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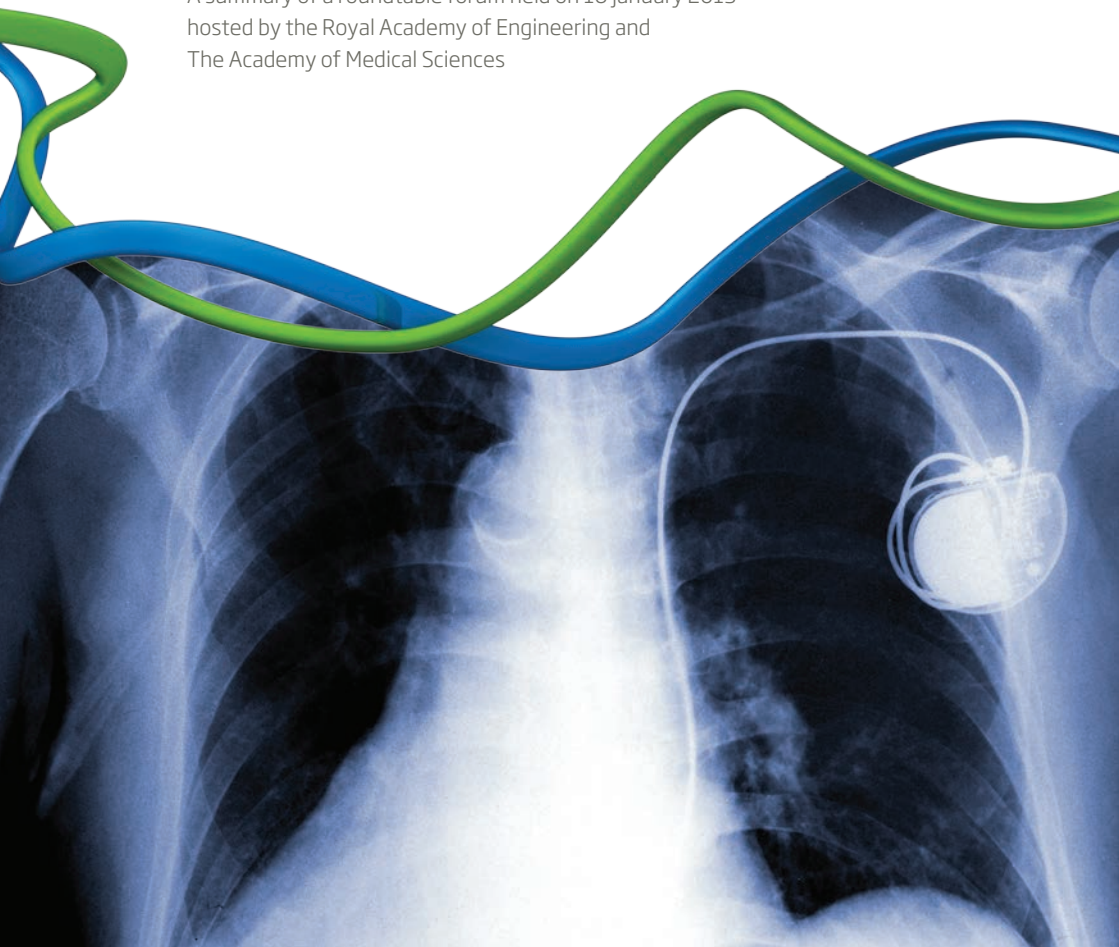
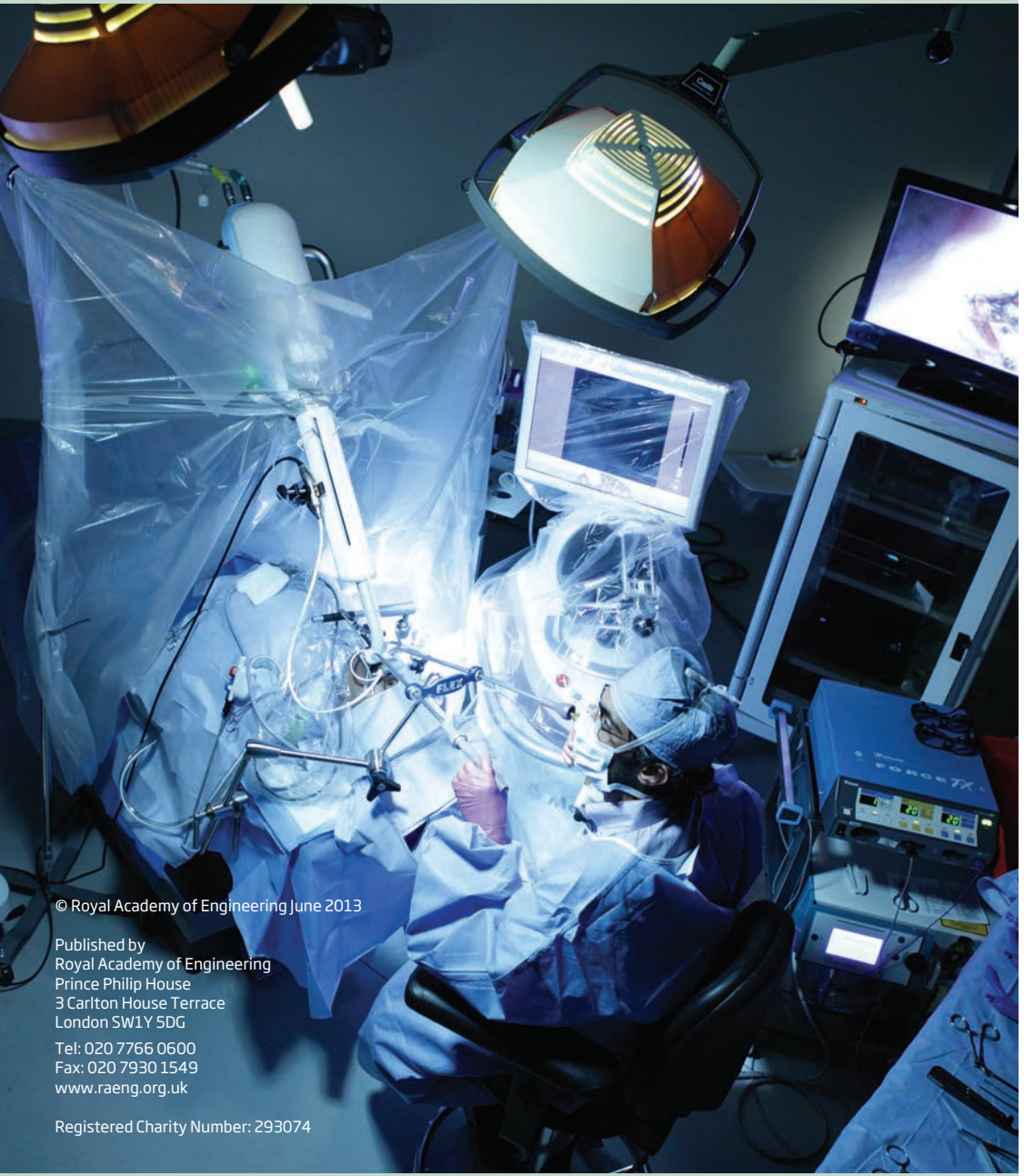
The Academy of Medical Sciences

Establishing high-level evidence for the safety and efficacy of medical devices and systems

A summary of a roundtable forum held on 16 January 2013 hosted by the Royal Academy of Engineering and The Academy of Medical Sciences





Published by
Royal Academy of Engineering
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www.raeng.org.uk

Registered Charity Number: 293074

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Contents

Executive summary

Medical devices play an important role in enhancing patients' quality of life and supporting the healthcare system, but there is a need for improved methodology to obtain evidence for their safety, performance and efficacy. With its strong research base and the NHS at its core, the UK is well placed to generate the necessary high-quality evidence. But guidance is needed on the nature of evidence required, and its implementation. New approaches are needed to produce robust, appropriate evidence that can foster innovation.

