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## Report from the HealthWatch Symposium 17th June 2019

# Evidence, Healthcare and Medical Devices & Implants

Technological developments in medicine and healthcare generate many new medical devices and implants. In contrast to the situation with new medicines, requirements to demonstrate the benefits of devices & implants for patients and society are much less clear cut. Recent media reports have highlighted the need for better regulation and better enforcement of regulations, but it is not clear how best to collect, analyse, summarise and disseminate the evidence required.

At HealthWatch we promote science and integrity in healthcare and the assessment and testing of all treatments, products and procedures. Therefore, to clarify the current issues facing evidence-based healthcare in the field of medical devices & implants we invited participants from a wide range of disciplines to join some of our members at this Symposium. (Appendix 1: List of participants.) We aimed to identify areas where organisations (including HealthWatch) might most productively concentrate their efforts to promote evidence-based practice. We hoped that by the end of the symposium participants would: have a clearer picture of the rules and regulations relating to medical devices; be able to identify areas where evidence requirements coincide with the interests of healthcare organisations and; have developed a priority list of potential actions and activities.

The full programme is shown in Appendix 2. We pre-circulated a briefing paper on current and proposed approval and regulatory processes (Appendix 3) and there were some introductory plenary presentations. The main part of the symposium was the multidisciplinary discussion groups looking in depth at four topics:

#### Programme Summary:

Welcome; Introduction and presentation of briefing paper

Plenary presentations by

**J Kirwan, T Bruckner; C Heneghan; P McCulloch; D Cohen**

Discussion groups with individual introductions by:

**A Judge, B Reeves, A Cook, N McGuire**

Groups discussions of the other 3 topics prior to plenary session

General session: Feedback from each group plus comments from the floor

Round up session:

Using a registry - How long-term follow-up provides relevant evidence.

Evidence and evidence synthesis for non-randomised studies of medical devices and implants.

Risk vs numbers – where do we concentrate?

How can the healthcare community better support regulation for patient benefit?

The reports from the groups and the final plenary discussion session, and the conclusions which emerged, are presented in this report. In summary, we concluded:

### Summary of conclusions

- Approval has been a technical rather than a medical process.
- The 'equivalence' system using Notified Bodies has failed.
- Using and recording device serial numbers would be a simple first step.
- The IDEAL-D framework provides for evidence-based implant development.
- Adequately funded registries are needed with compliance monitoring.
- Political action will be required to influence the developing rules and to draw agencies together.
- There are academic responsibilities: early reporting; development of evidential standards; guidelines for data reporting and appropriate data amalgamation procedures.
- Putting the issues into simple statements will be a powerful aid to progress.

## Plenary Presentations

**J Kirwan**, Emeritus Professor of Rheumatic Diseases at the University of Bristol, HealthWatch Trustee (and Symposium Convenor), welcomed everyone and reminded them of the meeting's aims and objectives. He pointed to the wide diversity of backgrounds and areas of expertise among participants, and thanked them all, particularly the invited speakers, presenters and discussants, for finding the time to attend the Symposium. The background paper (Appendix 3) and introductory talks (Appendix 4) would set the scene, but the main and most important part would be the discussion groups and their feedback.

**T Bruckner**, TranspariMED (Bristol), presented a brief overview of the pre-circulated background paper he had prepared (Appendix 3). In this widely researched paper there is much useful information about the current and proposed state of the regulatory environment in the European Union and the UK. The UK government sees the medical device industry as a strategically important high-tech manufacturing sector with growth potential. Government policy is geared towards promoting the future growth of the UK device industry. Three key issues emerge: the sufficiency and appropriateness of evidence; techniques for assessing the evidence; and transparency - making all the evidence available.

Those seeking to influence the development of evidence-based regulation and use of medical devices and implants face important constraints but there remain opportunities to influence developments in favour of evidence-based use and dissemination.

