

Chapter 7

Regulating the
technologies

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Chapter 7 - overview

The regulatory frameworks that apply to medical devices and to advanced therapeutic medicinal products (ATMPs), such as neural stem cell therapies, govern the entry of the technologies onto the European market, including the clinical investigations preceding this.

Using our ethical framework and the elements of responsible research and innovation developed in the preceding chapters we assess whether current regulatory provisions are effective and proportionate given the requirement to protect patients' safety, while also enhancing access to safe and effective therapies. The regimes applying to medical devices and ATMPs share a historical objective of securing a harmonised European market and each is concerned both with supporting innovation while protecting patient safety. However, the regulatory obligations upon manufacturers differ significantly between these two sectors in a number of respects. Concerns regarding effective oversight of medical devices apply especially urgently to invasive neurodevices, as these pose greater risks to patients' safety.

Pre-market oversight of medical devices in Europe is decentralised and relatively light-touch (especially for non-invasive devices) in terms of the evidence manufacturers must supply to demonstrate that their products conform to statutory safety and performance requirements. While this may support innovation by limiting regulatory burden, we nevertheless welcome European proposals to narrow the circumstances in which manufacturers can rely on evidence concerning similar devices (rather than conducting new clinical investigations) to demonstrate conformity. We recommend that, since neurodevices intervene in the brain, the case for relying on pre-existing evidence must be particularly sound (paragraph 7.33 and 7.47). We also recommend greater transparency about the basis of all decisions about the conformity of devices with regulatory requirements (paragraph 7.27).

Since pre-market scrutiny of neurodevices is light-touch, it is all the more important that post-market surveillance mechanisms are robust. We recommend that these should be strengthened by making it mandatory for clinicians to report adverse events – supported by a scheme to alert them to newly approved devices – and by making all information on adverse incidents and incident trends publically accessible (paragraph 7.55).

Uncertainty about the benefits, risks and mechanisms by which some novel neurotechnologies achieve their effects presents one of the central ethical challenges in this field; yet the regulation of medical devices does not itself encourage collection of extensive clinical evidence. In addition to recommending enhanced transparency in the regulatory system (paragraph 7.28), we suggest that collaborative efforts to improve information governance and data linkage by manufacturers, practitioners and others are needed. Improved evidence on the efficacy (or otherwise) of neurodevices is a particular priority as the regulatory system itself does not currently address this.

In contrast to medical devices, the steps required under the multiple regulatory frameworks applying to the licensing of ATMPs as commercial products are many, potentially lengthy and include centralised European authorisation. This complexity and the potentially overlapping roles of the various regulatory bodies involved is a source of concern, particularly given the economic risks that delays pose to companies developing products. Neural stem cell therapies, however, could present significant health risks if they do not perform as expected, so robust regulation is vital. We suggest that a responsible and proportionate approach to oversight should allow an evolution from a mode of protection to one of promotion as the science progresses (paragraph 7.72). We welcome recent developments in the governance of stem cell therapies that aim to streamline and speed up the regulatory and ethical oversight processes involved whilst maintaining rigorous standards for protecting patient safety.

There are various routes by which patients with particular needs can access medical devices and ATMPs that are not approved for wider market availability. These are welcome insofar as they may address otherwise unmet needs. However, given the intrinsic vulnerability of patients undergoing more experimental interventions, we raise concerns about the scope of regulatory and ethical oversight of therapies delivered via these routes. Some, such as 'off-label', 'in-house' and investigative uses of medical devices which are not aimed at commercial applications, may fall outside the regulator's remit altogether. Even where the supply of some technologies for exceptional or non-routine use is regulated by the Medicines and Healthcare products Regulatory Agency, we suggest that there need to be more thorough mechanisms for collecting and making publically accessible information on approval for these uses and their outcomes (paragraph 7.89).

Introduction

- 7.1 As is so often the case in the realm where ethics and novel technologies meet, there is little that is absolutely novel. Interventions in the brain are not new and, as the examples of psychosurgery considered in Chapter 1 illustrate, the challenges and criticisms raised about such techniques in the 1970s continue to have resonance today for many invasive

neurotechnologies.⁶³⁶ In regulatory terms, the enduring challenge is not so much about uncovering entirely unexplored issues; rather, it is about dealing with the vagaries of regulatory systems that have grown up over many years and in ensuring that they remain responsive to emerging developments. If the regulatory response to any given technological development is not outright prohibition, then the task becomes more nuanced in identifying how far and how well existing regulatory mechanisms capture an emergent technology, address adequately the range of technical, social and ethical issues associated with its adoption, and delivers the said technology safely and efficiently to its users. Where systems are found to function sub-optimally, then regulatory reform should follow.

- 7.2 The focus of this chapter is the regulatory regimes that determine whether neurodevices on one hand, and neural stem cell therapies on the other, are licensed to be marketed and used for the treatment of humans. These regimes impact on whether, and for what purposes, a neurotechnology may be made available and also set the conditions that shape both the investigatory routes followed by developers and post-market oversight. Our first step is to map the landscape of these regimes and the responsible authorities involved. It is a complex picture that has grown up over a number of years and involves actors and agencies at multiple levels. We then turn to a sector-specific analysis, considering whether these regulatory regimes raise any concerns about the effective and proportionate oversight of novel neurotechnologies in three distinct sectors: non-invasive devices, invasive devices and neural stem cell therapies.

Applying our ethical framework

- 7.3 The ethical framework developed in Chapter 4 serves here as the normative template through which to view these regulatory systems and to determine whether the controls they provide are appropriate. The present chapter considers the virtues from the regulators' perspective. The central question that we address here is whether regulatory approaches currently in place support practices that instantiate the virtues in ways that promote the key interests at stake. In the context of regulation of new technologies, the central interest is meeting unmet therapeutic need through the delivery of safe and effective innovations. This means that responsible regulatory approaches must attend not only to the needs of patients, research participants and those responsible for their care, but also to the pressures upon innovators, manufacturers and those with a wider economic interest in the design and delivery of new inventions. The interests of patients in the availability of safe and effective treatments coincide with the inventiveness and economic interests of those marketing them. However, the respective interests of these two groups may diverge in regard to the degree and nature of regulatory oversight that best serves them. As we describe in Chapter 6, when our ethical framework is applied to the concept of Responsible Research and Innovation (RRI), it reveals certain priorities that act as benchmarks against which any regulatory regime can be measured.
- 7.4 First and foremost, effective regulation must deliver safe neurotechnologies. Regulation must be effective in protecting the interests of those using these technologies, but also proportionate. Considerations of safety must be proportionate to the actual risks involved – as far as these can be determined – and any assessment must also be relative to the degree of any likely benefits that can be expected. An inefficient, slow or burdensome system that presents a barrier to the availability of effective innovations is not in the interests of patients. However, where wholly new neurotechnologies with limited histories of clinical use and potentially significant effects on brain functions are concerned, it is also vital that regulatory oversight is thorough.
- 7.5 One essential element of securing safety and making assessments of proportionality is the availability of high quality and transparent evidence of the risks and benefits of each technology.

⁶³⁶ Fins JJ (2003) From psychosurgery to neuromodulation and palliation: history's lessons for the ethical conduct and regulation of neuropsychiatric research *Neurosurgery Clinics of North America* 14(2): 303-19, at page ix-x.

A robust regulatory system is one that not only grounds its decision-making in high quality evidence and is responsive to changes in this evidence; it must also be one that incentivises generation of evidence and a culture of openness around its accessibility and use. Considerations of subsidiarity are also relevant here, that is, the question of which authorities are best placed to discharge regulatory responsibilities. This is particularly important in the European context where both national and European agencies have roles to play. International and national bodies must have an appropriate division of labour; equally, there should not be any undue overlap between the function of regulatory or professional bodies: good clinical practice and good research practice must function together. Finally, it must be recalled that there are limits to what can be achieved through regulation and that RRI is also supported by grass-roots and collaborative practices of all those involved in the innovation, marketing and use of new technologies.

- 7.6 A well-functioning regulatory system would be expected to deliver the innovations needed in a timely fashion and with a minimum of regulatory burden so long as considerations of safety and proportionality are met. In this chapter, we consider the particular challenges in achieving proportionality in the context of regulating novel neurotechnologies.

Surveying the regulatory landscape

- 7.7 This section offers a brief overview of the regulatory environments that apply to the novel neurotechnologies discussed in this report. Broadly, there are two regulatory spheres: medical devices and advanced therapeutic medicinal products (ATMPs). These are not neuro-specific, but apply to all medical devices and ATMPs. The devices used to administer transcranial brain stimulation (TBS) or deep brain stimulation (DBS) and in brain-computer interfaces (BCIs) are classed as medical devices where they are used, *inter alia*, for diagnostic, monitoring or treatment purposes or in the modification of a physiological process.⁶³⁷ Neural stem cell therapies are regulated as ATMPs.⁶³⁸ Regulation in the European context is thus a complex web of intersecting laws, standards, guidelines and regulatory authorities operating at European and national levels. Paragraphs 7.8 to 7.22 provide an overview of these.

European level

- 7.8 The European Union (EU) has legislated in both regulatory spheres of medical devices and ATMPs.

Medical devices

- 7.9 Three Directives regulate medical devices, respectively concerning:
- medical devices *per se*;⁶³⁹
 - active implantable medical devices;⁶⁴⁰ and
 - *in vitro* diagnostic medical devices.⁶⁴¹
- 7.10 Only the first two are pertinent to the technologies we are concerned with in this report. All of these Directives are now subject to proposals for reform (see Box 7.1 below).⁶⁴² The relevant

⁶³⁷ A full definition of a medical device may be found in: MHRA (2011) *Bulletin no. 17: medical devices and medicinal products*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007498.pdf>.

⁶³⁸ European Medicines Agency (2011) *Advanced therapies*, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&mid=WC0b01ac05800241e0; European Medicines Agency (2011) *Reflection paper on stem cell-based medicinal products* available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/02/WC500101692.pdf.

⁶³⁹ Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (MDD).

⁶⁴⁰ Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of Member States on the approximation of the laws of the Member States relating to active implantable medical devices.

⁶⁴¹ Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices.

UK implementing legislation for the original Directives is found in the Medical Devices Regulations 2002, as amended. This transposed the provisions of the Directives into domestic law and is designed to bring the UK into line with the objectives of the Directives.⁶⁴³ The historical purpose of the three Directives has been to remove technical barriers to trade by harmonising safety and manufacturing requirements for medical devices across Europe. The emphasis is now placed upon safeguarding public health by supporting innovation, whilst ensuring the safety of the products that reach the market. This means that manufacturers must demonstrate conformity with the essential requirements as set out in the relevant Directive. Once conformity has been established, devices may then carry the CE mark. There is considerable economic incentive for manufacturers of medical devices to receive CE marking - once products have a CE mark, they must be allowed to circulate freely in the European internal market.