A major theme of the roundtable forum was the potential to adopt methods from the engineering sector for medical devices. A transferable lesson from engineering is that engineers acknowledge that their products evolve and can fail, and therefore carry out continuous monitoring of systems in use. The framework encourages the reporting of near misses and accidents, so designs can be improved and risks mitigated. Continuous monitoring is analogous to post-market surveillance of medical devices.

Furthermore, the engineering framework for assessing safety has been built with input from non-regulators, recognising the wealth of highly relevant experience within the industrial sector. The development of a regulatory framework for medical devices would likely benefit from a similar level of dialogue to establish hazards, safety functional requirements and thresholds.

Another aspect of the value of dialogue was the development of devices that meet clinical need. Clinicians, device manufacturers and the 'end user' could work together to identify which devices need to be developed to meet patient need.

The value of observational studies was acknowledged where randomised controlled trials (RCTs) are not possible or appropriate. Observational studies are particularly important for demonstrating rare, catastrophic and delayed harms of treatments that are not captured by RCTs. Observational studies may be less academically rigorous than RCTs, and are prone to bias, but they can still deliver valuable information about how technologies function in real-world settings.

It was acknowledged that a major problem with designing trials for medical devices is that devices, unlike medicines, are increasingly part of complex systems that may include software, hardware, healthcare professionals, and even operating theatres. Different components of the system can influence the outcome of a trial, such as the experience of the surgeon or the quality of the implant. However, these complex interventions are revolutionising the way we deliver medical care and have the potential to offer enormous patient benefit. With appropriate design, meaningful trials for medical devices can and should be undertaken. Pipelines need to be established to develop this process, including specialist trial centres to develop methodologies and offer support, and clinical networks to oversee progress from early to late phase trials.

The workshop participants identified a number of steps that should be taken to improve the safety and efficacy of medical devices:

1. More use should be made in the medical devices industry of hazard analysis and safety functional requirements, with active steps taken to adapt and adopt the methods used in engineering.
2. The regulatory framework should specify the different levels of evidence required to ensure safety, performance and efficacy at different stages throughout the life and iterations of the medical device.
3. The roles and powers of Notified Bodies, and the CE marks they verify, are in need of review. The powers, inconsistencies and lack of transparency of Notified Bodies are cause for concern, as is the current CE system, which fails to promote evidence generation. This is expected to be addressed by new EU medical devices regulations proposed by the EC.
4. The regulatory framework should be prescriptive, yet responsive, ensuring the withdrawal of faulty products from the market as quickly as possible.
5. The design of medical devices would benefit from a more integrated contribution from a more diverse range of stakeholders including patients, engineers, manufacturers, healthcare professionals and economists.
6. Initiatives that promote best practice in the design of studies and methodologies are needed in order to bridge the evidence gap. This may include training and education programmes, and the establishment of further centres of clinical research excellence.
7. The NHS, with its unique patient identifier system, has the potential to facilitate the recruitment of patients into device trials. Wider adoption of the patient identifier should be promoted.

The Royal Academy of Engineering and The Academy of Medical Sciences will continue to engage with relevant bodies on these priority areas identified by the participants, in particular the first three conclusions above.

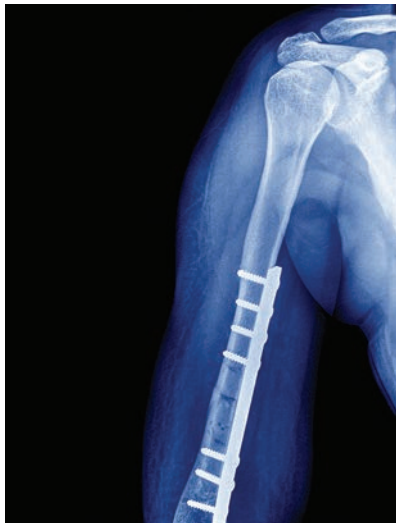
Introduction

Ensuring the safety and efficacy of all healthcare interventions is at the heart of patient care. For pharmaceutical innovation, the randomised controlled trial is the acknowledged gold standard for creating a body of high-quality evidence. But designing clinical trials to establish the evidence for medical devices has proven more problematic.

There are many innovative devices and systems now under development by engineers and clinicians that have the potential to be cost-effective solutions for delivering improved patient outcomes. However, their application in patient care is limited by the challenges of testing and regulation. Furthermore, the current system (appendix 1) of evidence generation is sometimes insufficient to adequately demonstrate patient safety and efficacy, leading to lack of uptake.

This meeting sought to explore alternative pathways to establishing the safety and efficacy of medical devices and systems for enhanced patient care and to promote access to and uptake of effective and novel medical devices. Hosted by the Royal Academy of Engineering and The Academy of Medical Sciences on 16 January 2013, it brought together clinicians and engineers from healthcare, industry and academia with research funders and regulators. The aim was to foster discussion and cross-disciplinary learning, with a view to identifying how best to obtain high-quality evidence for the safety and efficacy of medical devices.

This meeting sought to explore alternative pathways to establishing the safety and efficacy of medical devices and systems for enhanced patient care and to promote access to and uptake of effective and novel medical devices



This report aims to stimulate further dialogue between the Royal Academy of Engineering and the Academy of Medical Sciences with key organisations and policymakers on the priorities identified at the meeting to enhance evidence generation for medical devices.

While the workshop was hosted by the Royal Academy of Engineering and The Academy of Medical Sciences, the views expressed in this report represent those of the workshop participants (appendix 3), as reported at the meeting (appendix 2). Aspects of the discussions have been incorporated to the joint response from the Royal Academy of Engineering and The Academy of Medical Sciences to the Medicine and Healthcare product Regulatory Agency consultation on the revision of European legislation on medical devices and *in vitro* diagnostics devices [1].

Plenary session

Clinical research: the balance between benefits and risk

Presented by Professor Stuart Walker, Founder, Centre for Innovation in Regulatory Science (CIRS)

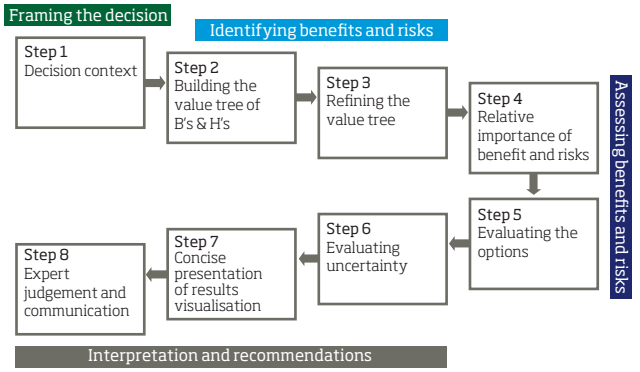
Medical regulators must weigh up the benefits and risks of new medicines in order to determine approval. But although they generally do a good job, inconsistencies exist. Offered the same data, different regulators can arrive at different decisions, and the process is sometimes hampered by a lack of coherent, structured information from the manufacturers.