Constraints	Opportunities
<ul style="list-style-type: none"><li>• The text of the Medical Device Regulation framework has already been finalised.</li><li>• The UK is likely to remain within the framework.</li><li>• Currently there is no political will for measures that would imperil UK exports.</li><li>• There may be limited ability for the UK to independently keep internationally approved devices off the national market.</li></ul>	<ul style="list-style-type: none"><li>• Important details of Medical Device Regulation implementation are still being developed.</li><li>• New data will be publicly available from May 2020.</li><li>• It will be possible to set stronger national standards (perhaps through requirements of MHRA and/or NICE).</li></ul>

Thus, there are several questions for HealthWatch (and other organisations) to consider:

- Should HealthWatch try to influence the Medical Device Regulation implementation rules while they are still being written?
- Once the Medical Device Regulation has come into in force, which aspects should HealthWatch focus on monitoring?
- Can the UK impose more stringent evidence, safety and/or transparency requirements?
- Are there important gaps in the current implant registry landscape in the UK?
- Should HealthWatch worry about EUDAMED potentially undermining clinical trial registries?

**C Heneghan**, Professor of Evidence-Based Medicine and Director of the Centre for Evidence-Based Medicine at the University of Oxford, reviewed 20 years of vaginal mesh device equivalence and the problems it has caused. Device equivalence is a method of approving medical devices and implants because they are 'equivalent' to an existing device, which has already been approved.

The first mesh implant was approved in the USA in 1996, but by 1999 serious adverse events led the US FDA to say it 'appears not to function as intended'. It was withdrawn from the market. Nevertheless, by then, other mesh products had been introduced as 'equivalent' and continued to be used.

In the UK in 2005 NICE recommended their use while, at the same time, saying there was a lack of long-term safety data. In 2008 the FDA said side effects from the then-used mesh implants were 'rare'. By 2011 the FDA issued a safety communication noting that serious adverse effects often

resulted in the need for further surgery and reclassified mesh implants as 'high risk'. The following year many types of mesh (which had been approved on the basis of 'equivalence' with the original mesh that had been withdrawn in 1999, or of equivalence with some of those devices) were withdrawn from the market by manufacturers.

To demonstrate the poor state of the approval system, scientists and journalists set up an undercover investigation using fruit netting as a proposed mesh and providing pretend documentation showing how it is equivalent to existing mesh products. They took the paperwork to various Notified Bodies (the companies approved by governments to certify new devices and implants) and argued that the new mesh was equivalent. Approval was granted.

A subsequent review of the evidence in detail for mesh implants showed that of 119 FDA approvals, in 79 (66%) the manufacturer ceased market distribution; in 26 (22%) the manufacturer had changed the indication. Only seven studies (6 cohorts and 1 randomised controlled trial) covering 11 approvals were recruiting participants and none had reported outcomes.

In 2017 NICE said mesh for vaginal wall prolapse should only be used in the context of research. In 2018 the UK government launched an enquiry and later that year halted vaginal mesh surgery in NHS hospitals. In 2019 the US FDA ordered all remaining transvaginal mesh products off the market.

And so, after many patients had unnecessary and inappropriate operations and many had suffered serious adverse effects, it was clear that there had never been any evidence to support the introduction of mesh in the first place. Approvals had been granted on the basis of 'equivalence' and



carried down from one product to another, even though the original product had been shown to be unsafe and had been withdrawn. Even the flimsiest information put together to support fruit netting as a new device could receive approval. It was clear that the 'equivalence' system had failed.

**P Mc Culloch**, Professor of Surgical Science and Practice and Chair of the IDEAL Collaboration at the University of Oxford, presented an overview of the IDEAL Collaboration and the notion of necessary evidence for introducing new surgical procedures. He suggested the IDEAL framework (idea; development; exploration; assessment; long-term monitoring), developed to support the introduction of new surgical procedures (see <http://www.ideal-collaboration.net>), could, with some modification, also be applied to medical devices and implants.