ATMPs

7.11 Similar objectives (of supporting innovation and harmonisation while protecting patient safety) underlie European law regulating ATMPs. The UK legislation giving effect to the European ATMP Regulation came into force on 19 August 2010.⁶⁴⁴ However, under the ATMP Regulation, ATMPs which are intended to be placed on the market in the European Community are subject to a *centralised* European authorisation procedure. The Committee for Advanced Therapies (CAT) of the European Medicines Agency (EMA) is responsible for preparing a draft opinion on the quality safety and efficacy of ATMPs for which marketing authorisation is sought. The opinion of CAT is then submitted to the EMA's Committee for Medicinal Products for Human Use (CHMP) for final approval.⁶⁴⁵

Harmonisation across Europe

7.12 A high degree of harmonisation exists with respect to the regulation of devices and ATMP regulation in Europe; at least as a matter of strict law. However, only ATMPs are subject to a centralised authorisation procedure. The EU has shared competence with Member States in a number of related areas beyond the specific regulation of devices and products. For example, it has sought to bring harmonisation to clinical research through the Clinical Trials Directive⁶⁴⁶ and the Tissues and Cells Directive. However, as we discuss below, harmonisation is not absolute. There is variability between Member States in the performance of Notified Bodies (the independent accredited organisations responsible for independently assessing conformity for all but low risk devices with regulatory requirements) and in the implementation of procedures that permit the production of ATMPs for on a non-routine basis for small numbers of patients. Furthermore, even when an ATMP has received pan-European marketing authorisation, matters such as labelling and reimbursement must still be dealt with at state level.

⁶⁴² Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁶⁴³ Later revisions to the MDD and AIMD are specified in Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market. These changes were transposed into UK law by Medical Devices Amendment Regulations SI 2008 No 2936.

⁶⁴⁴ Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending directive 2001/83/EC and regulation (EC) no 726/2004; MHRA (2010) *Guidance on the UK's arrangements under the hospital exemption scheme*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf>.

⁶⁴⁵ MHRA (2013) *How we regulate advanced therapy medicinal products*, available at: <http://www.mhra.gov.uk/Howweregulate/Advancedtherapymedicinalproducts/Aboutadvancedtherapymedicinalproducts/index.htm>.

⁶⁴⁶ Now subject to a proposal for a new Clinical Trials Regulation, see: Proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (17 July 2012).

National level

- 7.13 Member States of the EU are obliged to implement Directives and to give direct effect to European Regulations. They are at liberty to regulate above and beyond these measures but they must, as a minimum, adopt these measures.
- 7.14 A common feature of the regulatory architecture is the need for Member States to establish a national Competent Authority to discharge regulatory duties at a local level (and liaise with European agencies). In the UK, the Competent Authority ensuring implementation of the relevant European laws is the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA (and its equivalents in other Member States) acts as the pivotal regulator in both spheres affecting neurotechnologies. Its roles and powers are, however, limited by the regulatory objectives that it is designed to deliver, as dictated by the relevant European laws.
- 7.15 With respect to medical devices, the MHRA duties as Competent Authority include:⁶⁴⁷
- enforcing compliance of CE marked devices with regulations
 - monitoring and designating the 'Notified Bodies' that conduct conformity assessments;
 - registration of manufacturers of primarily low risk devices;
 - assessing notifications for clinical investigations; and
 - authorising the use of non-CE marked medical devices on humanitarian grounds and for custom-made purposes.
- 7.16 With respect to ATMPs, the MHRA is the supervisory authority for UK manufacturers or importers of those ATMPs that are centrally authorised at EU level. The MHRA's duties as Competent Authority in the UK include:⁶⁴⁸
- authorisation of clinical trials of ATMPs at a national level;
 - active involvement in the European system for authorisation of ATMPs by providing two members for CAT;
 - the provision of scientific advice at a European and national level;
 - authorisation of UK sites for manufacture and importation of ATMPs that are 'investigational medicinal products' (those to be used in a clinical trial); and
 - authorisation of UK sites where ATMPs are manufactured (this applies both to ATMPs authorised for the wider market and to products manufactured under the regulatory provisions permitting non-routine supply to single, or small numbers, of patients – the 'hospital exemption' and 'Specials' arrangements).

Requirements for evidence of efficacy

- 7.17 An important feature distinguishing the regulation of devices from ATMPs is the question of efficacy. Where ATMPs are concerned, the MHRA is required by law to establish their safety, quality and efficacy (in the same way as other medicinal products such as drugs). However, there is no parallel requirement for medical device manufacturers to demonstrate their products' efficacy. MHRA is only concerned with the safety, manufacturing quality, and performance of devices.
- 7.18 The difference between performance and efficacy may be understood as follows. A device will meet the criterion of performance if it operates as described (for example, that it administers an

⁶⁴⁷ Department of Health (2012) *Poly implant prothèse (PIP) silicone breast implants: review of the actions of the medicines and healthcare products regulatory agency (MHRA) and department of health*, available at: <http://www.meddevicesupplychain.com/public/06-12-MHRA.pdf>, at page 112.

⁶⁴⁸ MHRA (2013) *How we regulate advanced therapy medicinal products*, available at: <http://www.mhra.gov.uk/Howweregulate/Advancedtherapy Medicinal products/Aboutadvancedtherapy Medicinal products/index.htm>; MHRA (2013) *Scientific advice for licence applicants*, available at: <http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Informationforlicenceapplicants/Otherusefulservice sandinformation/Scientificadviceforlicenceapplicants/CON009534>.

electrical current through electrodes at xHz per second). Evidence of efficacy, meanwhile, would require demonstrating that the device achieved a particular outcome (for example, that it alleviates tremor in Parkinson's disease patients). The practical consequence of this distinction is that while useless and dangerous devices clearly would not be approved as a matter of risk-benefit analysis, the MHRA does not require evidence that a medical device will deliver a particular therapeutic outcome for users or improve on the efficacy of similar devices on the market. It may not always be possible to make a sharp distinction between evidence of performance and efficacy. However, as the exact mechanisms of action are still often unknown for many neurostimulation devices (such as those used in DBS) and outcomes will depend to a great extent on the skills of surgeons implanting them, there is an inferential gap from performance to efficacy of devices which means that these two terms cannot be read as synonymous.

Scope and limits of regulatory oversight

- 7.19 Alongside a concern for safeguarding public health, the second key focus for both of these regulatory regimes is whether a device or product is being developed with a view to introduction on the market. The regulatory driver here stems from the original objective of the EU, namely to create and maintain a single economic market. This means that the historical motive for regulating in this area has been to pave the way to market as much as to address concerns of safety for patients.
- 7.20 The practical consequence of this is that the MHRA has regulatory responsibility for only some kinds of activities involved in the clinical investigation or uses of novel neurotechnologies, but only where these are part of a pathway to marketing the product. For example, the MHRA must be notified when a pre-clinical assessment or a clinical investigation is to be conducted to obtain evidence prior to placing a medical device on the market.⁶⁴⁹ If, however, a device is manufactured by a health care establishment and only used on their *own* patients, the manufacturer is exempt from compliance with the medical device regulations.⁶⁵⁰ Similarly, it is not necessary for clinicians using CE marked devices for 'off-label' uses (uses other than those for which the device holds CE marking) to notify the MHRA, unless these uses are intended to be a pathway to marketing the device for this new purpose (see paragraphs 7.49 to 7.51 below).
- 7.21 Where regulatory agencies *are* engaged, there usually follows significant additional oversight. For example, clinical investigations involving medical devices that do not carry the CE-mark, and are intended for eventual market use, fall under the Medical Devices Regulations 2002 and require approval from the MHRA, which may take up to 60 days. For clinical investigations to proceed, approval must also be sought from an ethics committee appointed by the National Research Ethics Service (NRES).⁶⁵¹ For ATMPs involving cell therapies derived from stem cell lines, input is also required in the UK from the Gene Therapy Advisory Committee (GTAC) where there is an intention to market these products (we discuss this in further detail at paragraphs 7.70 to 7.72).
- 7.22 The significance of this is that, despite high levels of harmonisation in Europe, the regulatory regimes do not cover, to the same degree, all instances of innovation, experimental treatments or *ad hoc* investigations (which are a common feature of neurotechnology development),

⁶⁴⁹ MHRA (2012) *Guidance for manufacturers on clinical investigations to be carried out in the UK*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007504.pdf>, at page 6.

⁶⁵⁰ MHRA (2010) *In house manufacture*, available at: <http://www.mhra.gov.uk/Howweregulate/Devices/Inhousemanufacture/index.htm>. The removal of this exemption for devices manufactured and used in-house is one of the proposed changes under the revisions to European legislation: Article 4 of the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁶⁵¹ MHRA (2013) *Clinical trials for medical devices*, available at: <http://www.mhra.gov.uk/Howweregulate/Devices/Clinicaltrials/index.htm>.

although these may threaten patient safety. The close relationship between the intention to market a device or ATMP, and the degree of regulatory oversight this invites, raises questions about whether proportionality and appropriate regulatory orientation is achieved in the regulation of medical devices and ATMPs. We explore the consequences of this potentially uneven patchwork of regulatory oversight at paragraphs 7.49 to 7.51 and 7.73 to 7.89.

Box 7.1: Proposed revision of European legislation on medical devices

In September 2012, the European Commission produced proposals to address a number of matters arising in relation to the regulation of medical devices, predominantly in response to rapid changes in medical device technology.⁶⁵² At the time of writing, the MHRA (alongside the Competent Authorities of other Member States) is liaising with the Commission on these proposals.⁶⁵³ If adopted as they currently stand, some of the key changes of relevance to this report will include:

- Increasing transparency of the system by requiring, *inter alia*: manufacturers to register clinical investigations; manufacturers to improve information to the public about devices, to include details of warnings and precautions; the newly configured centralised European ‘Eudamed’ database in which this information is recorded to be made publically accessible.
- Strengthening criteria for clinical evaluation, for example by introducing ‘common technical specifications’ for safety and performance requirements; by requiring manufacturers to nominate a sponsor and to publish a summary of safety and performance evaluations for high-risk devices; and by requiring manufacturers to pursue post-market clinical follow-up strategies.
- Removing the full exemption of devices manufactured and used in-house by health care institutions from obligations to comply with the medical devices regulations (although some aspects of exemption will remain, including any requirement to record a summary of safety and performance on the centralised European database).
- Increasing oversight and audit of Notified Bodies, while also clarifying their duties and allowing joint assessments of Notified Bodies with other Member States and the European Commission.
- Requiring implantable and higher risk devices to undergo additional scrutiny for conformity by a new centralised European expert committee.
- Establishing an E U portal to which adverse events must be reported for automatic onwards transmission to competent authorities.

Sector-specific considerations

7.23 Having outlined the mechanisms by which the availability of novel neurotechnologies is regulated we now turn to assess the suitability of these regimes as they operate in the UK. The approach in this section will be to consider how the priorities we have established for RRI in this field and our ethical framework can assist in assessing the adequacy of current regulatory provisions and whether recommendations for reform are necessary. In doing, so we remain mindful of the need for effective and proportionate oversight and the possibility that regulatory burden may be no less detrimental to meeting therapeutic need and protecting patients’ safety than regulatory gaps. The following analysis divides the neurotechnologies with which we are concerned into three categories that capture the shared clusters of concerns that arise in respect of each. This division is based on the degree of invasiveness of a technology from the patient’s or research participant’s perspective: more invasive technologies are likely to carry higher risks and require tighter regulation. These sectors are: non-invasive neurodevices; invasive neurodevices; and neural stem cell therapies.