The importance of frameworks

Medical device regulators could benefit from a standardised framework to help assess the benefits and risks of new products. The framework would be underpinned by scientifically rigorous decision-making tools, such as the quality of decision-making orientation scheme (QoDoS) [2], and include a set of principles, guidelines and methods to guide decision-makers in selecting, organising, understanding, summarising, and communicating the relevant evidence. It would need to be transparent, dynamic, flexible and able to incorporate the views of different stakeholders, including patients.

Frameworks like this are used to guide decision-making within medicines regulation. Four such frameworks currently exist, but a 2012 Centre for Innovation in Regulatory Science (CIRS) workshop [2] proposed combining them into a single eight-step approach. The proposal has since been endorsed by an international group of regulators and drug companies.

Figure 1: Eight-step benefit/risk framework for devices



A benefit/risk framework for medical devices

A similar, standardised framework for medical devices need not be far off. Last year, the US Food and Drug Administration (FDA) published the report *Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications* [3]. Its recommendations can be shaped to fit within an eight-step benefit / risk framework (Figure 1), and could potentially provide the basis for a standardised approach to evaluating medical devices. This benefit-risk analysis must continue throughout the life of the product. Benefits, as well as the risks, must be continuously analysed; normally more risks are identified as time goes on.

Offered the same data, different regulators can arrive at different decisions, and the process is sometimes hampered by a lack of coherent, structured information from the manufacturers

Session 1: The nature of medical evidence

Part 1 – Safety

The nature of medical evidence: innovation and regulation in health

Presented by Dr Carl Heneghan, Director of the Centre of Evidence-Based Medicine (CEBM), and Clinical Reader, University of Oxford

Problems with the current systems

Medical devices bearing the CE mark can be marketed freely within the EU without further control. It should be noted, however, that CE marks are mandatory markings of conformity, not an assurance of safety or effectiveness. The CE mark for medical devices indicates that it complies with the essential requirements. In the US, manufacturers of new devices that are similar to existing FDA-approved products can seek regulatory approval on the basis of equivalence to a 'predicate device' – 510(k) [4]. But equivalent devices are not the same, and small changes in design can produce big changes in safety and in efficacy.

US regulators typically demand more evidence than EU regulators. For example, EU approval of the angioplasty-related device Guard Wire required a 22-patient study with no control group. In the US, as there was no predicate device, the FDA asked for an 800-patient multi-centre randomised controlled trial (RCT) under the premarket approval application (PMA) process [5]. Discrepancies of this magnitude present UK patients with an unacceptable level of risk.

The regulatory process is not keeping pace with the rapid development of technology. RCTs are expensive and slow. By the time a device receives its FDA approval following an RCT, the supporting evidence may be out of date; also, the product itself may be technologically out of date. The comparative underregulation within Europe results in UK (and EU) patients facing potentially avoidable risks of unclear benefit; however, more stringent processes may not be swift enough to respond to technological developments.

Fostering technology

The UK needs to foster technology, and incentivise the evidence-gathering process required to produce innovative, useful medical devices. We need a process that mirrors the rapid development of technology and that evolves with it.

General practice offers the perfect place for innovation in diagnostic technologies, providing an obvious route into the NHS. But GPs in general do not have access to these new innovative technologies.

The NHS gives the UK a unique opportunity to become a world leader in technology trials and recruitment. But while the UK excels in some areas, such as clinical trials for cancer treatment, it falls short in many others and lags behind many countries. It is felt by some that the UK needs to do more in order to make technological development more attractive in the UK.

Evidence gathering can be a lengthy process during which many devices fall by the wayside. To compensate, we need lots of technologies at the outset, to nurture technology in our research institutes, to have more products entering the pipeline with more case studies and to allow for failure.

To enable this, the initial design state needs to be more cost-effective. But this is at odds with the needs of industry. Manufacturers want to make devices that can be implemented straight away, so processes are needed that incentivise them to produce quality evidence and that enable clinical trials to be delivered more efficiently and cost-effectively.

A 2012 report *Innovation in diagnostics and healthcare: improving bench to bedside processes for testing* [6] raised three key points applicable to medical devices. Namely, we need to improve the generation of evidence for diagnostic tests, facilitate the generation of this evidence with industry and determine the essential studies needed before introduction into clinical practice. The challenge is how to implement these recommendations.

Ensuring the safety of medical devices

Presented by John Wilkinson, Director of Medical Devices, Medicines and Healthcare Products Regulatory Agency (MHRA)

The regulation of medical devices is about balancing benefit and risk. Regulation that is too free and easy encourages innovation – more devices, more potential benefit to patients – but it also means more potential risk. Regulation that is too cautious means fewer devices emerging through a more costly pipeline, and patients deprived of potentially useful treatments. The decision-making must be balanced and there should be clear articulation about expectation and timescale.

Medical devices are engineered products, the designs of which are iterated throughout their lifecycle, and the regulatory process needs to reflect this. Pre-market evidence is important, but a more accurate evaluation of benefits and risks can only be produced when the device is used in practice. Sometimes inconsistencies exist in the evidence needed to launch a product on the market. New proposed legislation seeks to address these and other issues.

Features of the new proposed EU legislation

Last year, the EC published proposals for revised legislation regarding medical devices and *in vitro* diagnostic devices [7]. Main features of the proposals relating to medical devices include:

Notified Bodies

- Work to improve the management and consistency of Notified Bodies
- Steps to tighten up the designation and audit of Notified Bodies
- Notified Bodies to play a role in vigilance and market surveillance, ensuring thorough testing and regular checks on manufacturers.

Clinical evidence

- Acceptance of equivalence for certain mature, established, technologies. Less mature technologies that include significant changes require more pre-market evidence
- Improve transparency by specifying the publication of safety and performance data, and making the supply chain more traceable
- Stricter requirements for clinical evidence, including post-market clinical follow-up, although details on the type and quality of evidence have not been specified
- A new, public, centralised database offering information on safety and serious incidents.

Pre-market

- Increased pre-market scrutiny for novel, high risk devices
- Common technical specifications about the evidence needed to launch specific products on the market
- Introduction and identification of a qualified, responsible, culpable person within the manufacturing company.

Vigilance

- Central database and coordination – work on exchanging information between EU member states
- Trend reporting and analysis post-market to signal when things go wrong and to identify problems more quickly.

Governance and oversight

- Establish a new governance structure of Member State experts and centralised clinical expertise. Improve coordination between Member States
- Wider and clearer scope of EU legislation, including devices without medical purpose such as cosmetic devices.

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials © HULTON/GETTY

Part 2 – Efficacy

The role of The Cochrane Collaboration in establishing evidence-based therapies

Presented by David Tovey, Editor in Chief, Cochrane Collaboration

The Cochrane Collaboration is an international organisation that aims to support informed healthcare decision-making by preparing systematic reviews of the effects of healthcare interventions. Cochrane evidence is used worldwide by a wide range of stakeholders in diverse products and activities.