For pharmaceuticals the US FDA had decided in 1976 that "effectiveness should be required to be established prior to marketing" but this had not included medical devices. Pharmaceutical companies responded over several decades by gradually amalgamating into giant corporations which could both invest in the required evidential activities and negotiate strong patent protection. This resulted in slow but evidence-based and relatively safe progress. In contrast, market-oriented approval processes had developed for devices, designed to have low grade, relatively vague standards and to promote rapid, competitive development processes where many small companies can hope to succeed. There was no coherent theory base or defining principles of evaluation and safety standards were not developed.

The resulting devices framework is centred on a decision to licence to market, which (except for the highest risk devices and those that have no equivalence to previous devices) usually requires technical (not clinical) data and has poor requirements for clinical post-marketing surveillance. Two things are needed: a theory to underpin a demand for stronger, clearer requirements for specific types of evaluation; and a total product life cycle approach to approval, linking graduated marketing approval to provision of evidence. The IDEAL Framework is designed to provide these. Studies at each stage should be designed to answer the key question for that stage, and the IDEAL

recommendations describe study formats that can do this. At each stage study methodology should be guided by ethical principles and the key principle is transparency.

**IDEAL** for devices (IDEAL-D) has been proposed to address the additional needs of medical devices and implants. A pre-implementation step in which the idea is explored technically and for feasibility is added at the beginning, with a minimum required data set. A flexible approach to interaction between development and exploration is included, and the introduction of long-term follow-up using registries from an early stage, with these developing and changing with needs. (See IDEAL-D: a rational framework for evaluating and regulating the use of medical devices *BMJ* 2016; 353 doi: <http://dx.doi.org/10.1136/bmj.i2372>). Marketing approval becomes a staged process, progressing to wider use and dissemination as more information becomes available. Safety depends on the use of high quality and comprehensive registry data. The impact of introducing IDEAL-D is likely to have only a moderate evaluation cost and the overall effect on speed of evaluation is likely to be positive. Standardisation of the process would yield major efficiency benefits and the effect on safety and evidence quality is likely to be substantial.

**D Cohen**, Investigative Journalist at the British Medical Journal and the BBC, joining by video link due to urgent filming requirements, gave a brief introduction to her work on medical devices and implants.

She first became interested when colleagues reported that the regulation of medical devices was inadequate. She began to look at the way metal-on-metal hip replacements had been introduced and promoted. She linked up with the International Consortium of Investigative Journalists, who made up a dossier for an imaginary new metal-on-metal hip replacement and then tried to register this made-up implant for a CE mark for market approval. Several Notified Bodies were ready to give approval, but as they did not have a factory to register, they ended the investigation there. But they had found out how these bodies work.

More recently she had looked at the registration of the newly developed cardiac implantable pacemakers. There is no transparency in the system, and she was unable to obtain information from MHRA, though some European colleagues had been able to find some information in their countries. She was very surprised at how little information was required to obtain marketing approval, and how little medical involvement was required. The key issue is one of increasing transparency.

### Discussion groups with individual introductions

Each discussion group started with an invited presentation on the main topic then this topic was explored in detail. Subsequently each group explored more briefly the other three topics in the programme. Plenary feedback for each discussion group first heard the issues raised by the main discussant group, then heard additional thoughts and contributions from the floor. A copy of each presentation and the notes made during the discussion groups and at the plenary feedback is provided in Appendix 5. A summary of the main points is reported below.



### **Group A: Using a registry – How long-term follow-up provides relevant evidence**

**A Judge**, Professor of Translational Statistics at the University of Bristol, gave the introductory presentation. A possible solution for post-marketing assessment of devices and implants has been in place since 2003. HQIP (Health Quality Improvement Partnership - a publicly funded body for England, Wales, NI and Isle of Man) runs 40 registries, including the National Joint Registry (NJR). The NJR covers hip and knee replacement operations, of which there are currently over 100,000

records. It captures data on each device, matched to patient and surgeon. The outcome data measured is simple: numbers of additional procedures needed to revise the initial operation. The system is easy to use and NJR now has virtually 100% compliance. There are approximately 50 registries in different countries of Europe.

