BMJ

BMJ 2011;342:d2839 doi: 10.1136/bmj.d2839

FEATURE

Commentary: Evaluating and regulating device therapy

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The current European regulatory framework—CE marking—might provide sufficient safeguards for electric toasters and kettles, but it is not adequate for treatments that can affect symptoms, health related quality of life, serious morbidity, and mortality.

There are many kinds of medical devices for myriad purposes in healthcare. All require an adequate regulatory framework to ensure that patients gain clear benefits and are not placed at unreasonable and avoidable risk. The so called class III devices have been defined by the US Food and Drug Administration as "those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury."[1] Examples include pacemakers, stents, and prostheses. Class III devices share many of the challenges of drug treatments, which historically have had more regulatory attention and rigour.

The FDA evaluates the safety and effectiveness of class III devices in a process parallel to that of drugs, although differences exist that some people think are inappropriate.[2] In Europe, the process is different from that for drugs. Market access is granted if a device displays a CE mark. It is ultimately the manufacturer that decides whether to display the mark, which indicates that it is satisfied that its product conforms with the EU's quality standards and that "it is fit for its intended purpose."[3] Is the CE mark approach sufficient for a sophisticated clinical therapy?

Devices do present some additional challenges to regulatory agencies compared with drugs. Whereas the dose and formulation of drugs is fixed through the regulatory process, with marketing authorisation given to specific form and usage, devices may go through a more continuous development process characterised by a series of incremental steps in design and manufacture. Evolution may be helpful, although there is the risk that manufacturers may react to perverse incentives and aim for targets that are not in the best interests of patients or health systems. For example, manufacturers of sophisticated pacemakers have emphasised reducing device size rather than increasing battery life, which would benefit patients and health systems by reducing the frequency of explanting and reimplanting devices. Evolution also raises the prospect that a device used in practice may differ in some important aspect from that evaluated as part of the regulatory process.

Although the Medicines and Healthcare Products Regulatory Agency (MHRA) provides statistical guidance for device trials,[4] it is less methodologically sound than the related guidance available for drug trials.[5] MHRA guidance states explicitly that the trial programme for devices will not be adequately sized to address questions of safety,[4] a self-fulfilling prophecy that contrasts with drug regulation, where the randomised trial programme plays a key part in such evaluation.[5]

Long term data

Regulation is important since it drives the information available to inform clinicians and patients about the likely benefits and possible risks of treatment options. Cardiac resynchronisation devices for heart failure became available for use when only short term randomised trials were available; follow-up was 3-6 months, and all participants received devices but they were switched on according to randomisation.[6] Such trials cannot provide adequate evidence on the risks associated with implantation because all participants received devices, and evaluation of benefits was effectively limited to short term symptoms and quality of life. Class III devices should be evaluated using high quality randomised trials similar to those to which we aspire for drugs.

The manner in which industry sponsors trials of CE marked devices also contrasts with the situation for drugs. In drug trials, the investigational drug is paid for by the sponsor. However, in trials of devices, the experimental therapy may be funded indirectly by payments per patient (which may depend on the allocated treatment). This may not always fully cover the cost of the device. As contracts are complex and not generally in the public domain, this raises the risk of inadvertent public sponsorship of commercially organised trials.

Confirmatory trials that aim to establish the effect of a device on serious morbidity and mortality require adequate numbers of participants and sufficiently long follow-up, just as they do for drugs. Longer term follow-up trials of devices evaluating mortality and serious morbidity have often been of poor quality. Describing attempts to interpret one such device trial, a regulator commented that the trial was so challenged methodologically through loss to follow-up and device implantation in participants randomised to medical therapy alone as to be best interpretable as an observational study.

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But high quality trials can be conducted. Bardy and colleagues compared placebo with amiodarone or an implantable cardioverter-defibrillator (ICD) in 2521 patients with a median follow up of 45.5 months and a primary outcome of all cause mortality.[7] Data on the primary outcome were available for all participants at the final planned visit. Despite the long follow-up, only 11% of participants randomised to placebo or amiodarone received an ICD during follow-up.[7]

Safety of devices must also be examined properly in the regulatory process. Thousands of patients receiving ICDs have experienced device malfunction,[8] with a substantial rate of complications, including death, associated with elective generator replacement of ICDs known to malfunction.[9] It is not clear that those responsible for regulating devices have dealt adequately with the challenges associated with device safety.

Class III devices share many characteristics with drugs and could be evaluated within a common framework examining efficacy, effectiveness, safety, and quality. Rather than devices being subject to an inferior regulatory model, we should extend and strengthen the approach taken for pharmaceuticals.

Competing interests: NF has completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from him) and declares no support from any organisation for the submitted work; NF is a member of Data Safety and Monitoring Boards for two trials sponsored by Medtronic Inc; and declares no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

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Cite this as: *BMJ* 2011;342:d2839