Cochrane reviews very often concentrate on RCTs, which are recognised as being the method of testing treatment effectiveness that is least prone to bias. In most scenarios, they remain the best way to compare present interventions with possible future ones. Designed appropriately, they can be also used to evaluate complex interventions and medical devices. There are circumstances where RCTs are not feasible or available, for example where the magnitude of benefit is very large (for example, we would not carry out an RCT for the efficacy of parachutes – there is clearly a huge benefit over not having them!). In such circumstances, observational studies can provide useful information, but because such studies are prone to unpredictable levels of bias, researchers need to be careful in placing too much emphasis on non-randomised studies. Observational studies are particularly important for demonstrating rare, catastrophic and delayed harms of treatments however, since these are unlikely to be captured by RCTs.

Cochrane Reviews also present their results in Summary of Findings tables using a methodological approach called GRADE [8]. This approach implicitly acknowledges that evidence from observational studies can increase confidence in an estimation of healthcare effectiveness. In line with this, a thorough assessment of the efficacy of a medical device will require more than just RCT evidence. Other sources of evidence, including qualitative and economic information, may be of value.

> Drug trials are comparatively simple – they involve comparing pill A with pill B (usually a placebo), making it relatively easy to get patients, clinicians and trialists on board. Devices, however, tend to be a component of a complex intervention – which may be carried out with subtle differences by different surgeons

The following issues were highlighted regarding the right approach to medical testing:

- Realism is key – over-optimistic assumptions about new drugs and devices have sometimes led to a lack of realism
- Problems of hidden data – it is sometimes impossible to access all the data needed to evaluate drug and device interventions
- Overdiagnosis – as devices become more sophisticated, reports may highlight cases of problems that may never cause harm. This causes patient anxiety, and places burdens on the healthcare system.

The role of randomised controlled trials for medical devices

Presented by Professor Dion Morton, Director of Research, Royal College of Surgeons

RCTs allow risk and benefit to be measured in parallel, and so are the best way to deliver quality evidence on safety and efficacy. They are best done in large, multi-centre trials, making the results generalisable while enabling the detection of small, clinically significant effects that smaller trials might miss. We have this evidence for medicines, but it is lacking for medical devices.

Part of the reason may be the inherent differences between testing drugs and devices. Drug trials are comparatively simple – they involve comparing pill A with pill B (usually a placebo), making it relatively easy to get patients, clinicians and trialists on board. Devices, however, tend to be a component of a complex intervention – which may be carried out with subtle differences by different surgeons. With a complex intervention, the trial outcome is more likely to be influenced by clinician bias and, in some cases, patient behaviour. Trialists too

are likely to influence the procedure, requesting standardisation of complex variables at the expense of generalisable data.

Complex interventions are revolutionising the way we deliver medical care and have the potential to offer enormous patient benefit. With appropriate design, meaningful trials for medical devices can and should be undertaken, and unlike other trials of medicines, the benefits may go beyond the trial's primary outcome. Devices iterate and change, so adaptive designs using Bayesian statistics that capture changing levels of knowledge will sometimes be needed.

Pipelines need establishing to develop this process, including specialist trial centres to develop methodologies and offer support, and clinical networks to oversee progress from early to late phase trials. National leadership within interventional disciplines, such as Growing Recruitment in Interventional Surgical Trials (GRIST) [9] is also required. Together these initiatives should help evidence keep pace with technology and aid the rapid dissemination of new, trialled technologies across the NHS.

It is important to consider the endpoint of what the device is intended to achieve. Reducing the harm of a device may be more useful than increasing the benefits of the device.

Session 2: The nature of evidence in engineering

The safety framework for engineering products

Presented by Paul Anuzis, Chief Reliability Engineer, Rolls-Royce

The aerospace industry is highly regulated, with a prescriptive regulatory framework well established for assessing safety. The framework is in two parts – design assurance (pre-market testing) and continuous monitoring (post-market testing).

The process of design assurance

1. **Identify the hazards** posing an immediate threat to safety and assign them to one of the four hazard levels: (1) minor, (2) major, (3) hazardous or (4) catastrophic.

   In certifying an aircraft fit for purpose, regulators would focus on hazard levels 3 (engine-related) and 4 (loss of an aeroplane).

2. **Identify the failures** that would lead to, for example, a level 3 hazard, such as uncontained high-energy debris or uncontrolled fires.

3. **Identify 'safety functional requirements'**, the processes needed to protect against these hazards. These are then set as standards within the regulatory framework.

   For example, turbine blades which may accidentally shear off need to be confined to protect against uncontained high-energy debris.

A company designing a new jet engine must build a **safety case**. The company would approach the regulator, who will advise which safety functional requirements apply. These can change over time. The company will then submit a strategy, detailing how they intend to demonstrate compliance.

The Rolls-Royce Trent 1000 engine which powers the Boeing 787 Dreamliner

Compliance is then demonstrated through test and analysis, with controls such as life limitations or inspections often applied. This might involve the fire testing of sensitive components, and the analysis of blade containment using worst-case scenarios.

Finally, the company reports its findings against each safety functional requirement in a certification report. Each claim is backed up by traceable reports, analyses and tests. For a safety case, a specific report documenting all reasonably expected failures is produced via a 'failure mode, effects and criticality analysis' (FMECA). This enables the manufacturer to declare to the regulator all failures that could result in major or hazardous consequences.

The process of identifying hazards affords manufacturers the opportunity to design them out, mitigate them, or control failures to an acceptable rate. For a new engine, the system will require thousands of hours of testing, and several years before the prototype can enter into service.

Continuous Monitoring /market surveillance

The regulatory framework acknowledges that failures do happen, hence the requirement for continuous monitoring. Continuous monitoring of a fleet of engines, for example, enables risks to be characterised and enumerated. This quantitative data can then be compared against documented thresholds and limits of acceptable risk (which are themselves based on empirical data and industry experience), enabling calculation of the 'reaction time to fix' – the time period in this scenario, during which the fleet continues to operate while all engines are fixed.

Safety cases and accident investigation

Presented by Dr Chris Elliott FREng, System Engineer and Barrister

Safety cases

In safety-critical industries, manufacturers must demonstrate to regulators that their new product is acceptably safe. They do this by complying with any specific regulatory requirements, and by building a pre-market safety case.

A safety case provides a structured argument, supported by a body of evidence that provides a compelling, comprehensive and valid case that a system is acceptably safe for a given application and a given context. The process is systematic and explicit, and asks manufacturers to consider, not how a product works, but how it might fail. The key questions are, what are the risks and how might these risks be appropriately controlled?

The core of a safety case is typically a risk-based argument backed up by corresponding evidence and assumptions to demonstrate that all risks associated with a particular system have been identified and that risk controls have been put in place. Data and evidence are collected and documented in a quantitative manner. Very often, the real value of a safety case comes not from the end product, but from the process of developing it – the evidence-gathering, the challenging of assumptions and the dialogue process.

The use of safety cases is an accepted best practice in UK safety-critical industries, but it is not widely used in the healthcare system, where it could prove a valuable tool for assessing safety [10, 11].

Accident investigation

Accident investigation is part of post-market surveillance. In the UK, accident investigation of air, marine and rail accidents falls under the remit of independent public accident investigation bodies that are required by statute to look for cause not blame. The process aims to improve safety and prevent accident recurrence. There is legal protection to encourage open investigation but a culture of blame and fear of litigation are making this increasingly difficult.

One accident investigation model, used by the airline Qantas, asks whether an accident was caused by a 'system-induced violation.' Blame is inappropriate if the 'system' is designed in such a way that another person could make the same mistake in the same situation.

Models like this could increase confidence in accident reporting. The aviation industry has spent decades learning from its mistakes and making aeroplanes one of the safest ways to travel. With healthcare, there is the potential to replicate this culture that encourages people to report accidents and near misses, and an investigation system that seeks cause and not blame.