In discussion it was noted that NJR's automated data generation can flag outliers in real time, the data can help to design more in-depth research, it is possible to apply for access to the data and countries too small to have their own registries can apply to access other country's data to support public health decision-making on devices in their own countries.

The following issues were highlighted:

- There are over 2000 combinations of the various stems and cups in hip replacement, but the basic designs have good outcomes. New devices are adopted very quickly for non-clinical reasons.
- Devices with poorer and more difficult to measure outcomes might be more difficult to manage in a registry.
- Joint replacements can have a life of 25 years but information on outcomes for patients who had these implants before data was collected is not available.
- The data analysis finds patterns of poor outcomes retrospectively, but signals should be sought earlier to enable action.
- Private healthcare can show a lower fail rate, reflecting a bias towards undertaking straightforward operations while complex ones are dealt with by NHS.
- How can reporting be made a mandatory part of every surgical procedure?
- Funding, accountability and defining the outcomes to measure require further investigation.
- Data publication and sharing of all information should be strongly encouraged from all sources and from all who conduct studies including manufacturers, academic institutions, and implant retrieval centres.
- There is a clear need for patient engagement, education, and consent to agree sharing of follow-up and results.

The following additional points emerged during the plenary discussion of this topic:

Sometimes registry maintenance just stops; why is there continuing innovation even if current implants are already performing well? There may be bias in data if supplied by non-disinterested sources (industry, implanter); invest in areas of high risk; need political will to enforce sanctions; while registries are relatively inexpensive, they will add costs and are not a panacea.

## Group B - Evidence and evidence synthesis for non-randomised studies of medical devices and implants.

**B Reeves**, Professorial Research Fellow in Health Services Research at the University of Bristol and Co-Chair of the Cochrane Non-Randomised Studies Methods Group, explained the barriers to producing good evidence around medical devices in his introductory presentation. Given the nature of implants and devices, sources of evidence are likely to be from a surgical setting where existing devices they are being compared with may work well. Hence the aim is to detect a small incremental benefit, requiring a large sample size. Adverse outcomes of interest are often rare (but potentially have large impacts on the patient) or long term, yet device 'life cycle' may be too short to detect them.

Current evidence, for this reason, rarely comes from randomised controlled trials. There are guidelines for checking the risk of bias in non-randomised studies (ROBINS-I: Sterne JAC, et al. BMJ 2016; 355: i4919) but there are no established guidelines for judging quality of non-comparative studies. To combine and compare studies one should apply the usual systematic methods for reviews of the effectiveness of an intervention – but in addition extract the study design features, apply ROBINS-I guidelines and do not include evidence at critical risk of bias. This is difficult to do and time-consuming. Comprehensive registers can provide descriptive estimates of outcomes but

not effectiveness. Appropriate developments in this area might include mandatory registers; mandatory recording by hospitals (doctors and coders) of device-related complications in Hospital Episode Statistics with the new Classification of Interventions and Procedures version 4 procedure codes.

**One** simple and potentially effective method might be to use bar code systems in theatre for easy data capture, linked with a national database of device identities or serial numbers. (cf. Appendix 3: Unique Device Identifiers, EUDAMED, Bruckner, p.8) and only issue marketing approval if the manufacturer provides the serial numbers of all devices sold in the country.

**In discussion** it was noted that registries should collect appropriate and relevant data and not be burdened with irrelevant data that could obscure and confound vital analysis. Some registries had failed because they had been too ambitious. The costs of setting up many different registries could be significant and there need to be systematic ways of continually analysing data to spot issues, ideally at an early stage. A representative of a device manufacturer said that all devices would be tracked and traced through a modern manufacturing process and subject to strict quality and statistical process controls. The idea of a CONSORT-type process was raised whereby all devices could be tracked from their manufacture and use. Missing data was a concern as was data integrity, security and patient confidentiality, and the issue of informed consent and how that can properly be obtained.