Non- invasive neurodevices

7.24 Transcranial magnetic stimulation (TMS) provides an illustration of some of the challenges posed by non-invasive neurodevices and associated technologies (though much of what we

⁶⁵² Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁶⁵³ MHRA (2013) *New legislation on medical devices*, available at: <http://www.mhra.gov.uk/Howweregulate/Devices/NewLegislationonMedicalDevices/>.

discuss in this section applies equally to transcranial brain stimulation (TBS) and non-invasive BCI devices). TMS devices currently have European market approval (CE marking) for use in, for example, the treatment of drug-resistant major depressive disorder in adults⁶⁵⁴ and neuropathic chronic pain.⁶⁵⁵ The European regulatory procedures involve assigning a medical device (marketed for a particular purpose) to one of four classes (see Box 7.2 below); these determine which regulatory pathway will be followed. Classification depends on a number of factors, including likely length of use, invasiveness (surgical or otherwise), whether the device is implantable or active, and whether the device also contains a therapeutic substance.⁶⁵⁶ TMS devices are non-invasive, but they are also “active” and are intended to “administer energy”.⁶⁵⁷ They are, therefore, likely to be assigned to one of the two ‘medium risk’ categories. Whether they are assigned to Class IIa or Class IIb will depend on how hazardous their use is considered to be in view of the purpose for which they are intended, and the mode of action by which the manufacturer intends this to be achieved.⁶⁵⁸

Box 7.2: Risk-based classification of medical devices in Europe

- **Class I** – generally regarded as low risk
- **Class IIa** – generally regarded as medium risk
- **Class IIb** – generally regarded as medium risk
- **Class III** – generally regarded as high risk

These classifications are established by the European Medical Devices Directive.⁶⁵⁹ These classifications determine the level of regulatory control proportionate to the degree of risk associated with the device and, therefore, the kind of conformity assessment the manufacturer and Notified Body must undertake in order for the device to receive a CE mark.⁶⁶⁰ Non-invasive medical devices will often fall under Class I. However, the particular functions of the kinds of active neurodevices with which we are concerned in this report will also engage particular additional rules under the Directive that place them in a medium risk class. For example ‘active therapeutic devices’ that administer or exchange energy (including electrical or magnetic energy), or those that perform a diagnostic function by monitoring physiological processes will be placed in Class IIa. If they perform these functions in a potentially hazardous way or are used in critical conditions they may be placed in Class IIb.

7.25 It is likely that TBS devices would be similarly assigned to Class II. Non-invasive BCI devices used for assistive purposes might also be assigned to a ‘moderate risk’ class insofar as they are judged to be used to “monitor physiological processes”.⁶⁶¹ This means that regulatory controls of all such non-invasive neurodevices are relatively light touch. Despite the fact that these devices are not classified as ‘high risk’, questions about the adequacy of regulatory oversight do arise, as we now go on to discuss.

Effective and proportionate oversight: the role of Notified Bodies

7.26 A central feature of the European regulatory system is the role played by Notified Bodies. These are independent agencies accredited by national regulators (such as the MHRA) to make judgments about the conformity of moderate and high risk devices to the criteria laid down in

⁶⁵⁴ PR Newswire (4 June 2012) *Neuronetics, inc. receives ce mark approval for neuroStar TMS therapy*, available at: <http://www.prnewswire.com/news-releases/neuronetics-inc-receives-ce-mark-approval-for-neurostar-tms-therapy-156965925.html>.

⁶⁵⁵ BioTuesday (2 July 2012) *Brainsway gets ce mark to treat neuropathic chronic pain*, available at: <http://biotuesdays.com/2012/07/02/brainsway-gets-ce-mark-to-treat-neuropathic-chronic-pain/>.

⁶⁵⁶ See: Annex IX of the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁶⁵⁷ MHRA (2011) *Bulletin no. 10: the classification rules*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007495.pdf>.

⁶⁵⁸ European Commission (2010) *Guidelines relating to the application of the Council directive 93/42/EEC on medical devices*, available at: http://ec.europa.eu/health/medical-devices/files/meddev/2_4_1_rev_9_classification_en.pdf.

⁶⁵⁹ Article 9 and Annex IX of the Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.

⁶⁶⁰ MHRA (2011) *Bulletin no. 10: the classification rules*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007495.pdf>.

⁶⁶¹ *Ibid.*

legislation.⁶⁶² Importantly, however, the European system is one of self-certification. For Class II devices (as well as Class III and ‘active implantable’ devices), this means that a manufacturer will work with a Notified Body to satisfy itself that their device meets minimum requirements of performance and safety.⁶⁶³ The MHRA does no more than oversee and audit the processes. The decision to assign these classifications falls to manufacturers and Notified Bodies, acting in accordance with rules and guidance; the MHRA only becomes involved with the decision-making process when there is disagreement between these parties.⁶⁶⁴ Notified Bodies are responsible for verifying the correct classification (and therefore the correct regulatory pathway) and whether sufficient evidence has been provided to support this. If these verifications are made, the manufacturer can attach the CE-mark.

7.27 There are currently 76 Notified Bodies in Europe operating in the field of medical devices, of which six are in the UK.⁶⁶⁵ It has been suggested that this decentralised system has sped up the approval process, but it has also been criticised for lacking transparency.⁶⁶⁶ These bodies do not publish the basis of their decisions regarding the conformity of a device with legal requirements for performance and safety, and do not make publically available the information on which it was based.⁶⁶⁷ This is because Notified Bodies consider themselves to be ‘clients’ of manufacturers, and so under no obligation to disclose information that could be commercially sensitive and covered by the law of commercial confidentiality.⁶⁶⁸ There are also concerns about variable standards between Notified Bodies across Europe. This is particularly worrying given that manufacturers have discretion to decide to which notifying body they will submit their data. In addition, there is little systematic Europe-wide monitoring of devices once they enter the market. If a device must later be removed from the market, it is the responsibility of the Notified Body to alert the national competent authority (the MHRA in the UK). Following the PIP breast implant controversy, the European Health and Consumer Policy Commissioner called for tighter controls on Notified Bodies.⁶⁶⁹ These are now echoed in the European Commission’s proposed reforms to the regulation of medical devices.⁶⁷⁰ **We welcome these proposals, but suggest that in the interests of transparency there is still a pressing need for the evidential bases on which Notified Bodies reach compliance decisions to be a matter of public record.**

7.28 The lack of transparency in the European system arguably perpetuates the scarcity of evidence upon which patients, health professionals, and public health services can take decisions about the uptake and use of medical devices. However, in 2013, the European Commission announced the establishment of a voluntary European Health Technology Assessment (HTA) network that will enable “easier sharing of HTA knowledge concerning devices and other health technologies among Member States” and “...make it easier for health decision-makers to identify which new devices can contribute to efficiency gains and improved services.”⁶⁷¹ The

⁶⁶² European Commission: Enterprise and Industry (2012) *Notified bodies*, available at:

http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=13.

⁶⁶³ MHRA (2008) *Bulletin No. 4: conformity assessment procedures*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007492.pdf>.

⁶⁶⁴ MHRA (2011) *Bulletin no. 10: the classification rules*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007495.pdf>.

⁶⁶⁵ European Commission: Enterprise and Industry (2012) *Notified bodies*, available at:

http://ec.europa.eu/enterprise/newapproach/nando/index.cfm?fuseaction=directive.notifiedbody&dir_id=13.

⁶⁶⁶ Cohen D and Billingsley M (2011) Europeans are left to their own devices *British Medical Journal* **342:d2748**: 1-7, at page 2.

⁶⁶⁷ *Ibid*

⁶⁶⁸ Fraser AG, Daubert J-C, Van de Werf F *et al.* (2011) Clinical evaluation of cardiovascular devices: principles, problems, and proposals for European regulatory reform: report of a policy conference of the European Society of Cardiology *European Heart Journal* **32(13)**: 1673-86, at page 1684.

⁶⁶⁹ European Commission (2012) *Medical devices: European Commission calls for immediate actions - tighten controls, increase surveillance, restore confidence*, available at: http://europa.eu/rapid/press-release_IP-12-119_en.htm.

⁶⁷⁰ Articles 28 to 40 of the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁶⁷¹ European Commission (2012) *Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions: safe, effective and innovative medical devices and in vitro diagnostic medical devices for the benefit of patients, consumers and healthcare professionals* available at: http://ec.europa.eu/health/medical-devices/files/revision_docs/com_2012_540_revision_en.pdf, at paragraph 3.3.

European Databank on Medical Devices (Eudamed),⁶⁷² which captures information on medical devices for the benefit of regulators, is not currently accessible to the public. Transparency is also likely to be improved by forthcoming European regulatory changes. The European Commission's proposals include making key aspects of an expanded and newly configured Eudamed publically accessible and enhancing the range of data it contains, including that on clinical investigations.⁶⁷³ **We welcome these proposed changes and the extent to which they would enhance the transparency of the European system. However, we suggest to the European Commission that Eudamed should aspire to a similar degree of transparency as that which operates in the US Food and Drug Administration (US FDA), the body charged with regulating medical devices in the US.** The FDA operates a publically accessible database through which information on, for example, approved medical devices and incident reports, can be searched and accessed.

Effective and proportionate oversight: pre-market evidence requirements

- 7.29 The regulation of medical devices in Europe may be characterised as one that is relatively light touch in terms of pre-market scrutiny when compared, for example, with that operating in the US. Indeed, the European regime has been described as one that relies "...more on postmarketing surveillance than it does on premarket testing."⁶⁷⁴ Like the European system, the US FDA is also responsible for overseeing the safety of products and market access regimes and also adopts an approach whereby regulatory requirements become increasingly stringent in proportion to the level of risk. However, in contrast, the FDA operates a highly centralised system, which brings both benefits and challenges. The US system has advantages in terms of transparency of the evidence on which decisions are based.⁶⁷⁵ A register is maintained of all devices and this includes details of the intended use and pre- and post-market evaluations. Unlike the European system, before medical devices can be marketed under the US system, it is usually necessary to demonstrate that they are not only safe, but also *effective*.⁶⁷⁶
- 7.30 There are examples of medical devices being denied approval in the US, despite prior-approval in the EU.⁶⁷⁷ The apparently more stringent compliance standards in the US system that might be seen, *prima facie*, as offering better protection to prospective patients' interests than the European system. However, the US system is regarded as scoring less well in terms of alacrity. Delays and bureaucracy in the US system may be also seen as threatening patient safety insofar as they postpone access to therapies.⁶⁷⁸ These factors can mean that market costs are correspondingly high thus creating further barriers to access. However, accounts of such delays are mixed; one published literature review suggests that, in general, approval times under the US and European systems are comparable for all but high-risk devices.⁶⁷⁹ Nevertheless, anecdotal evidence suggests that manufacturers of some types of medical devices (for

⁶⁷² European Commission: Consumer Affairs (2011) *European databank on medical devices*, available at: <http://ec.europa.eu/consumers/sectors/medical-devices/market-surveillance-vigilance/eudamed/>.

⁶⁷³ Article 27 of the European Commission (2012) *Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012)*.

⁶⁷⁴ Cohen D and Billingsley M (2011) Europeans are left to their own devices *BMJ* **342**:d2748, at page 5.

⁶⁷⁵ House of Commons Science and Technology Committee (2012) *Regulation of medical implants in the EU and UK* available at: <http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/163/163.pdf>, at paragraph 37.

⁶⁷⁶ It is not necessary to demonstrate effectiveness under the US Humanitarian Device Exemption described further in Box 7.5.

⁶⁷⁷ Cohen D and Billingsley M (2011) Europeans are left to their own devices *BMJ* **342**:d2748, at page 4. For example, in 2007 Medtronic's device 'Chronicle', an implantable device designed to measure and record haemodynamic variables was approved for market authorisation in Europe but was refused by the FDA due to "lack of clinical effectiveness".

⁶⁷⁸ House of Commons Science and Technology Committee (2012) *Regulation of medical implants in the EU and UK* available at: <http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/163/163.pdf>, at paragraph 44.

