evidence components, which are an essential requirement to develop safe and effective technologies, these are:

1. **Role of regulation**
2. **Clinical Trials**
3. **Hierarchies of evidence**
4. **Health Technology Assessments**
5. **Health Technology Programme**
6. **NICE**
7. **Current UK Initiatives to improve innovation**

1. Role of regulation in assessing new and innovative devices

Whilst new drugs require at least randomized controlled trials to gain regulatory approval, for medical devices even under the more stringent US system (PMA approval process) only one controlled trial (not necessarily randomized trial) is required. However, an even more worrying issue with device regulation in both the EU and US is the use of 'substantially equivalent' in evidence submissions for regulatory purposes.

In 1976, in the US many devices were already on the market, so a less burdensome alternative to PMA known as 510(k) provision was approved. The 510 (k) pathway did not require clinical trials; the manufacturer was only required to demonstrate a device was "substantially equivalent" to another device already on the market. The problem now is that the definition of equivalence is interpreted so loosely that the FDA admits they need to "clarify the meaning of 'substantial equivalence.'"

The predicate of equivalence is also used within the European Union (EU) regulatory system for device regulation. There are three European Directives related to device regulation. These directives, which lead to CE marking and access to the European market, state the extent and nature of clinical data required for approval.

Problems occur because even for implantable devices, the scrutiny of evidence at the outset is left to private organizations known as Notified Bodies; and second, clinical data required for the equivalent route can involve as little as "a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device". The use of equivalence is therefore left to the manufacturer and the Notified Bodies to determine, without any outside scrutiny of the decision making process centrally or within each EU country.

The level of clinical data required for a new device can be minimal. For example, a directive would

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include as evidence for approval "a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device". This is a very low level of evidence and could be obtained in a few days, contrasting markedly with the type and extent of clinical trial data required for new drugs.

The specific council directives allow studies of other similar devices to be sufficient in a literature review for regulatory approval

►B COUNCIL DIRECTIVE 93/42/EEC and 90/385/EEC
• _(k) 'clinical data' means the safety and/or performance information that is generated from the use of a device.

Clinical data are sourced from:
• _— clinical investigation(s) of the device concerned, or
• _— clinical investigation(s) or other studies reported in the scientific literature, of a similar device for which equivalence to the device in question can be demonstrated, or — published and/or unpublished reports on other clinical experience of either the device in question or a similar device for which equivalence to the device in question can be demonstrated.

Even for the more stringent PMA process, there are profound differences in evidence requirements between the US and EU.

Rejected Devices by the US FDA that were approved in the EU:

Covidien PleuraSeal lung sealant system

This device went on the EU market in November 2007 and is used during elective pulmonary resection as an adjunct to standard closure techniques for visceral pleural air leaks. However, the Investigational Device Exemption (IDE) study (a clinical study for FDA regulatory purposes) produced unexpected interim results. In October 2010 Covidien announced a worldwide recall of all PleuraSeal lung sealant systems

Medtronic Chronicle

The Chronicle is an implanted system designed to measure and record haemodynamic variables continuously. In March 2007, an FDA panel refused to approve the device, citing statistically insignificant results as "lack of clinical effectiveness." It was nonetheless approved in Europe.

PIP breast implants

In 1991, breast implants manufactured by Poly Implant Prosthese (PIP) received a CE mark for its silicone breast implants But in 2001 they changed the gel, so that it was different from the one described in the CE marking file. This modification led to rupture rates higher than silicone implants made by other manufacturers. On 30 March 2010, the French regulator—AFSSAPS— issued a recall of all pre-filled silicone breast implants manufactured by PIP, affecting an estimated 35 000-45 000 women worldwide.

Trilucent breast implants

First marketed in the UK in 1995 by LipMatrix, Trilucent implants were recalled and withdrawn from the market in 1999. The filler of the implants, which was derived from soybean oil, broke down in the body and leaked through the shell, causing ruptures. The breakdown of the filler was significantly different from that predicted during preclinical testing, and many patients had to have implants removed.