> Clinical trials are the main method used to demonstrate efficacy, but trials can be prohibitively expensive and time-consuming, meaning that potentially good products never make it to market

Ensuring efficacy of medical devices – insights from the field of skeletal repair

Presented by Professor Serena Best, FREng, Professor of Materials and Metallurgy, University of Cambridge

Efficacy, and how to demonstrate it, are key issues for any company or research institution producing a new medicine or medical device. Clinical trials are the main method used to demonstrate efficacy, but trials can be prohibitively expensive and time-consuming, meaning that potentially good products never make it to market.

Trials have their limitations. Some deliver data on relative rather than absolute efficacy. And efficacy tests of different devices have their own idiosyncratic problems. For example, efficacy testing in orthopaedics is complicated by the fact that some outcomes, such as pain relief, are subjective, while objective measures, for example based on histological samples, are not possible.

Small companies struggle to fund and organise the trials needed to demonstrate the efficacy of new medical devices. And many large orthopaedic companies do not have the capability to run clinical trials required for the FDA's PMA submissions as a result of years of reliance on the FDA 510(k) equivalence submissions. Investors too often prefer to take the 510(k) route, which obviates the need for additional efficacy testing, rather than try and market something truly innovative. And all too often, funders are more focused on business plans than they are on efficacy studies.

Pre-market studies are another important source of efficacy data. Pre-market analyses vary widely depending on the product, and can be used to demonstrate the efficacy of a new medical device in its functional environment. Clinical trials, performed pre-market, offer efficacy data in their relevant environment, the clinical setting. As more combination devices emerge (such as scaffolds delivering biological compounds), clinical trials are becoming more important than ever.

If they are not done properly, clinical trials present a barrier to innovation. The NHS is potentially a huge asset for supporting clinical trials, and centres performing clinical evidence-based research should be encouraged. We have the capacity to synthesise huge amounts of data but need funding to do so. To prevent funding being wasted, we also need evidence of clinical failures. Positive and negative results must be reported. Better *in vitro* models and indicators of clinical success could help focus and refine the trials process. Get it right, and we will succeed in the goal of producing an environment that fosters innovation and the development of medical devices that deliver healthcare benefits.

The NHS is potentially a huge asset for supporting clinical trials, and centres performing clinical evidence-based research should be encouraged

Session 3: A worked example: the introduction of telehealth technology into the NHS

Evaluating the Whole Systems Demonstrator trial

Presented by Adam Steventon, Senior Research Analyst, Nuffield Trust

Telehealth is the delivery of healthcare-related services and information at a distance via telecommunication technologies. In one approach, patients use home-based devices, such as blood glucose monitors, to measure physiological variables (vital signs) and report symptoms to healthcare professionals working remotely. It has been argued that the approach has the potential to reduce hospital admissions, increase quality of life, and save costs, but evidence has been of variable quality.

The Whole Systems Demonstrator randomised clinical trial

The **Whole Systems Demonstrator** [12] trial was a large, multi-centre cluster randomised study aiming to assess the effectiveness of telehealth for patients with chronic obstructive pulmonary disease (COPD), heart failure and diabetes. Over 3,000 patients were recruited from three sites in England (Cornwall, Kent and Newham) for a one year period. Those in the intervention group received home-based vital sign monitoring devices and electronic symptom questionnaires, with the resulting data being transmitted back to healthcare professionals. The patients in the control group received usual care. Other information, including hospital admissions, clinical practice data and patient-reported outcomes, was also collected and analysed.

The study found that telehealth patients were less likely to be admitted to hospital in an emergency and less likely to die than patients receiving usual care. However, the telehealth intervention yielded no cost reductions through reduced hospital care activity. Further, emergency admissions appeared to increase for control patients after recruitment into the trial and this may explain some of the between-group differences observed. Though the reasons for the increase in admission for control patients were unclear, patients could not be blinded to which trial arm they had been randomised. Therefore, a perceived lack of support for patients in the control group could have provoked anxiety leading to hospital visits.
A nested sub-study examined the impact of telehealth on quality of life and psychological symptoms, and this revealed no differences between the groups [13].

A study found that telehealth patients were less likely to be admitted to hospital in an emergency and less likely to die than patients receiving usual care

The trial has incorporated several other analyses, exploring how patient, professional and organisational factors relate to implementation. But overall, although the trial demonstrated some changes in mortality and admissions, the health benefits failed to translate to financial savings or improvements in the quality of life for survivors. It shows some of the limitations of randomised controlled trials in this area as the trial design may have influenced the outcomes, as well as limited the extent to which the trial sites could innovate and enhance patient care [14].

Telehealth is an example of a complex intervention, with technology embedded in people's lives, influenced by interactions and relations with healthcare networks. The telehealth technology itself may have had limited impact compared with how it was delivered as part of a wider service model. Further, it could have different impacts to those reported in this trial if delivered in other ways, in other settings, or for other patients.

The response to the trial has been to mainstream telehealth over the next five years [15]. This raises questions on how far clinical trials should inform decision making, and what other information is of value in making these decisions.

The value of observational studies

For telehealth, smaller, less costly prospective observational studies are an important source of evidence. These are able to capture the effects for patients referred into telehealth in routine settings, who may differ from those recruited in a randomised controlled trial. Further, observational studies can capture the range of service models introduced in routine settings, helping us to understand which models are most effective.

One such observational study, based in North Yorkshire, is using large administrative datasets to provide quarterly data feedback on the effectiveness of telehealth in

avoiding hospital admissions. The non-intervention group consists of non-telehealth users who appear similar to those in the intervention group according to variables recorded in the hospital data. Although this provides a benchmark rather than a definitive control measure, the design of the study means that admission rates for non-intervention patients cannot be affected by the conduct of the study.

Observational studies provide an opportunity to monitor and give feed back on progress, nudging systems towards best practice. In the US, the Center for Medicare and Medicaid Innovation has a large budget to test new service delivery models using quarterly feedback to evaluate the impact of service delivery changes on cost and outcome. The NHS could be well placed to do something similar. Observational studies may be less academically rigorous than clinical trials, but they can still deliver valuable information about how technologies function in real-world settings, and contribute to structured improvement programmes, fostering good practice and enhancing patient care.

The nature of evidence for telehealth

Presented by George MacGinnis, Assistive Technology Lead and Director, PA Consulting

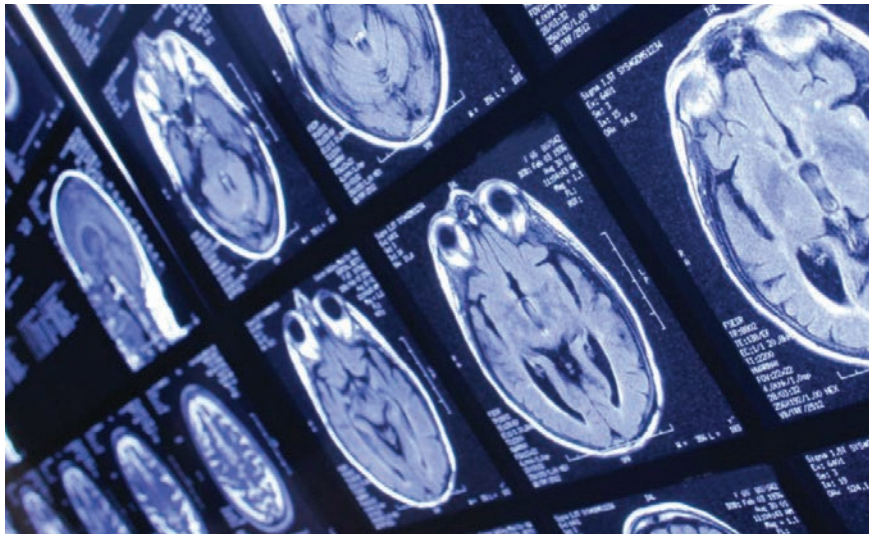
The Whole System Demonstrator was born from a desire to innovate. Evidence is now accruing to suggest that telehealth can have a positive benefit on individuals and the healthcare system, but the vast majority of the evidence is still based on small-scale or pilot projects [16].