⁶⁷⁹ Kramer DB, Xu S and Kesselheim AS (2012) How does medical device regulation perform in the United States and the European Union? A systematic review *PLoS Medicine* **9**(7): e1001276. Note, however, the authors acknowledge the potential limits of data in the literature, especially where studies have not been peer reviewed.

example, DBS devices) may increasingly seek to enter the market in Europe *first* for this reason.⁶⁸⁰

- 7.31 Devices assigned to Class II under the European Medical Devices Directive, such as those delivering TMS, will not necessarily require manufacturers to pursue their own clinical investigations. Approval can also be granted on the basis of literature alone, provided the literature pertains to an established device already on the market which the manufacturer can demonstrate is ‘equivalent’ to the new device in terms of “technology, critical performance, design, principles of operation, biological safety, population involved, conditions of use and clinical purpose”.⁶⁸¹ This regulatory route is attractive to manufacturers because it entails less onerous evidence requirements, thus potentially offering a faster and less costly route to market and more time to exercise time-limited intellectual property rights (IPRs). As we noted in Chapter 3, a similar system operates in the US under the so-called ‘510(k)’ or premarket notification route (see paragraph 3.57). The FDA has attracted criticism for permitting what has been viewed as inappropriate use of the 510(k) route (see Box 7.3). In the UK, the Chief Executive of the MHRA has expressed the view that it is “critical” to reduce the extent to which manufacturers are able to rely on substantial equivalence.⁶⁸² The criterion of equivalence may be seen as particularly ill-suited to the assessment of neurodevices as their benefits and risks depend crucially on the region of the brain that is stimulated, not solely on the performance of the device itself.⁶⁸³

Box 7.3: Market notification using predicate devices in the US

Under regulations operated by the FDA, low and moderate risk devices may receive a license to be marketed in the US by submitting a ‘premarket notification’ (also known as a 510(k)) without having to follow the most stringent pathway of ‘premarket approval’ (PMA). The 510(k) route requires manufacturers to demonstrate that: “the device to be marketed is at least as safe and effective, that is substantially equivalent, to a legally marketed device... that is not subject to PMA”.⁶⁸⁴ As we observed in Chapter 3, the 510(k) ‘premarket notification’ pathway is attractive to neurotechnology companies wishing to reach the market as quickly as possible, and concerns have been raised about whether the 510(k) route strikes an appropriate balance between public safety and market access.

A device is substantially equivalent to a legally marketed device under 510(k) if it has both the same intended use and the same technological characteristics. There may also be substantial equivalence if the device has the same intended use but different technological characteristics compared with the legally marketed device, as long as the device does not raise new questions of safety and efficacy. In the case of *Medtronic, Inc. v. Lohr* (concerning a cardiac pacemaker cleared by the 510(k) process) a regulatory expert noted that: “A determination of ‘substantial equivalence’ by [the] FDA does not signify an agency endorsement of the safety and effectiveness of the device but is merely a clearance to market.”⁶⁸⁵

In 2007, Neuronetics Inc. sought 510(k) clearance for its NeuroStar rTMS device to treat drug resistant depression on the basis that the TMS device was substantially equivalent to electroconvulsive therapy (ECT). In relation to the fact that the FDA had originally required not only that Neuronetics demonstrate that rTMS treatment was favourable and comparable to ECT, but that any reduction in effectiveness of the former was counter-balanced by a reduction in risk, the President of the National Research Center for Women & Families observed that: “It is not clear how that qualifies a product for the 510(k) process.”⁶⁸⁶ In this instance, the FDA Advisory Panel found that the risk-benefit profile of the rTMS device was not

⁶⁸⁰ Medtronic (2012) *Grand designs – how to take your medical device innovation from patent to production*, available at: http://www.medtronic-eureka.com/innovation-articles/making-it-happen/patent_to_production.

⁶⁸¹ MHRA (2012) *Guidance for manufacturers on clinical investigations to be carried out in the UK*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007504.pdf>, at paragraph 12.

⁶⁸² House of Commons Science and Technology Committee (2012) *Regulation of medical implants in the EU and UK* available at: <http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/163/163.pdf>, at paragraph 29.

⁶⁸³ Fins JJ, Mayberg HS, Nuttin B *et al.* (2011) Misuse of the FDA Humanitarian Device Exemption in deep brain stimulation for obsessive-compulsive disorder *Health Affairs* **30(2)**: 302-11, at page 304.

⁶⁸⁴ FDA (2010) *Premarket notification (510k)*, available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default.htm>. Note that a legally marketed device is “a device that was legally marketed prior to May 28, 1976... for which PMA is not required, or a device which has been reclassified from Class III to Class II or I, or a device which has been found SE through the 510(k) process”.

⁶⁸⁵ Fins JJ, Mayberg HS, Nuttin B *et al.* (2011) Misuse of the FDA Humanitarian Device Exemption in deep brain stimulation for obsessive-compulsive disorder *Health Affairs* **30(2)**: 302-11, pp. 304-5.

⁶⁸⁶ National Research Center for Women & Families (2012) *Statement of Diana Zuckerman, PhD., president, National Research Center for Women & Families at the FDA Advisory Panel meeting, regarding the neuroStar TMS system for major depression*, available at: <http://center4research.org/public-policy/testimony-briefings-statements/statement-of-diana-zuckerman-phd-president-national-research-center-for-women-families-at-the-fda-advisory-panel-meeting-regarding-the-neurostar-tms-system-for-major-depression/>.

comparable to that of ECT and declined to pass the device on the basis of substantial equivalence. It did, however, grant marketing approval to NeuroStar on the evidence of its own efficacy and safety.⁶⁸⁷ Subsequent transcranial brain stimulation devices may now follow the 510(k) pathway with less controversy, as more closely comparable devices are on the market. For example, in 2013 the Brainsway Deep rTMS System received clearance on grounds of substantial equivalence to be marketed in the US for the treatment of major depression.⁶⁸⁸

With criticisms of the 510(k) process in mind, the FDA asked the US Institute of Medicine (IOM) to evaluate this pathway. The IOM reported in July 2011, finding that the reliance on substantial equivalence could not ensure safety and efficacy, since the majority of devices used as comparators were never themselves evaluated on these criteria. The IOM recommended that, rather than trying to fix an inherently flawed system, the FDA should develop a new framework integrating premarket and post-market regulation.⁶⁸⁹ The IOM added, as an imperative, that the new process should not unduly delay progress or be burdensome.

- 7.32 The absence of the strictest pre-market evidence requirements for non-invasive neurodevices under European regulations might entail less bureaucracy, meaning that therapies may be developed, and thus reach patients, more quickly. However, it could also be criticised for placing the interests of the market above the safety of patients and the associated need for more robust evidence about how these new technologies function.⁶⁹⁰ In the context of devices that intervene in the brain – even if not through surgical means – patient safety and well-being are of primary concern. The virtue of responsibility requires that regulators and manufacturers reflect on the need for robust evidence before neurodevices are allowed to enter the market. Moreover, lighter pre-market regulatory controls are no guarantee that the market alone will deliver the range or quality of products required to meet therapeutic need. As we observe in Chapter 3, the availability of routes to market approval based on equivalence data, and the willingness of manufacturers to exploit these, could potentially inhibit the kinds of innovation that fill the most important gaps in the market for devices that address unmet patient needs, by encouraging more conservative approaches that reproduce similar products.⁶⁹¹ Furthermore, innovation in this field is often conducted by smaller businesses with limited resources. Where demand is limited to the few people with the most intractable and severe manifestations of serious conditions, there may be little financial incentive for companies to pursue (or for investors to support) commercial development of devices. We return to consider how the regulatory system serves the needs of patients for whom there are no suitable devices on the market in paragraphs 7.73 to 7.89.
- 7.33 We recognise that that permitting the provision of data pertaining to ‘equivalent’ products may in some circumstances represent a proportionate approach for some kinds of medical devices and that any efforts to narrow the availability of this route must be mindful of unintended consequences, such as discouraging innovation. Nevertheless, this might not always be a proportionate approach for devices that intervene in the brain. As a responsible regulatory approach, we therefore welcome the MHRA’s position that reliance on equivalence data should be minimised. We also welcome the introduction of more specific criteria for the demonstration of equivalence by the European Commission proposals for revised legislation on medical devices.⁶⁹² **In recognition of the special status of the brain and continued uncertainty regarding the consequences of intervening in it, we recommend to the MHRA that, where equivalence data are relied upon to demonstrate the regulatory conformity of a**

⁶⁸⁷ FDA (2008) *Repetitive transcranial magnetic stimulator for treatment of major depressive disorder*, available at: http://www.accessdata.fda.gov/cdrh_docs/pdf6/K061053.pdf.

⁶⁸⁸ FDA (2013) *Brainsway deep TMS system*, available at: http://www.accessdata.fda.gov/cdrh_docs/pdf12/K122288.pdf.

⁶⁸⁹ The National Academies (29 July 2011) *FDA should invest in developing a new regulatory framework to replace flawed 510(k) medical device clearance process*, available at: <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=13150>.

⁶⁹⁰ Cohen D and Billingsley M (2011) Europeans are left to their own devices *British Medical Journal* **342:d2748**: 1-7.

⁶⁹¹ Royal Academy of Engineering and The Academy of Medical Sciences (2013) *Establishing high-level evidence for the safety and efficacy of medical devices and systems* available at: http://www.raeng.org.uk/Medical_devices_and_systems.pdf, at page 17.

⁶⁹² Annex XIII of the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

neurodevice, the condition of equivalence must be satisfied in relation to its effect, not only its purpose, performance and safety. Furthermore, clear justification for approving neurodevices on the basis of equivalence data alone must always be provided and open to public scrutiny.

Obstacles to generating robust evidence

7.34 Effective regulation of devices and products that intervene in the brain should not only proceed on the basis of the best possible evidence of the safety and impacts of these interventions, it should also support the *generation* of this evidence. However, there is a well-acknowledged problem in the medical devices sector of incentivising or generating a rich body of evidence, in particular about the efficacy and long-term unintended impacts of devices.⁶⁹³ This is not only attributable to structural factors such as the relative lack of transparency and decentralisation of the decision-making of Notified Bodies, but also to the absence of any requirement under European regulations for manufacturers to provide evidence of the efficacy of their devices.

7.35 There are, therefore, few incentives for developers and manufacturers to pursue research to build a robust body of evidence about the clinical applications of neurodevices this end. This problem of is well summarised by the Chair of the Medical Technologies Advisory Committee of NICE:

“Medical technologies are often evaluated using limited evidence. This is partly because the regulation of medical devices worldwide does not require as much research data as does the regulation of drugs; partly because new technologies are often developed by small companies that have little experience in research; and partly because new technologies typically reach market early, before many research findings are available.”⁶⁹⁴

Providing a complementary perspective on the same issue, the MHRA has argued that, for a number of reasons, including the rapid and iterative nature of medical device innovation, the vast numbers of devices seeking approval and sporadic or wear-and-tear-related nature of faults, requirements for extensive pre-market clinical research would be ill-suited to regulation in this sector.⁶⁹⁵

7.36 This reveals the limitations of the regulatory system’s own capacity to incentivise and to capture the scientific knowledge of the effects of medical devices and to tackle the persistent problem of uncertainty. This then presents a significant challenge to responsible governance of clinical practices and healthcare provision where neurodevices are involved. A lack of evidence leaves clinicians under-equipped to provide the best advice to patients could hinder informed decision-making by patients and research participants. It also presents a challenge to NICE in drawing on the best and most complete evidence to guide health service purchasing decisions. The virtues of responsibility and inventiveness therefore then demand that a range of actors address the question of what is the most appropriate means of obtaining sufficiently relevant and robust evidence of the safety and benefits of these technologies and work towards this goal.