Conor CoStar drug eluting stent

CoStar is a cobalt, chromium, paclitaxel eluting coronary stent and received EU approval in 2006. In May 2007, Johnson and Johnson announced that a pivotal clinical study of the device had failed to find a significant difference on the primary end point, possibly because patients got a suboptimal therapeutic dose of paclitaxel. The trial did not identify safety issues. As a result of this trial, Conor terminated ongoing clinical trials and chose not to conclude the submission of its US premarketing approval. Conor discontinued the sale of the stent in Europe, Asia, and Latin America.

Reproduced from Cohen D. Out of joint: the story of the ASR. BMJ. 2011 May 13;342:d2905. doi: 10.1136/bmj.d2905.

Perhaps what is even more concerning than the device recalls and high profile cases (such as the MoM hips and PIP implants) is that many medical device problems go unnoticed.

However, it seems as though the tide is turning in terms of regulatory requirements. The US system is coming under increased scrutiny with calls for the removal of the 510(k) process. The influential Institute of Medicine has recommended the FDA do away with the 510(k) approval process and replace it "with an integrated premarket and post-market regulatory framework that effectively provides a reasonable assurance of safety and effectiveness throughout the device life cycle." It is possible that all implantable devices in particular will require PMA approval and thus clinical trial data in the future. However, more stringent regulations are unlikely to be passed into law in the US without a substantial battle with the medical device industry.

Analysis of manufacturers' submission challenges, to the NICE medical technology program, reveals there are significant issues in relation to basic and

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general research skills that need to be addressed amongst manufacturers.

In addition, interviews with manufacturers highlight the current status quo: 'pharmaceutical and medical technologies were also considered very different by manufacturers.' As such, the wide spread belief is, that devices do not require the same level of evidence as drugs to gain access to a market and be used in clinical practice.

Failures of medical devices cause harm and cost money. More stringent requirements to provide evidence from clinical trials for the efficacy and safety medical devices before they are approved should therefore be welcomed by patients, clinicians and the medical device industry.

Evidence for new devices must also be open to scrutiny by patients in individual countries, as well as health care providers and researchers. The potential risk of a new device should match the type of evidence required prior to approval for use in clinical settings. Without these changes to current systems, it is likely we will continue to see substantial complications arising from faulty devices.

2. Clinical trials

Clinical trials and drug studies are big business, valued at $30 billion across 105 countries, and in less developed countries the number of trials is growing rapidly. Yet, in direct contrast, the number of drug trials in the UK has fallen substantially, from 728 in 2008 to 470 in 2010.

This suggests a potentially worrying global trend whereby expediency in the conduct of trials, for example by minimising regulation in different countries around the world assumes a greater value than mechanisms to ensure that trials are conducted with integrity and quality.

The proposal for a regulation of the European Parliament and of the council on clinical trials on medicinal products for human use and, and repealing Directive 2011/20/EC highlights the problems that have occurred. The substantial increases in administrative burdens required in the EU at the outset of a clinical trial, lead to an increased delay for launching a clinical trial by 90%, which now takes on average 152 days.

This length of delay is untenable and directly contributing to relocation of many trials outside the EU and the UK, to no doubt less burdensome environments. In addition, the near 100% increase in administrative costs have not demonstrated parallel increases in safety and highlight all that is wrong with the current system. Too burdensome, too slow, and beset with unnecessary administrative problems without clear upsides.

3. Hierarchies of Evidence

There are many different 'hierarchies" or 'levels of evidence' for studies. An understanding of the difference evidence requirements for improving healthcare is essential.

Early evidence hierarchies were introduced primarily to appraise the quality of evidence for therapeutic effects, while more recent attempts to assign levels to evidence have been designed to help systematic reviewers, or guideline developers and those involved n implementation.

More recent evidence-ranking schemes such as GRADE avoid common objection by allowing observational studies with dramatic effects to be 'upgraded', and trials may be 'downgraded' for quality and other reasons. Another advantage of the GRADE approach is that it takes other important factors such as directness, precision, and consistency when appraising quality of evidence.