RCTs have their place but they can be costly, bureaucratic and fail to deliver the expected outcomes – when a project is scaled up, it often does not work. When a trial does deliver evidence of a positive health benefit, the systems and people required to roll it out into a wider clinical setting may not be in place. A recent report [17] suggests that large clinical trials can present a barrier to innovation. It has been suggested that the medical profession is biased towards clinical trials, and they do have their place. The economic case for large medical device trials can be strengthened if they occur in parallel with technology development to mitigate costs.

Smaller, non-randomised studies are also important and can provide meaningful, clinically applicable data. They are already embedded within a healthcare system, so the translational issues of larger clinical trials do not apply. They can be economically viable, as evidenced by a landmark US Veterans Administration telehealth study based on empirical rather than randomised control data [18].

There is insight to be had from large clinical trials and smaller studies alike. Medical devices and complex interventions require appropriate levels of evidence at appropriate stages of their lifecycle.

Participant discussion



The following points were made during the discussion session.

Since the original European legislation on medical devices was first drafted over 20 years ago, the number of member states within the EU has more than doubled and medical devices are more numerous and technically advanced than ever before. Recent high-profile cases, such as PIP breast implants and metal-on-metal hip replacements, have raised concerns about the safety and regulation of medical devices.

Initiatives do exist to raise standards. The British Orthopaedic Association (BOA) and the Medicines and Healthcare products Regulatory Agency (MHRA) for example, have a project, Beyond Compliance [19], which promotes the concept that the safest, best and most successful systems are those that always go beyond merely complying with the minimum standards required by regulation. But the fact remains that most medical devices have little or no supportive evidence indicative of clinical utility or cost-effectiveness. Indeed a recent study of orthopaedic devices found that 22% of hip replacements lack any such evidence (in press).

There are over 70 Notified Bodies within the EU. Most are commercial organisations yet have the power to make decisions about evidence requirements; decisions, it has been argued, that are best left to independent regulators. Notified Bodies may ask for limited testing of a new device, but there is no regulatory requirement for clinical utility data. Different Notified Bodies have different evidence requirements, and different levels of transparency and competence. Certification via equivalence encourages the flow of iterative medical devices onto the market. But the process is perceived by some to stymie innovation, lower safety standards and contribute to a skills gap in trial design.

Lessons from engineering

The engineering industry is highly regulated, with a transparent, prescriptive, evidence-based regulatory framework that is well established for assessing safety. Structured approaches have proved effective in safety-critical industries, such as aviation. Although specifics would need amending, workshop attendees felt that the process is readily applicable to medical devices to establish safety and efficacy. But although the FDA has commissioned work to develop a safety case for infusion pumps [20], there are very few safety cases available for medical devices.

The engineering approach focuses on design assurance and continuous monitoring; ensuring the product is acceptably safe before and after it enters the market. Pre-market safety cases capture all the safety-related assumptions and evidence in context, a feature relevant to healthcare, where, for example, patients with different severities of illness are likely to tolerate different levels of risk. Sources of pre-market evidence for medical devices could include modelling studies (*in vivo, in vitro and in silico*), qualitative and economic information, materials development, scale-up data, research papers and patents. Safety cases focus on hazards, enabling potential flaws to be designed out and risks minimised before the product reaches the market, a practice that would make devices safer.

Engineers acknowledge that their products evolve and can fail, which is the reason for continuous monitoring of systems in use. The framework encourages the reporting of near misses and accidents, so designs can be improved and risks mitigated. Continuous monitoring is analogous to post-market surveillance of medical devices. In addition, the legislation requires timely, coordinated action and provision of information between the manufacturer

> RCTs remain the gold standard for generating evidence on medical effectiveness and adverse effects, but they have their limitations

and authorities when medical devices do not perform as intended (vigilance). Negative results and near misses, however, are seldom reported in a timely manner, and it can take years to remove faulty products from the marketplace.

The engineering framework has been built with input from non-regulators. Rolls-Royce, for example, contributed to the development of safety functional requirements for their aero-engines. Engineers recognise the wealth of highly relevant experience within the industrial sector, and their guidelines have become stringent and focused as a result. The development of a regulatory framework for medical devices would likely benefit from a similar level of dialogue to establish hazards, safety functional requirements and thresholds.

Some healthcare professionals feel that there is a need for NICE to define a system whereby there is more dialogue between clinicians, device manufacturers and the 'end user'. Clinicians should be asked which devices they need to have developed rather than manufacturers developing technologies which may not necessarily meet clinical needs.

A framework for medical devices

Medical devices would benefit from a regulatory framework that standardises their evaluation – a quantitative approach to benefit/risk assessment, underpinned by scientific methods, that guides decisions about the nature and acquisition of evidence. Similar, potentially applicable frameworks already exist – within engineering as described, but also within medicine. The Idea, Development, Exploration, Assessment, Long-term (IDEAL) collaboration [21], for example, puts forward a framework for developing appropriate clinical evidence at different stages in the lifecycle of a surgical operation.

A framework for medical devices would have to encompass and respond to the idiosyncrasies of the technology. Evidence would be needed to assess benefit and risk in context – risky products can sometimes be justified if the risk is outweighed by the benefit. The framework would have to be flexible and reactive to incorporate iterations and failures, and with different levels of evidence appropriate at different stages of the process. IDEAL, for example, includes an early development phase, that is exempt from conclusive efficacy and safety data. Some steps in the process will have an obvious, heightened risk and require more evidence. Some seemingly small steps, such as the shift to metal-on-metal hip implants, can sometimes generate huge, unforeseen problems, while other small steps might make a device applicable from a secondary, specialist setting right into primary care. The challenge for regulators is to manage these iterations and the evidence base that goes with them. Should problems arise, flexibility would enable the regulator to revisit the decision-making process, see how the evidence has changed and offer continued guidance. It may be beneficial to facilitate greater engagement of healthcare professionals as Notified Bodies and regulators may become aware of an issue too late. It has been said that a lot of 'near misses' in medicine go unreported, but the data in reports of near misses would be a potentially rich source of information. There are NHS guidance and international standards similar to the engineering 'safety case' but adoption is poor.

Sources of evidence – randomised controlled trials

RCTs remain the gold standard for generating evidence on medical effectiveness and adverse effects, but they have their limitations. Critics argue they are prohibitively expensive and time-consuming. They sometimes address unhelpful comparisons that compare new treatments against placebo rather than current treatments, or fail to focus on patient-centred outcomes. They are often conducted in idealised, unrepresentative patient groups and settings, making it hard to generalise from the data to the real world. Research in the telehealth field has shown that sometimes, non-blinded control measures can influence behaviour and outcomes; and sometimes the act of scaling a study up can itself have a significant impact.