Limitations of randomised controlled trials

7.37 Randomised controlled trials (RCTs) are often characterised as the gold standard for generating evidence about the effectiveness and risks of health care interventions. Recent evidence submitted to a Congressional debate in the US on medical devices raised the question of why

⁶⁹³ Royal Academy of Engineering and The Academy of Medical Sciences (2013) *Establishing high-level evidence for the safety and efficacy of medical devices and systems* available at: http://www.raeng.org.uk/Medical_devices_and_systems.pdf.

⁶⁹⁴ Campbell B (2012) How to judge the value of innovation *British Medical Journal* **344**:e1457: 1-2, at page 1. See also: Campbell B (2011) NICE medical technology guidance: devices and diagnostics *Heart* **97**(21): 1794-5.

⁶⁹⁵ House of Commons Science and Technology Committee (2012) *Regulation of medical implants in the EU and UK* available at: <http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/163/163.pdf>, at paragraph 28.

clinical trials – which are so central to confirming patient safety in the pharmaceutical sector – are not also required in the medical devices field.⁶⁹⁶ The pharmaceutical sector has been at the vanguard of much regulatory reform, and it is the experience of the UK that the adoption of the European Directive relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use ('the Clinical Trials Directive')⁶⁹⁷ was the catalyst to conduct a wholesale review of research governance. This review ultimately led to the establishment of NRES in 2006 (which in turn became the core function of the Health Research Authority (HRA) established in December 2011). NRES provides central administration for the ethics review service in the UK and seeks to “facilitate and promote robust ethical research”.⁶⁹⁸ Much of the framework and procedures of organisations such as the MHRA (and its equivalents in other countries), including the EMA at European level, have been shaped by the clinical trials paradigm.

- 7.38 The arguments are, however, finely balanced as to whether RCTs and the standards of evidence approximating to these are appropriate in the medical devices sector. It is certainly the case that medical devices are far more complex and potentially risky compared to several decades ago when the regulatory regimes were established. On the other hand, there are a number of methodological reasons why RCTs may *not* be a suitable approach in this sector.⁶⁹⁹ The numbers of patients with the most severe and intractable neurological and mental health disorders, for whom these technologies might offer most benefit, are very small, meaning that full-scale control trials might not be possible. Trials using robustly blinded control arms also may not be achievable for the kinds of neurodevices addressed by this report. This is not just because of the ethical challenges posed by sham surgery (as discussed at paragraphs 5.36 to 5.41), but also because even non-invasive stimulation may be detectable by participants. For example, TMS produces a contraction in the muscles of the scalp directly beneath the area of application.⁷⁰⁰ Furthermore, an RCT approach is hypothesis-driven and dependent on an existing evidence base against which to test the hypothesis and from which to inform participants and ethical oversight bodies of likely risks and benefits. Where there is little existing evidence of exactly how a device achieves therapeutic effects or of unintended effects, as is the case with some interventions using neurostimulation, it may not be possible to develop the same kind of research protocol that is needed to conduct a clinical trial.

Alternative sources of evidence

- 7.39 The results of randomised controlled trials do not have a monopoly on valuable evidence of the safety and efficacy. Cochrane Reviews and the development of NICE guidance, both respected evidence-based processes for assessing health care interventions, draw on a much wider range of sources, including patients' experiences.⁷⁰¹ The virtue of inventiveness suggests that an open approach to what constitutes sufficient and appropriate evidence of the safety and efficacy of neurodevices (and embracing incremental approaches to accruing this) would be of value in this sector, provided that mechanisms are in place to gather it and assure its quality. Observational

⁶⁹⁶ University of California, San Francisco (2011) *Testimony of Rita F. Redberg*, available at: http://democrats.energycommerce.house.gov/sites/default/files/image_uploads/RitaRedberg.pdf.

⁶⁹⁷ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. The Directive was implemented in the UK by the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended by SIs 2006/1928, 2006/2984, and 2008/941. There are now proposals for reform: Proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (17 July 2012).

⁶⁹⁸ NRES (2013) *How we work*, available at: <http://www.nres.nhs.uk/about-the-national-research-ethics-service/about-nres/how-we-work/>.

⁶⁹⁹ Royal Academy of Engineering and The Academy of Medical Sciences (2013) *Establishing high-level evidence for the safety and efficacy of medical devices and systems* available at: http://www.raeng.org.uk/Medical_devices_and_systems.pdf.

⁷⁰⁰ Lisanby SH, Kinnunen LH and Crupain MJ (2002) Applications of TMS to therapy in psychiatry *Journal of Clinical Neurophysiology* **19**(4): 344-60, at page 345.

⁷⁰¹ NICE (2012) *How we work*, available at: http://www.nice.org.uk/aboutnice/howwework/how_we_work.jsp.

studies and small scale pilots as well as modelling may also provide potentially useful sources of evidence.⁷⁰² The registers of clinical experience that we recommend at paragraph 5.63 would provide a valuable means of capturing precisely these types of evidence.

- 7.40 The fragmented nature of top-down regulatory mechanisms in Europe has led to attempts at self-governance amongst practitioners working with TMS and rTMS. One research group has published information on the role of international consensus guidelines in this area, updating previous measures in light of growing evidence from the thousands of healthy volunteers and patients with a range of neurological and psychiatric conditions who have undergone TMS; this has revealed not only better understandings of risk, but also a very low occurrence of seizures (the most serious TMS-related adverse reaction).⁷⁰³ The resultant review of international guidelines encompasses issues of risk and safety and proposes limits for TMS parameters in various clinical circumstances.⁷⁰⁴ A consortium of French scientific societies commissioned a comprehensive literature review of the evidence of safety and efficacy of rTMS,⁷⁰⁵ culminating in a consensus statement from the review group in light of the evidence gathered, including assessments that reported side effects are very low. Many of the recommendations mirror the conclusions of the aforementioned review, but go further by representing the first attempt to establish the therapeutic indications for rTMS.
- 7.41 These examples of professional initiatives to improve the evidence base of understanding of new technologies are to be lauded. They exemplify the virtues of inventiveness and responsibility in that the science community, on its own initiative, has sought to engage with some of the intractable challenges of neurotechnologies – specifically uncertainty, and the absence of sound evidence. The value of coordinated grassroots efforts to improve the availability of robust scientific evidence of efficacy and longer-term risks of neurodevices is unquestionable. They may not, however, be sufficient on their own, not least because there are no mechanisms to oversee their use by clinicians, and far less to *require* this. This is an example of where it matters very much whether clinical uses of TMS are seen as experimental treatment – and so regulated by clinical standards – or as a form of research, which is more likely to involve independent approval and oversight by ethics bodies. These limitations notwithstanding, other opportunities for generating and sharing robust data could be better exploited. For example, the establishment of the International Medical Devices Regulators Forum (IMDRF) in February 2011, continuing the work of the Global Harmonization Task Force on Medical Devices (GHTF), not only signals a commitment to increased international harmonisation, but also provides an ideal platform for further integration of the regulator and practitioner communities via open stakeholder forums.⁷⁰⁶

Robust evidence through effective information governance

- 7.42 The diverse means of gathering and making accessible greater quantities of robust data about the efficacy and safety of neurodevices, as described in the preceding paragraphs, are potentially invaluable where the regulatory system does not itself drive the generation of this evidence. However, the risk is that their findings are isolated in diffuse locations, making outputs inaccessible to a wide range of interested parties. A further risk is that diverse methods of recording data preclude their comparability, verifiability, or linkage.
- 7.43 Existing mechanisms for collecting information about the benefits and risks of neurodevices and their therapeutic applications could be more effectively exploited if an overarching approach to

⁷⁰² Royal Academy of Engineering and The Academy of Medical Sciences (2013) *Establishing high-level evidence for the safety and efficacy of medical devices and systems* available at: http://www.raeng.org.uk/Medical_devices_and_systems.pdf, pp21-2.

⁷⁰³ Rossi S, Hallett M, Rossini PM and Pascual-Leone A (2009) Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research *Clinical Neurophysiology* **120**(12): 2008-39.

⁷⁰⁴ *Ibid*, at page 2028.

⁷⁰⁵ Le Faucheur J, André-Obadia N, Poulet E *et al.* (2011) [French guidelines on the use of repetitive transcranial magnetic stimulation (rTMS): safety and therapeutic indications] *Neurophysiologie Clinique* **41**(5-6): 221-95.

⁷⁰⁶ IMDRF (2013) *International medical device regulators forum*, available at: <http://www.imdrf.org/>.

information governance were to be adopted in order to facilitate their transparency and linkage. The Royal Society's *Science as an open enterprise* report makes a number of recommendations to meet the public interest in promoting science as an open enterprise.⁷⁰⁷ These include the recommendations that common standards for sharing information should be adopted to make it widely usable and that science journals should require the accessibility of the underlying research data as a condition of publication of an article. In these ways, the self-correcting precepts of scientific endeavour can best operate to allow verifiability of data. We endorse this commitment to openness. There are a number of UK projects that aim to maximise the linkage and utility of NHS patient data, while keeping appropriate scrutiny undiluted. These include the Clinical Practice Research Datalink, the Scottish Informatics Programme and the recently-launched e-Health Informatics Research Centres and Network.⁷⁰⁸ The remits of such initiatives are clearly much wider than neurological health. We suggest that similar efforts to achieve a 'meta-network' between information repositories holding data on the risks and benefits of neurodevices would support the regulatory system by ensuring that oversight is proportionate to the current best evidence, facilitate research and enhance innovation by highlighting areas of unmet need and, ultimately and most importantly, protect patients interests in receiving safe and effective treatments. This network would not itself be a data repository but would extend the reach and value of the data held in any existing information holdings in order to strengthen capability and competitiveness in the development of neurodevices.

7.44 Efforts at achieving open approaches to health information governance are necessarily multiplatform, interdisciplinary, and international; they rely on the parallel and collaborative efforts of a number of stakeholders, including funders, regulators, manufacturers, researchers, health care providers, and patients' groups. As the preceding paragraphs suggest, the information sources captured by such a collaboration must extend much wider than data from clinical trials, to encompass evidence from small-scale research studies and experimental approaches to treatment, patient-reported outcomes and post-market surveillance data. The aspiration would be for a meta-network to facilitate linkage between the kinds of clinical experience registries discussed in Chapter 5, but also to extend far beyond these kinds of data to capture those generated in manufacturing, academic, and regulatory contexts including, for example, the newly-purposed centralised European regulatory database for medical devices, Eudamed. In an effort to capture the widest possible body of evidence, international linkage would be an asset. The linking and mining of data in such circumstances raises further questions about how to deliver public benefit through research, while ensuring appropriate protection of privacy in respect of personal data. The Nuffield Council on Bioethics has recently convened a separate Working Party to examine ethical issues in sharing and linking biological data and health records.⁷⁰⁹

Invasive neurodevices

7.45 Invasive neurodevices, which in the context of this report include those used to deliver DBS and invasive BCIs, are examples of technologies that involve surgical invasion of the patient's bodily or cerebral integrity to some degree. As we note in Chapter 2 and in our ethical framework, the physical risks of invasive neurodevices extend beyond the surgery itself, to those relating to the long-term implantation of electrodes in the brain, and to the possible unintended psychological and behavioural effects of invasive neurostimulation. As such, these invasive neurotechnologies give rise to inherently more acute concerns about the safety of their use and the need to

⁷⁰⁷ The Royal Society (2012) *Science as an open enterprise*, available at:

http://royalsociety.org/uploadedFiles/Royal_Society_Content/policy/projects/sape/2012-06-20-SAOE.pdf.