However, what GRADE has gained in accuracy, it may have lost in simplicity and efficiency. The GRADE system takes time to master and moreover is intended for appraising systematic reviews used in the production of guidelines.

The 'bar' for how much and what kind of evidence is considered sufficient for fast track adoption are perceived by many in industry as being very unclear. There is no universal checklist or agreed set of evidence criteria, and decision makers across Europe adopt different approaches. In addition, the overall level of understanding by industry, regulators, clinicians about evidence and study designs - beyond initial validation studies - is often quite unclear.

This lack of clarity clashes with the global strategies of companies, who set up studies that are not

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necessarily specific to the UK market. In fact, compared to larger markets such as the US, the UK market is often not seen as a priority, and studies are primarily designed to meet the requirements of the bigger markets.

One of the most important developments over the last 25 years has been the establishment of the Cochrane Library, which produces high quality systematic reviews, which are at the tope of the evidence hierarchy. Currently half of the Cochrane groups are located in the UK and funded by the NIHR.

It is therefore essential to have an understanding and support the development of high quality evidence.

4. Health Technology Assessments

The development of NICE's Technology Appraisal Guidance involves independent assessment of the evidence. Individual teams, in academic centres, hosted in seven universities, across the UK, undertake these assessments.

The TAR centres prepare Technology Assessment Reports (TARs) for NICE's Multiple Technology Appraisal process, and Evidence Review Group (ERG) reports for its Single Technology Appraisal process, for consideration by the NICE Appraisal Committees. These assessments combine evidence for clinical effectiveness with cost effectiveness data, forming the basis for NICE decision making

5. Health Technology Programme

The HTA Programme is the largest of the NIHR programmes, funding independent research about the effectiveness, costs and broader impact of healthcare treatments and tests for those who plan, provide or receive care in the NHS.

Studies are funded via a number of routes including commissioned and researcher-led workstreams.

The research serves a variety of key stakeholders including: decision-makers in local government, policy-makers (including NICE), researchers, NHS health professionals, other NIHR stakeholders, and the general public.

6. Role of NICE

A key element of the regulatory system has been the National Institute for Health and Clinical Excellence (NICE), and a key aspect of NICE's decisions has been not just value, but also value for money. This has not been without controversy.

NICE also uses many strategies to support implementation of NICE guidance, including support products such as commissioning guides, costing spread sheets, generic business cases for capital purchases, pod-casts and a range of bespoke tools tailored on a case-by-case basis. Implementation support activities at NICE have recently been augmented by the transfer of the former National Technology Adoption Centre to NICE. Now known as the Health Technology Adoption Programme, activities include detailed adoption and site demonstrator projects which detail the "real life" impact on care pathways and cash flows as well as identifying and mitigating the key barriers to adoption.

Another key initiative to support adoption of NICE recommended technologies is the NICE Implementation Collaborative, established in response to a recommendation in the NHS Innovation Health and Wealth report. This is a partnership between the NHS, the life sciences industry, healthcare professional bodies, key health organisations and the public, who have committed to work with each other and other organisations to understand and analyse the barriers that exist to the implementation of NICE recommendations.

7. Current Initiatives to improve innovation in the UK

NIHR Diagnostics Evidence Cooperatives four Diagnostic Evidence Cooperatives that aim to stimulate collaborations between different stakeholders in diagnostic testing. For example, the aim of the Oxford NIHR DEC is to improve the implementation of IVDs in primary care settings.
Academic Health Science Networks (AHSN): which aim to improve health care through faster identification, adoption and spread of proven innovations, including through collaboration with industry.
Technology Strategy Board (TSB): is the UK's innovation agency with a goal is to accelerate

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economic growth by stimulating and supporting business-led innovation.

NIHR Biomedical Research Centres (BRCs): drive progress on innovation and translational research in biomedicine into NHS practice.

NIHR CLAHRC:

NIHR CLAHRCs are an alliance of academic and healthcare organisations working to develop and promote a more efficient, accelerated and sustainable uptake of clinically innovative and cost-effective research interventions into patient care

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