**The following issues were highlighted:**

- Who regulates the registry? In the case of NJR it is HQIP and the NHS (Public Health England). But would they intervene effectively if compliance went down?
- If all devices are now to be identifiable, tracking the person who received faulty ones should be easy. But there is a huge IT challenge to be able to apply that information in context of a shaky NHS computer system.
- Evidence generation is left to industry. No-one is responsible for delivering clinically. NICE cannot ask the questions; it can only process the available data and make recommendations based on that.
- There will be increased vigilance requirements for post-market surveillance, periodic safety update reports; specific reporting requirements and time frames for notifying the MHRA of incidents and preparation of reports under the new system.



**The following additional points emerged during the plenary discussion of this topic:**

Data storage and the General Data Protection Regulations; informed consent – how to pass on information about devices/implants so that patients are able to evaluate the evidence; use techniques from industrial monitoring to identify anomalies in real time.

### **Group C - Risk vs numbers – where do we concentrate?**

**A Cook**, Consultant in Public Health Medicine and Fellow in Health Technology Assessment at the University of Southampton gave the introductory presentation. The simple notion of multiplying the likelihood of an adverse event (e.g. low, medium or high) by its consequences (e.g. mild, moderate or serious) in order to focus on high risk outcomes presupposes that an adequate estimate of the likelihood and consequences can be made. Recent adverse events, such as with metal-on-metal hips and vaginal mesh, would have been difficult to foresee.

**Perhaps** there is no valid reason why the approach to devices should differ from that taken to pharmaceuticals, even for 'me too' devices that claim equivalence. (See Neugebauer EAM, et al. Specific barriers to the conduct of randomised clinical trials on medical devices. *Trials* 2017; 18:427. doi:10.1186/s13063-017-2168-0) Devices used for different indications (e.g. hip replacement for osteoarthritis or for fractured neck of femur) might be pooled as in 'does the device adequately replace the joint?', and may (perhaps more easily) be pooled for long term safety monitoring. Long

term registry or similar follow up looks like the only way to identify longer term adverse effects. NICE combines data from similar devices (e.g. implantable defibrillators), encourages the use of and endorses registries, but does not manage registries. NICE relies on regulators to identify and remove individually dangerous devices and uses data from older versions to comment on newer versions of devices. NIHR and the Efficacy and Mechanism Evaluation programme offer approaches to device trials that fit into some stages of the IDEAL-D programme.

In discussion and during the plenary discussion of this topic it was noted that the IDEAL-D framework looks very useful for evaluating risks and benefits, but there are few incentives for manufacturers to conduct clinical trials. The question of how patients could give informed consent to use of an implant or device was explored, because there is not enough information available. It is left to the manufacturer to produce communications for the patient and for the surgeon. Even the surgeon has no independent data because there is none. Health technology authorities and the Government do not stand up for patients' need to get unbiased information from doctors. Is there any reason not to require registries for all devices – or at least those implanted? The cost might be funded from savings by (say) the NHS? What about an insurance-based scheme for manufacturers with low premiums for good data backup? Academically the development of a 'Cochrane for medical devices' would be useful, with a clear evaluation of the evidence from non-randomised studies.

#### **Group D - How can the healthcare community better support regulation for patient benefit?**

**N McGuire**, Senior Clinician for Devices at the MHRA (Medicines & Healthcare products Regulatory Agency), London gave the introductory presentation. This is the publicly funded UK competent authority, at arms-length from the Dept of Health. One role is to audit Notified Bodies, which it does every 8 months. Another is to monitor and investigate device-related incidents and reports, monitor investigations, and take action to prevent or reduce the likelihood of recurrence. When an issue is reported the MHRA will endeavour to meet with the manufacturer promptly to investigate. The MHRA can issue restrictions, product recalls, can notify other organisations including the FDA, or can publish a notice or medical device alert. It can also require manufacturers to submit vigilance reports.