⁷⁰⁸ Clinical Practice Research Datalink (2013) *Welcome to the clinical practice research datalink*, available at:

<http://www.cprd.com/intro.asp>; MRC (2013) *Background to the Health Informatics Research Centres* available at:

<http://www.mrc.ac.uk/consumption/groups/public/documents/content/MRC009053.pdf>; Scottish Informatics Programme

(2012) *Scottish informatics programme*, available at: <http://www.scot-ship.ac.uk/>.

⁷⁰⁹ See: Nuffield Council on Bioethics (2013) *The collection, linking, use and exploitation of biological and health data: ethical issues*, available at: <http://nuffieldbioethics.org/biological-and-health-data>.

exercise responsibility and humility in not intervening in the brain unnecessarily. The concerns we have raised about the effective and proportionate regulation of non-invasive neurodevices and the availability of robust evidence in the previous section therefore apply *a fortiori* to invasive devices.

- 7.46 Under the regulatory regime operating in the UK and the rest of Europe, the invasive neurodevices we discuss in this report are regulated under the Active Implantable Medical Devices Directive (AIMD).⁷¹⁰ According to the AIMD, medical devices are automatically considered to be ‘high risk’. As such, the pre-market regulatory oversight of *invasive* medical devices it is more demanding than that which applies to non-invasive devices, including the pathways for assessing conformity with the legislation. This reflects greater caution commensurate with the greater risks involved.
- 7.47 If the proposals for revised European legislation are implemented without significant deviation from their current form, then it is likely that oversight of higher risk and implantable devices will be further strengthened, for example by requiring that these devices undergo additional scrutiny for conformity by a new centralised European expert committee and that the manufacturers publish a summary of safety and performance evaluations (see Box 7.1 above). **In light of our recommendation at paragraph 7.33 we welcome the European Commission’s legislative proposals which state that, for implantable and high risk devices, demonstration of equivalence with existing devices will “generally not be considered as sufficient justification” for relying on existing clinical data alone.**⁷¹¹ This means that manufacturers who seek to market invasive neurodevices will ‘generally’ have to conduct clinical evaluations of the device for its intended purpose.
- 7.48 However, as we have already observed, whether a device is subject to regulatory scrutiny at all depends chiefly on whether there is an intention to market the device. This could be seen as giving rise to some uneven distribution of regulatory oversight which is a particular concern for invasive devices, which is perhaps most notable in the context of the pursuit of clinical investigations of these devices, as we explore in the following paragraphs.

Effective and proportionate oversight: clinical investigations and experimental treatment

- 7.49 Where a medical device does not have a CE-mark, the MHRA must be notified in advance of clinical investigations of its safety and performance, and the provisions of the relevant Directive will be engaged. The same is true when a clinician modifies a CE-marked device or uses it for a new ‘off-label’ purpose if they anticipate a commercial application of this. In effect, each of these provisions treats such investigations as potential steps on a device’s route to market.⁷¹² The focus of much of the regulatory regime upon the marketability of devices can lead to unlooked-for consequences, as illustrated by an example from a factfinding meeting with clinicians conducted by the Working Party as part of the preparation of this report. In this example, a clinician wanted to hold a trial investigating the use of DBS for the treatment of OCD.⁷¹³ The clinician reached an agreement with a device company such that they would donate the (expensive) equipment for this study. The company agreed to have no involvement in the study (for example, regarding protocol design) because they did not want to become involved with associated regulatory requirements. The clinician reasoned that the trial did not have to be notified to the MHRA, given that there was no company involvement, and that the trial’s aim was solely research-focused. The MHRA disagreed, however, and argued that the company was

⁷¹⁰ Devices for DBS fall under the Active Implantable Medical Devices Directive (AIMD). If a device falls within the terms of the AIMD Directive then, technically, each component belonging to the system is also covered by the AIMD and must comply with its requirement. See: Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of Member States relating to active implantable medical devices.

⁷¹¹ Annex XIII of the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁷¹² MHRA (2012) *Guidance for manufacturers on clinical investigations to be carried out in the UK*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007504.pdf>, at paragraphs 14-27.

⁷¹³ Ludvic Zrinzo, contributing to a Factfinding meeting with clinicians, 16 February 2012.

effectively a sponsor as they might use the information in the future to obtain a CE-mark. Thus, if the company donated the equipment, the MHRA would have to be notified and the appropriate regulations engaged. As a result, the industry rescinded its interest and it was necessary for the clinician to raise significant funds for the equipment himself. The irony here is that regulatory attention was attracted not because of a concern about securing patient safety, but because the investigation was viewed by the regulator as a possible route to market.

- 7.50 This example may be contrasted with the situation that applies where there is, unambiguously, *no* intention to market a device on a commercial basis. For example, when a CE-marked device is used off-label or a device is manufactured ‘in-house’ by a health care establishment with the intention to use it only in investigations involving patients in the care of that establishment, the MHRA need not be notified.⁷¹⁴ The realm where such investigations are most likely to happen is that concerning *ad hoc* experimental treatment using these devices, in the absence of any other available therapeutic options. This raises the question of whether there is a regulatory lacuna, one that potentially means that interventions using the least developed devices with the most vulnerable patients occur outside the oversight of the regulator. If the device is used as part of a formal research study then the intervention of a REC might fill this gap. However, if it is used as an investigative treatment, it is likely to be governed by professional medical ethics alone.
- 7.51 Given that patient safety is a primary concern, particularly in the realm of invasive neurodevices, we might question whether the orientation of the current regulatory system is appropriate. The focus upon the prospective marketability of devices fails to capture some of the most pressing concerns arising in the use of these technologies in the early stages of their development trajectories. In light of this, we welcome the proposal of the European Commission to remove the exemption of medical devices manufactured by health care establishments for in-house uses from the requirement to comply with some obligations under the device regulation.⁷¹⁵ It is, however, regrettable that these devices would still be exempt from the requirement to record clinical data or adverse events relating to these on the central European database.⁷¹⁶ The patchwork nature of the regulatory coverage provided by the medical device Directives suggests that there is a need for more clarity on the ethical issues at stake in the investigatory stages of invasive neurodevices and clearer routes of responsibility, accountability, and transparency.

Continuous reflexive evaluation and post-market vigilance

- 7.52 As we have already observed, the European regulatory system may be praised for its relative speed but this might be a product of its relatively light-touch approach to pre-market approval and its non-centralised operation. These aspects, as we have suggested, can be seen as being to the detriment of transparency and of ensuring that devices are approved for market on the basis of the most suitable evidence. Pre-market oversight is more rigorous for invasive devices. However, the risks and negative impacts of patients’ quality of life resulting from equipment failures are also potentially more serious where invasive devices are concerned (see Box 7.4 below). These factors mean that the imperative for effective and enforceable post-market vigilance arrangements is all the stronger. In recognition of the particular challenges to practically and reliably predicting medium and longer-term equipment failures affecting invasive neurostimulation devices through pre-market clinical investigations, and the seriousness of associated risks, the MHRA has produced guidance to manufacturers specifically in relation to

⁷¹⁴ MHRA (2012) *Guidance for manufacturers on clinical investigations to be carried out in the UK*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007504.pdf>, at paragraph 26.

⁷¹⁵ Article 4 of the Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

⁷¹⁶ *Ibid.*

their responsibilities for post-market vigilance and adverse-incident reporting for this category of devices.⁷¹⁷

Box 7.4: A personal experience of DBS equipment failures

The following example illustrates the kinds of equipment failures that can affect components of devices used for DBS and the serious consequences these will have for the individual patient. It demonstrates why it is so important that effective use is made of regulatory mechanisms to record, disseminate information about, and respond to such incidents.

“The operation I had in July last year was, in my opinion, a success. But at the end of December/beginning of January (2010-1), I suddenly felt that something wasn’t right. It transpired that one of the two cables running from the battery [in my chest] had severed at the connection with the battery. The doctors didn’t know that yet, they just knew that the current wasn’t reaching the stimulators. The old pain was coming back so at the end of March I went in and had one of the cables replaced. They also tested the other cable and it was fine. But about a week later the other cable severed at the other end. I went back into hospital in July so that both cables could be replaced. By this time the manufacturer had replaced the type of cable with a spiral cord to give it more flexibility... At the end of September (2011) I was “recharging” myself and I noticed that the battery was charging itself initially and then it stopped charging. I reported this immediately and they tested it with two other chargers but it wasn’t working. They wanted to operate straight away but I had too much work on at the office. In the interim I would turn it on when I needed to be in public and turn it off when I didn’t to preserve the battery life. When they replaced the battery they found that the transistor had failed. So that was three bits of hardware that had broken... Of course, we all know with hardware that things do go wrong. But it seems rather hard that things should have gone wrong with me and that I underwent three general anaesthetics in less than six months.”

Factfinding meeting with Richard Smith, DBS patient, 20th November 2012.

- 7.53 Device manufacturers who place medical devices on the market in Europe are legally bound to report adverse incidents (meeting certain criteria) to the national competent authority of the country in which the incident occurred.⁷¹⁸ Manufacturers are also expected to establish systems to monitor trends in expected and foreseeable adverse incidents and to report these trends. Incident reporting by clinicians is not mandatory. National competent authorities can take action at any time and are expected to nominate a single coordinating competent authority in cases of transnational incidents. No centralised body exists, as yet, to assist in the execution of these guidelines. While manufacturers are required to report adverse events to the central European database directly, there is little coordinated action or analysis.⁷¹⁹ Only a few EU Member States provide the majority of reports and safety notices.⁷²⁰ Moreover, there is little evidence of coordinated action by Notified Bodies in policing the system.
- 7.54 The system’s decentralised nature may be seen as preventing regulators, clinicians, and patients from gaining the full picture where the safety of invasive medical devices is concerned. However, a number of changes are included in the proposed revisions to the European legislation. If adopted, these will include obligations on manufacturers to report serious adverse incidents directly to a centralised European database and national regulators similarly to record incidents reported by clinicians centrally.⁷²¹ We welcome EC proposals to centralise the collection of this important information. It is to be hoped that that this will be amongst the information held on Eudamed that is made publically available so that this information can form part of a valuable web of networked evidence that improves understanding of the risks of neurodevices and permits regulatory oversight to be proportionate to the imperative to protect the safety of patients using invasive neurodevices.

⁷¹⁷ Reportable incidents are deterioration or malfunctions that have led or might lead to a serious deterioration in health and include tissue damage and electrical failures in pulse generation; MHRA (2009) *Guidance on the vigilance system for CE-marked medical devices: neurostimulators*, available at: <http://www.mhra.gov.uk/home/groups/dts-bs/documents/publication/con065418.pdf>.

⁷¹⁸ MHRA (2008) *Directives Bulletin no. 3 guidance on the operation of the EU vigilance system in the UK* available at: <http://www.mhra.gov.uk/home/groups/dts-bi/documents/publication/con2033936.pdf>, at page 6.

⁷¹⁹ Kramer DB, Xu S and Kesselheim AS (2012) Regulation of medical devices in the US and European Union *New England Journal of Medicine* **366**(9): 848-55, at page 849.

⁷²⁰ Villarraga ML, Guerin HL and Lam T (2007) Medical device recalls from 2004-2006: a focus on class I recalls *Food & Drug Law Journal* **62**: 581-92.

⁷²¹ Proposal for a regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (26 September 2012).