The problems are not insurmountable and proposals are afoot to redress them. The Clinical Practice Research Datalink[22], for example, is an observational data and interventional research service, jointly funded by the NHS, the National Institute for Health Research (NIHR) and the MHRA. It includes a database of over five million patients (expanding to 15 million by the end of 2013), which could be utilised for RCTs within normal clinical practice. Similarly, the current proposal for pragmatic randomised trials using routine electronic health records aims to make clinical research part and parcel of general practice [23].

RCTs for medical devices are few and far between. In many cases, this is because it is not possible to conduct these trials because of the nature of the technology and its use. Another aspect is that many of the best, most innovative devices are being developed by small companies who lack the funds and experience to carry out studies of this nature. And the continued reliance of some companies on 'approval by equivalence' circumvents the need for clinical trials, contributing to a clinical sector that lacks the skills and knowledge to design and implement such studies. But just because they are difficult to do, does not mean that they should not be carried out.

With appropriate guidance and regulation, many of the difficulties can be overcome. While 'sham' or placebo surgery, for example, does not seem to be an acceptable way of testing surgery, cases have been documented, for example with the surgical removal of bone spurs from painful joints, where placebo procedures have yielded patient benefit. So the case for placebo surgery should not be dismissed out of hand, but considered within a contextual regulatory framework.

A major problem with designing trials for medical devices is that devices, unlike medicines, are increasingly

part of complex systems that may include software, hardware, healthcare professionals, and even operating theatres. Each component can influence the outcome of a trial – the experience of the surgeon, the quality of the implant, etc – so clinical trials require careful design to address these issues.

Alternative sources of evidence

Alternative sources of evidence do exist, including observational data and non-randomised early phase trials. These are generally faster and cheaper than RCTs, and can yield highly relevant information that RCTs cannot. Their importance is underscored by the medical evidence programme at NICE and by Cochrane reviews, which incorporate different levels of evidence.

Telehealth studies have shown how prospective observational data offers an opportunity to feed back into ongoing research, improving efficacy along the way, while demonstrating effectiveness of a complex intervention in a real-world setting – two useful features that RCTs struggle to achieve. The quality of observational data can be maximised by a prescriptive framework that details specifics, such as inclusion and exclusion criteria, and primary and secondary outcomes. Early phase trials, for example, of trachea transplants, also have value. Although numbers may be small and non-randomised, the study can still be done in a controlled environment, and provide highly relevant information on safety and efficacy.

Alternative sources of evidence, including observational data and early phase trials offer valuable sources of data, which can contribute to a medical device regulatory framework. Alongside clinical trials, they comprise a suite of study methods that can be used to construct an appropriate evidence base. Ultimately, safety can only really be assessed in the environment where the device will be used, so the level of evidence required will differ not just through the life of a device, it will also depend on context.

Study design

Expertise is needed to help guide best practice on study design, whether for large scale clinical trials or observational studies of medical devices. Suggestions have been made about conducting an observational study, followed by an RCT that involves enough centres that have gone through the 'learning curve' in the use of the device, and then another long-term observational study. Basic principles need to be established, such as the level of experience required to operate a device, and the standardisation of technical procedures through initiatives such as NICE guidance, interventional procedures, training and education. Studies should include clearly defined outcomes that incorporate patient feedback as well as clinical endpoints.

In some instances, flexibility will offer an advantage. Unexpected results, positive and negative, could be used to refocus and improve a study, but guidelines are needed to inform these decisions. Similarly, post hoc analysis may be of value; this would involve reviewers and editors accepting such analyses in peer-reviewed papers.

Advice on trial design is available, through the MHRA and others, but it would benefit from being built into a regulatory framework. Specialist centres for evidence-based research do exist. The Royal College of Surgeons (RCS), for example, has an initiative to develop a network of clinical trial units with specialist expertise in surgical and implant device-related trials [24]. But the safety and efficacy of medical devices would benefit from more of these initiatives.

Funding

The generation of high-quality evidence requires substantial levels of funding. Funders, in turn, have an important role in promoting evidence synthesis, not just by financing the studies themselves, but by facilitating the presentation of existing evidence to inform funding decisions. Medical device companies find it particularly hard to bridge the gap from research to clinic. In the UK, National Institute for Health Research (NIHR) funding opportunities specifically for the device industry exist, but are not well publicised. Many of the newest, most innovative devices sit at the interface of research disciplines – neuroprosthetics, for example, straddle neuroscience and biomedical engineering – and so may struggle to compete for more mainstream funding opportunities. Competition aside, the funding process can take a long time, and struggles to match the rapid pace of technology development.

There are a variety of models aimed at incentivising innovation, evidence gathering and funding. This year, the NIHR established eight new Healthcare Technology Co-operatives [25], teams of frontline individuals funded to identify unmet clinical needs for new technologies, and formulate the case for clinical research. Underpinned by a sound, research-based proposal, the study can then compete for funding at a relative advantage. The Diagnostic Evidence Co-Operatives [26], to be set up later this year, are similar, offering funding for NHS organisations to act as centres of expertise and catalyse the generation of evidence on *in vitro* diagnostics (IVDs), including cost-effectiveness. And in both cases, evidence is generated by diverse stakeholders, including members of industry, clinical practitioners and the general public.

A different model aims to use multiple, smaller studies of clinical interventions to springboard funding for larger trials. This model, which requires a good primary – secondary healthcare interface, has already been successful. For example, a recent meta-analysis of 11 small, self-monitoring oral anticoagulation studies has been used to successfully prompt a much larger, funded RCT [27].

Another model, endorsed by NICE, encourages independent trials funded by industry but performed by independent clinical research partners. The funders cannot influence trial design or execution and can only access the resulting data when publicly available. This avoids funding bias, and the model has been designed to help small companies promoting innovative medical devices.

Issues arising following the meeting

Following the meeting, discussions by the Royal Academy of Engineering's Panel for Biomedical Engineering highlighted the following issues:

Impact on SMEs: There is concern about how the revisions to the EU legislation will impact on early-stage SME companies and the pipeline of innovation technologies. It is beyond the resource of many medical device manufacturers to establish the necessary bodies of evidence, especially SMEs. There is also concern over the capability of SMEs to have consistently robust quality assurance systems.

Role of medical professionals: General Practice could support innovation in diagnostic technologies, providing a route into the broader NHS market. However, it was questioned why GPs in general do not have access to these new innovative technologies. Negative results and 'near misses' due to the improper use of a device are seldom reported by clinicians. Even with the Yellow Card Scheme [28] there is reluctance among medical professionals to report all possible adverse reactions which would be a potentially rich source of information.

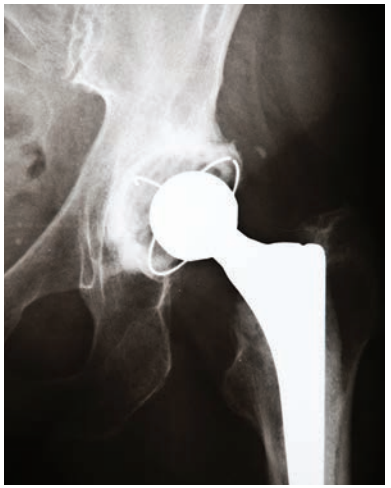
Frameworks: Standardised frameworks are limited in their effectiveness because they are typically out of date by the time they come into use. The medical device directives must promote a dynamic system.