There are several weaknesses in the structure and operation of the system. Notification of MHRA is currently 'trust-based' and requires cooperative, collaborative working between all concerned parties which is not always forthcoming. Sometimes key information is withheld from the MHRA during periods of national political change. MHRA is under-resourced for its role and there are many devices in use (about 600,000). A key source of information is from 'Yellow Card' reports, which can be completed by anyone including individual clinicians and members of the public. Academic involvement often adds a considerable delay in reporting, which might be due to culturally ingrained conduct of withholding findings or failing to share results in advance of publication or at more formative stages of investigation. The MHRA considered this to be a serious problem.

In discussion it was noted that MHRA oversight does not begin until patients are involved. It can be a very difficult process to obtain information at an earlier stage. There ought, perhaps, to be a role for earlier intervention to streamline and oversee relevant information, monitor and share reports, and take a greater role in preventing harmful incidents. A representative of a device manufacturer discussed the processes of registering a trial before market and how this pre-market stage would be an appropriate stage for regulatory oversight to begin. Continuous evaluation pre-market and improved sharing of clinical safety data from similar devices, would lead to more prompt reporting and investigation of device issues from the point of performance studies. While the Yellow Card scheme allows anyone to report an issue, Dr McGuire noted there may be an increased need to engage patient organisations or groups to assist in reporting potential issues. This might avoid the situation where lone voices or single-issue groups campaign and can lack balance. There is a need

to improve health care professionals' knowledge of, and collaboration with, reporting to the MHRA – perhaps through engaging with professional institutions.

The following issues were highlighted:

- Who has responsibility/ownership of the problem? If a problem is found with one device, what can be done regarding similar devices? Why can licences not be withdrawn?
- The MHRA is not a panacea, there are many parts and it may be too complicated.
- Although manufacturers might complain that their competitiveness would be disadvantaged, this would not be the case if all were subject to the same regulation.
- We need to know better who we should be talking to, and we need a few simple messages, to put to IDEAL, Cochrane and manufacturers.

The following additional points emerged during the plenary discussion of this topic: with more than 600,000 devices in use regulation is a huge challenge – cannot expect a single agency to manage all this; publish or perish inhibits early sharing – academic institutions should take some responsibility; no clear message to patients as to where the evidence and information is available.

### Closing comments from speakers and presenters

- Interesting conversations; there is no one panacea, including MHRA! –We need to fit the different parts of the regulatory system to the appropriate questions. No fault compensation might help.
- Registries need to capture some short-term as well as long term outcomes including outcomes relevant to patients. Unlike medicines, one cannot stop taking an implant.
- Light touch on data collection – manufacturers of CE marked devices to provide identifiers, NHS (or other provider of treatment) then responsible for link to patient – develop a standardised rule for tracing all devices.
- NIHR will continue to fund device trial/studies but these are likely to be short term – mandated follow-up mechanisms would increase value of these studies.
- 30% of device trials are not registered – let's get them registered.

### Conclusions

Some conclusions can be drawn from the wide variety of contributions to the symposium:

- Approval has been a technical rather than a medical process, resulting in unforeseen medical problems. The 'equivalence' system using Notified Bodies has failed.
- Manufacturers will not necessarily be against standardised regulation, if it applies to everyone. Using and recording serial numbers would be a simple first step.
- The IDEAL-D proposal offers a realistic bridge between initial experimentation and developmental steps of devices & implants and randomised controlled trials. We could tax devices to pay for an IDEAL-D setup (with evidence synthesis).
- Registries offer real possibilities, but will need to be relatively few and lean for adequate funding, compliance, etc.
- Safety monitoring is a public health issue.
- Political engagement will be required to influence the developing rules, and to draw together the different agencies, especially the NHS.
- There are academic responsibilities which need encouragement: early reporting; development of evidential standards; guidelines for data reporting and appropriate data amalgamation procedures.
- Putting the issues into simple statements or even slogans will be a powerful aid to progress.

Appendices: 1 List of participants; 2 Full programme details; 3 Background paper: An overview of medical device governance in the UK by Till Bruckner; 4 Slides from the introductory talks; 5 Presentations to discussion groups and reporters' notes