7.55 Lessons might be learned from the pharmaceutical sector, where considerable improvements have been secured in the harmonisation of approaches throughout Europe, including the capture of data about adverse events and schemes to deal with gaps in knowledge relating to the effects of newer medicines on populations. One example of this is the MHRA's *Black Triangle Scheme*, according to which newer medicines are denoted by an inverted black triangle symbol.⁷²² Through the use of such schemes, the MHRA and the Commission on Human Medicines (CHM) aim to highlight a medicine's status of being newly-licensed and to prompt reporting of suspected adverse drug reactions (ADRs) by patients and health care professionals. Reporting ADRs to medicines occurs through the *Yellow Card Scheme*, whereby it is a legal requirement for industry to relay all reports to the MHRA for robust assessment.⁷²³ While the MHRA does operate a similar system for clinicians, health and social care workers, and patients to report adverse incidents involving medical devices to the regulator, this is not underpinned by a mechanism for alerting users to particular reasons for vigilance, such as the novelty of a device. **We endorse the House of Commons Science and Technology Committee's recommendation that a *Black Triangle Scheme*, similar to that used in the pharmaceutical sector, be introduced (especially when devices have received marketing approval on the basis of equivalence data) to signal to patients and professionals when an invasive medical devices is newly approved and to encourage incident reporting.⁷²⁴ We further recommend to the Medicines and Healthcare products Regulatory Agency that the reporting of adverse incidents involving *all* neurodevices by professionals should be mandatory. Information regarding adverse incidents and incident trend reports should be made publically available.**

The complementary role of the National Institute for Health and Care Excellence (NICE)

7.56 The proposed changes (see Box 7.1) to the European legislation on medical devices system – if adopted – would be an undoubted improvement to the current system, but a number of matters that we have highlighted as concerns here will remain unchanged. While the proposals to make the Eudamed database publically accessible, and to require summaries of safety and performance evidence for high-risk devices to be published, are something of an advance, this falls far short of providing an extensive evidence base across technologies (invasive, non-invasive, low or high risk), such that the fundamental ethical interests in this area can be properly advanced. As we have suggested at paragraphs 7.34 to 7.36, the regulatory system alone is not currently set up to achieve this end.

7.57 In the UK, NICE adds a valuable complementary layer of governance that helps to fill some of the gaps relating to regulatory silence on the efficacy of medical devices and in advancing the body of clinical evidence more widely. As we note in Chapter 5, NICE's Interventional Procedures Programme (IPP) plays an important role in presenting the current state of knowledge regarding how well new procedures work (in the context of known risks).⁷²⁵ 'Interventional procedures' include procedures involving both non-invasive and invasive neurodevices, provided these devices have marketing approval. NICE is in a position to address the current best evidence of how well an intervention works (in a way that the MHRA is not charged with doing), and to provide valuable practical guidance to health care providers on matters such as the provision of additional oversight and informed consent procedures. The NICE IPP also fosters inventiveness by being an important means of introducing innovative procedures into the health service.

⁷²² MHRA (2013) *Black Triangle Scheme – new medicines and vaccines subject to EU-wide additional monitoring*, available at: <http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/BlackTriangleproducts/index.htm>.

⁷²³ MHRA (2013) *Yellow Card: helping to make medicines safer*, available at: <https://yellowcard.mhra.gov.uk/>.

⁷²⁴ The Committee uses different terminology from this report and talks not of "invasive devices" in this context but of "medical implants": House of Commons Science and Technology Committee (2012) *Regulation of medical implants in the EU and UK* available at: <http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/163/163.pdf>, at paragraph 67.

⁷²⁵ NICE (2013) *Interventional procedures*, available at: <http://www.nice.org.uk/guidance/ip/index.jsp>.

- 7.58 NICE’s Medical Technologies Evaluation and Technology Appraisals Programmes could also play a useful role in addressing uncertainty about the comparative value of neurodevices in health care – though none of the novel neurotechnologies we discuss in this report has yet been assessed under these programmes. These programmes provide evidence-based assessments to guide (or make recommendations to) the NHS in its commissioning of efficient and cost-effective technologies. They therefore help to fill gaps in terms of enhancing the understanding of the ‘value’ (in terms cost-effectiveness) of particular technologies.⁷²⁶
- 7.59 As part of these core functions, NICE also plays an important role in building the evidence base regarding the benefits and risks of new technologies and enhancing patients’, practitioners’ and regulators’ understandings of these invasive techniques. The advisory committee responsible for overseeing the development of the *Medical technologies guidance* operates a concept of ‘plausible promise’.⁷²⁷ For promising medical technologies, NICE is able to commission and encourage third parties to seek out an evidence base for interventions that seem worthy of further clinical investigations. Independent assessors are used to oversee the integrity of the findings and all recommendation that feature in its guidance are made available to researchers to ensure that uncertainties in important topics considered by NICE influence the research agenda.⁷²⁸ As we note at paragraph 5.23 above, NICE takes an inclusive view of what counts as valuable evidence: information on negative outcomes or inefficacy and the experiences of both experts and patients are included as important parts of the full picture. It is hoped that the recommendations we make in this report in respect of the development of clinical experience registers, and networks for enhanced information governance and data linkage with respect to medical devices, will further support NICE’s work in delivering valuable guidance.

Neural stem cell therapies

- 7.60 In a discussion of regulatory systems based on proportionate risk assessments, the area of neural stem cell therapies represents that in which the health risks are potentially the highest, and the regulatory intervention likely to be at its most intense. This is also the field where regulators have most experience in that, although the technologies here are novel in *themselves*, the regulatory pathways are *not* – following, in large part, the well-established routes for medicinal products. The overarching questions that arise here from our ethical framework are whether the system strikes the right balance between concerns for safety and delivering an effective and proportionate system (notwithstanding the potentially very serious risks involved), and whether the system can effectively support inventiveness so that both investors and patients can benefit from safe innovations in light of considerations of high-costs and small markets.
- 7.61 Two different regulatory pathways may be distinguished in the development of neural stem cell therapies. These may be characterised broadly as that followed by a standardised product developed for widespread market use and that followed by the development of a product on a patient-by-patient basis. Where a patient is treated with stem cells derived from his or her own body (in what is known as autologous transplantation) these cells could, under certain circumstances, be classified as a medicine and subject to regulatory oversight by the MHRA, rather than simply as human tissue (the use of which would be governed under the Human Tissue Act 2004). Autologous cells will only fall outside the sphere of regulation as an ATMP if they have *not* been subject to extensive manipulation. Manipulation is defined widely and includes, for example, cell expansion. However, if manipulated cells are not intended for wider market availability, but only for the treatment of an individual patient, the MHRA will oversee their manufacture under the ‘hospital exemption’ or ‘Specials’ arrangements (described further

⁷²⁶ ‘Value’ in this context is construed by NICE in one of two possible ways: either that it has been demonstrated by sufficient evidence that a more expensive intervention works better than those already available, or the evidence indicates that it works just as well and releases resources back into the public health system.

⁷²⁷ Campbell B (2012) How to judge the value of innovation *British Medical Journal* **344**:e1457: 1-2.

⁷²⁸ NICE (2012) *Research and development*, available at:
<http://www.nice.org.uk/guidance/GuidanceResearchRecommendations.jsp>.

at paragraphs 7.77 to 7.82 below), which effectively free manufacturers from the central authorisation procedure and the need for clinical trials described in the following section.

Steps of development for market use

- 7.62 This section, expanding on the introduction given at the start of this chapter, outlines the regulatory pathway that must be followed by stem cell therapies seeking market approval. No medicines based on stem cell development have yet received authorisation for distribution on the market in the EU. At a European level, matters are overseen by the EMA. In the UK, the primary role of oversight falls to the MHRA. Both agencies have advised and supported companies in development for many years.
- 7.63 In the UK development for market use is currently exemplified by an ongoing clinical trial of a neural stem cell therapy for disabled stroke patients (see paragraph 2.81).⁷²⁹ This trial is being funded by ReNeuron as part of the Pilot Investigation of Stem Cells in Stroke (PISCES) study and is being conducted at the Institute of Neurological Sciences, Glasgow.⁷³⁰
- 7.64 The Department of Health, the MHRA, the GTAC, and other regulatory bodies have developed the *UK Stem Cell Tool Kit*.⁷³¹ This is a reference tool to indicate the regulatory landscape to those involved with stem cell clinical research and manufacture, and who are aiming to develop clinical applications. The kit is applicable to stem cell therapy in general, not only neural cells. The step-by-step account in Box 7.5 below illustrates the complex and incremental development of the regulatory regime. Its complexity helps to explain some of the features of the innovation pathways of these products that we discussed in Chapter 3, including uncertainties about the duration and outcome of regulatory processes and the very high costs involved (which are many times higher than those most medical device manufacturers would face). It also allows us to understand a key difference between the regulatory requirements faced by a new stem cell therapy and neurodevices – as with medicines, but not medical devices, stem cell therapies *do* have to demonstrate efficacy before market approval. This means that it must be shown that the new intervention does no more harm than – and is at least as effective as – treatments that are already available.

Box 7.5: Regulatory pathway for the development of stem cell therapies in the UK

Donation, procurement and testing of stem cells⁷³²

- The donation, procurement and testing of stem cells that are to be used in a medicinal product is covered by the Tissues and Cells Directive 2004/23/EC, for which the Human Tissue Authority (HTA) is the competent authority in the UK.⁷³³ The research establishment involved requires a licence from the HTA to be able to carry out these activities, covering donation, procurement, testing, and processing activities up until the point where a Master Cell Bank has been established, and there is a reasonable expectation of clinical utility in a medicinal product.
- There are also separate requirements relating to the *type* of stem cell. For example, if human embryonic stem cells (hESC) are to be used to derive the stem cell line, a licence must be sought from the Human Fertilisation and Embryology Authority (HFEA). In the case of genetically modified stem cells, the Health and Safety Executive (HSE) must be notified.

⁷²⁹ Webster A, Haddad C and Waldby C (2011) Experimental heterogeneity and standardisation: stem cell products and the clinical trial process *BioSocieties* **6(4)**: 401-19, at page 402.

⁷³⁰ ReNeuron (2013) *Clinical trials in disabled stroke patients*, available at: <http://www.reneuron.com/the-piscs-clinical-trial-in-disabled-stroke-patients>.

⁷³¹ Department of Health (2013) *UK stem cell tool kit*, available at: <http://www.sc-toolkit.ac.uk/home.cfm>.

⁷³² MHRA (2013) *How we regulate advanced therapy medicinal products*, available at: <http://www.mhra.gov.uk/Howweregulate/Advancedtherapymedicinalproducts/Aboutadvancedtherapymedicinalproducts/index.htm>.

⁷³³ HTA (2007) *EU tissue and cells directives*, available at: <http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/legislation/eutissueandcellsdirectives.cfm>.

Animal and clinical studies⁷³⁴

- No neural stem cell trial would pass directly to humans. Animal models will be used first. Before the stem cells can be tested in animals to establish their safety and efficacy, there must be dialogue with the MHRA on which animal models will be approved. The research must also be approved by the Home Office Animal Licensing Inspectorate. The stem cells must be expanded in culture, and the facilities in which this occurs must be approved by MHRA Good Manufacturing Practice (GMP) Inspectors. For example, the PISCES neural stem cell trial now underway in Glasgow⁷³⁵ is based on pre-clinical data acquired from the rat MCAo (middle cerebral artery occlusion) model, the most widely accepted animal model of ischaemic stroke.⁷³⁶
- Before a clinical trial can begin, approval by the MHRA Clinical Trials Unit is necessary as the trial will involve somatic cell transfer. Further, as the trial involves a cell therapy derived from a stem cell line,⁷³⁷ GTAC must also give a 'favourable opinion' (see paragraph for further discussion of the changing role of GTAC). The NHS Research and Development Office (NHS R&D) must also give its approval. In case of GM cells stem cell, the HSE must be notified of the trial.