The regulatory framework should specify different levels of evidence for device safety and efficacy at market release and then throughout the device's lifetime; for example, the use of acceptance through equivalence for mature technologies or staged market release for new, high-risk devices which can be achieved through observational studies (before a full market release), and the use of comparative baseline data from standard clinical practice. During a device's lifetime, post-market surveillance (in the form of a registry) and a requirement to report device failures by companies into a central database should provide a valuable source of information.

> General practice could support innovation in diagnostic technologies, providing a route into the broader NHS market

Concluding remarks and next steps

> The design of medical devices would benefit from a more integrated contribution from patients, engineers, manufacturers, healthcare professionals and economists



1. More use should be made in the medical devices industry of hazard analysis and safety functional requirements, with active steps taken to adapt and adopt the methods used in engineering.

2. The regulatory framework should specify the different levels of evidence required to ensure safety, performance and efficacy at different stages throughout the life and iterations of the medical device.

3. The roles and powers of Notified Bodies, and the CE marks they verify, are in need of review. The powers, inconsistencies and lack of transparency of Notified Bodies are cause for concern, as is the current CE system, which fails to promote evidence generation. This is expected to be addressed by new EU medical devices regulations proposed by the EC.

4. The regulatory framework should be prescriptive, yet responsive, ensuring the withdrawal of faulty products from the market as quickly as possible.

5. The design of medical devices would benefit from a more integrated contribution from a more diverse range of stakeholders including patients, engineers, manufacturers, healthcare professionals and economists.

6. Initiatives that promote best practice in the design of studies and methodologies are needed in order to bridge the evidence gap. This may include training and education programmes, and the establishment of further centres of clinical research excellence.

7. The NHS, with its unique patient identifier system, has the potential to facilitate the recruitment of patients into device trials. Wider adoption of the patient identifier should be promoted.

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Appendix 1: The current system

Notified Bodies [29], such as the UK's British Standards Institution, are the organisations that test whether or not a medical device meets the standards required for a CE mark. For certain category of devices, verification by a Notified Body is required before the product can be sold within the EU with a CE mark.

Competent authorities, such as the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, assess whether or not organisations are sufficiently qualified to act as Notified Bodies. Competent authorities periodically audit Notified Bodies, and have the power to withdraw Notified Body status. Within the current regulatory system, each EU country is required to have its own competent authority which is responsible for licensing the Notified Bodies within its own jurisdiction. The competence of the Competent Authorities is considered to be highly variable, as is the competence of the Notified Bodies.

EU legislation regulating medical devices was introduced in 1992, but is currently under review [7]. In September 2012, the EC published proposals for two new regulations on medical devices and *in vitro* diagnostics, which will replace existing legislation. The MHRA has completed a public consultation on the revised legislation [30]. In response to a 2012–13 House of Commons Science and Technology Committee Report on the regulation of medical implants [31], the government has endorsed the tightening of EU regulation. The new legislation is scheduled for adoption in 2014, with new rules coming into effect from 2015 to 2019.

Appendix 2: Roundtable programme

Welcome and introductions
Professor Lionel Tarassenko CBE FREng FMedSci, Professor Duncan (Gus) McGrouther FMedSci and Professor Sir Alasdair Breckenridge CBE FRSE FMedSci

Plenary session
Clinical research: the balance between benefits and risk
Professor Stuart Walker, Founder, Centre for Innovation in Regulatory Science

Session 1: The nature of medical evidence
Chair: Professor Duncan (Gus) McGrouther FMedSci

Part 1: Safety
Safety 1
Dr Carl Heneghan, Director of the Centre of Evidence-Based Medicine, University of Oxford

Safety 2
John Wilkinson, Director of Medical Devices, Medicines and Healthcare Products Regulatory Agency

Part 2: Efficacy
Efficacy 1
Dr David Tovey, Editor in Chief, Cochrane Collaboration

Efficacy 2
Professor Dion Morton, Director of Research, Royal College of Surgeons

Session 2: The nature of evidence in engineering
Chair: Professor Lionel Tarassenko CBE FREng FMedSci

Safety 1
Paul Anuzis, Chief Reliability Engineer, Rolls-Royce

Safety 2
Dr Chris Elliott FREng, Director, Systems Engineer and Barrister

Efficacy
Professor Serena Best FREng, Professor of Materials and Metallurgy, University of Cambridge

Session 3: A worked example: the introduction of telehealth technology into the NHS
Chair: Professor Lionel Tarassenko CBE FREng FMedSci

Evaluating the Whole System Demonstrator trial
Adam Steventon, Senior Research Analyst, Nuffield Trust

The nature of evidence for telehealth
George MacGinnis, Assistive Technology Lead and Director, PA Consulting

Appendix 3: Roundtable participants

Professor Sir Alasdair Breckenridge CBE FRSE FMedSci, Medicines and Healthcare Products Regulatory Agency [Chair]

Professor Duncan (Gus) McGrouther FMedSci, University of Manchester [Chair]

Professor Lionel Tarassenko CBE FREng FMedSci, University of Oxford [Chair]

Professor Andy Adam CBE FMedSci, Kings College London

Paul Anuzis, Rolls-Royce

Professor Serena Best FREng, University of Cambridge

Professor Bruce Campbell, National Institute for Health and Care Excellence

Professor Andy Carr FMedSci, University of Oxford

Professor Sir Alfred Cuschieri FRSE FMedSci, Institute of Medical Sciences andTechnology, Dundee and St Andrews Universities

Simon Denegri, INVOLVE; National Institute for Health Research

Jill Dhell, Department of Health

Dr Christopher Elliot FREng, System Engineer and Barrister

Dr Ursula Gebhardt, Medical Device Consultant

Will Greenacre, Wellcome Trust

Philip Greenish CBE, Royal Academy of Engineering

Dr Carl Heneghan, Centre of Evidence-Based Medicine, University of Oxford

Dr Tim Knott, Wellcome Trust

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Gary Slack, British Standards Institute

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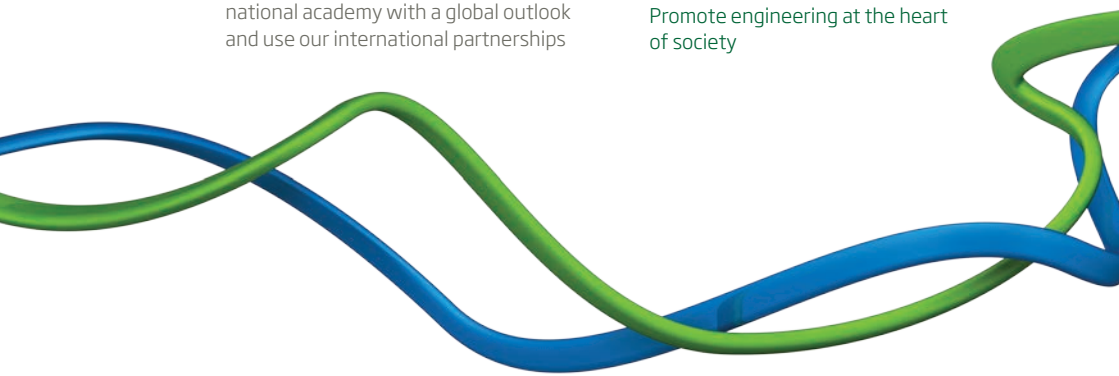

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