Clinical trials in the context of 'novel' technologies

- With regards to clinical trials of novel technologies, the MHRA's Expert Advisory Group (EAG) must be engaged before starting the trial. EAG's remit includes the duty to advise the Commission on Human Medicines on 'first time in man' (FTIM) studies with new compounds acting (directly or indirectly) via the immune system with a novel target or a novel mechanism of action or having a secondary potential effect on the immune system via a mechanism of action which currently is not well characterised".⁷³⁸ All clinical trials involving humans are regulated in the UK under the Clinical Trials Regulations.

Seeking market approval at European level

- As outlined at paragraph 7.11 above, under the ATMP Regulation, a centralised authorisation procedure applies to those ATMPs that are intended to be placed on the European Community market. The MHRA is the 'supervisory authority' for UK manufacturers or importers of those ATMPs that are centrally authorised.

Effective and proportionate oversight

7.65 There are very few regulatory issues reported in the literature regarding development of neural stem cell therapies for market use. This is unsurprising given that there are, to date, very few instances of clinical trials of neural stem cell therapies. The UK-based PISCES study is the world's first fully regulated clinical trial of a neural stem cell therapy for disabled stroke patients.

7.66 As the level of detail given in Box 7.5 illustrates, the regulatory process for developing neurotechnologies involving biological material and establishing a clinical trial is complex, with many agencies and regulatory bodies playing a role. The path from development to therapy is a long and potentially arduous one, which may raise concerns about regulatory burden in terms of delay and regulatory overlap between the functions of many bodies with responsibility for oversight of this process. Complexities in the regulatory pathways governing neural stem cell therapies matter from an *ethical* perspective because delays in undertaking trials mean delays to subsequent stages of clinical research, manufacture and ultimately to therapeutic products reaching the market. Moreover, neural stem cell therapies may offer perhaps the *only* possible option for treating the serious and debilitating effects of brain damage or disease. The

⁷³⁴ UK Stem Cell Tool Kit: Scenarios (2013) *Therapeutic use of dopaminergic neurons purified from chemically-differentiated human embryonic stem cells*, available at: <http://www.sc-toolkit.ac.uk/scenarios/acelltherapyderivedfromahumanembryonicstemcellline.cfm>.

⁷³⁵ ReNeuron (2013) *Clinical trials in disabled stroke patients*, available at: <http://www.reneuron.com/the-piscs-clinical-trial-in-disabled-stroke-patients>.

⁷³⁶ Pollock K, Stroemer P, Patel S *et al.* (2006) A conditionally immortal clonal stem cell line from human cortical neuroepithelium for the treatment of ischemic stroke *Experimental Neurology* **199(1)**: 143-55; Stevanato L, Corteling RL, Stroemer P *et al.* (2009) c-MycERTAM transgene silencing in a genetically modified human neural stem cell line implanted into MCAo rodent brain *BMC Neuroscience* **10(1)**: 86.

⁷³⁷ "A stem cell line is a permanently established culture of unspecialised cells derived from a single parental cell, or group of parental cells, that can (1) proliferate *in vitro* for a prolonged period when given appropriate nutrition and space and (2) be made to differentiate in culture into more specialised types of cells when given appropriate chemical or molecular cues." See: UK Stem Cell Tool Kit: Glossary (2013) *Serious adverse event/serious adverse reaction*, available at: http://www.sc-toolkit.ac.uk/glossary.cfm?cit_id=0&startLetter=S.

⁷³⁸ MHRA (2013) *Clinical trials expert advisory group of the commission on human medicines*, available at: <http://www.mhra.gov.uk/Committees/Medicinesadvisorybodies/CommissiononHumanMedicines/ExpertAdvisoryGroups/ClinicalTrials/index.htm>.

regulatory principles of proportionality, subsidiarity and regulatory orientation are particularly engaged here, given the dense regulatory framework, multiple regulators, and multi-level actions that must be negotiated. Many of these concerns are not unique to *neural* stem cells, but are shared by the wider field of regenerative medicine.

- 7.67 Lengthy and multi-layered regulatory pathways can contribute to economic pressures upon those conducting trials and attempting to bring products to market. Delays in undertaking trials and the preparation of multiple different dossiers of evidence to meet the requirements of different oversight bodies are themselves resource-intensive. The risks associated with this will vary between larger companies and smaller biotech companies. They might, as in the case of Geron (see paragraph 3.44), result in the trials being abandoned and the company deciding to direct its research efforts elsewhere. This not only impacts upon the wider public interest in developing effective therapies, but also potentially causes significant disruption to any existing trial participants. The length of development trajectories in this field may affect investor confidence across the sector, resulting in the ‘valley of death’ phenomenon discussed in Chapter 3 (see paragraphs 3.41 to 3.47). Investors, particularly venture capitalists, may not be attracted to enterprises that still have a long way to go before delivering a marketable product. As a result, smaller companies may not be able to survive delays and uncertainty regarding regulatory approval to progress to clinical trials if they cannot attract funding to bridge the development process from academic laboratory to viable commercial concern.
- 7.68 The perception of regulatory oversight as unduly burdensome is, perhaps inevitably, a matter of perspective. The same requirements that can be framed as costly regulatory hurdles that threaten the existence of small and medium sized enterprises (SMEs) struggling to secure funding to bring useful products to market, can also be seen as unavoidable aspects of ensuring participant and, ultimately, patient safety. For example, in response to the consultation conducted for this report, the Wellcome Trust noted that some in the research community broadly “consider research with neural stem cells to be well regulated in the UK, allowing pioneering work to proceed in a carefully controlled manner.”⁷³⁹
- 7.69 We do not seek here to question the need to proceed with humility and caution in the regulatory oversight of neural stem cell therapies. The justifications for doing so are, of course, that interventions in the brain may carry significant risks to many aspects of patients’ health and well-being if they do not perform as expected. These therapies are highly invasive; biological manipulation potentially presents considerable dangers and in such a new area of innovation, the risk-benefit ratio is still uncertain. However, exercise of the virtue of responsibility through regulatory processes entails that caution is not the only ethical guide to appropriate regulatory orientation where practices need to be kept under review in light of evolving evidence. Furthermore, multiple layers of oversight, although rightly directed at protecting patient safety, could paradoxically risk undermining this very goal. Where no other therapeutic options are available in the UK, this might drive patients to seek treatment in other countries. These could include countries where regulatory oversight is not as robust and treatment practices are less scrupulous (see Box 3.5).

Recent developments in the UK regulatory landscape

- 7.70 A number of changes are taking place in the practical arrangements for the regulation of regenerative medicine (which encompasses neural stem cell therapies) in the UK to reduce regulatory overlap and unnecessary obstacles, and to reduce approval times for ethical review. Measures to improve partnership working between the four regulators with responsibilities in

⁷³⁹ Wellcome Trust, responding to the Working Party’s consultation.

this field are one aspect of this.⁷⁴⁰ These measures include the introduction of joint inspections by the MHRA and HTA of licensed establishments and measures to streamline the information requirements and submission of research applications to the MHRA and GTAC. In addition, in early 2013, the MHRA launched its 'Innovation office' to promote early discussions between the MHRA and organisations involved in developing innovative medicines or medical devices to help the organisations navigate the regulatory process.⁷⁴¹

- 7.71 A further significant development has been the changing oversight and functioning of GTAC. GTAC is the UK national Research Ethics Committee (REC) for clinical trials of gene therapy, ATMPs, and certain other types of research, including those involving stem cell therapies.⁷⁴² GTAC performs an important function in the regulation of clinical investigations of ATMPs, as its members bring particular technical expertise in relevant scientific fields to their determinations. However, its role in the regulatory process had previously been viewed as a possible source of some delay. In the spirit of achieving proportionate governance, the UK Government established the Health Research Authority (HRA) in 2011.⁷⁴³ Since September 2012, GTAC has been one of the RECs within NRES operating within the Health Research Authority (HRA).⁷⁴⁴ The aim is that that these changes will improve the service offered to researchers by providing more timely ethical review by meeting more frequently and operating across a wider geographical area. Indeed, since these changes were introduced in 2012, approval times for ethical review have been significantly reduced, with all studies reviewed within the legal requirement of 90 days. The most recent study was approved in 38 days, (compared with pre-2012 timelines of between 82 and 144 days).⁷⁴⁵ Reviews of applications will now follow NRES Standard Operating Procedures which clearly distinguish the role of the MHRA from that of RECs.
- 7.72 Precisely because neural stem cell therapy is a pioneering field, the current evidence of benefits and risks is limited. Inflexible caution maintained in the face of equivocal evidence may deliver diminishing returns in terms of protecting public health. In view of the need for safe and effective therapies for brain damage there is a need for the regulatory system to support inventiveness so that the evidence can be generated to permit this field of science to move forwards. Proportionate and effective regulation must therefore be flexible enough to accommodate an evolution from protection to promotion. In light of this, **we welcome the recent and ongoing changes to achieve effective collaboration between the regulators responsible for overseeing regenerative medicine in the UK. We would encourage continued dialogue between regulators and researchers, genuine sharing of experiences, and reflexive systems of oversight in order to foster innovation while protecting patient safety.**

Meeting the needs of small patient populations

- 7.73 This final section of this chapter considers an area of the regulatory framework which we have not yet addressed in great detail. That is, oversight of the supply of products to meet the needs of patients that are *not* met by traditional market-driven approaches to innovation. As we have noted in Chapter 3, bringing novel neurotechnologies – particularly neural stem cell therapies – to market may require significant investment. This potentially introduces an economic

⁷⁴⁰ Joint submission from the MHRA, HTA, HFEA and HRA to the House of Lords Select Committee on regenerative medicine: HTA (2013) *HTA responses to consultations*, available at: <http://www.hta.gov.uk/consultations/htaresponsestoconsultations.cfm>.

⁷⁴¹ Joint submission from the MHRA, HFEA, NTA and HRA to the House of Lords Select Committee on regenerative medicine; *Ibid*; MHRA (2013) *Innovation Office*, available at: <http://www.mhra.gov.uk/Howweregulate/Innovation/index.htm>.

⁷⁴² NRES (2013) *Gene therapy and other advanced therapy medicinal products*, available at: <http://www.nres.nhs.uk/applications/approval-requirements/ethical-review-requirements/gene-therapy-and-other-advanced-therapy-medicinal-products/>.

⁷⁴³ Health Research Authority (2013) *Health Research Authority*, available at: <http://www.hra.nhs.uk/>.

⁷⁴⁴ NRES (2013) *New arrangements for the Gene Therapy Advisory Committee (GTAC)*, available at: <http://www.nres.nhs.uk/nres-publications/news/new-arrangements-for-the-gene-therapy-advisory-committee/>.

⁷⁴⁵ Presentation by HRA to MHRA and the London Regenerative Medicine Network (4 April 2013). Health Research Authority (2013) *New GTAC arrangements and experience to-date*, available at: <http://www.hra.nhs.uk/EasysiteWeb/getresource.axd?AssetID=152412&type=Full&servicetype=Attachment>

disincentive to developing products that will find only a small market. There is, therefore, a risk of a gap between what the market (operating without intervention) will supply and the provision of licensed products to meet the therapeutic needs of patients with rare neurological disorders or those that require bespoke therapies. In the UK, there are several regulatory mechanisms in place to facilitate and oversee patients' access to medical devices or to ATMPs that do not have full market authorisation.

Medical devices: exceptional use and custom-made

7.74 Under exceptional circumstances the MHRA has responsibility for authorising the exceptional use of non-CE marked devices on humanitarian grounds; that is, in the interests of single patients. This is provided for under the Medical Devices Regulations 2002,⁷⁴⁶ And applications are typically made on a patient-by-patient basis. The manufacturer has legal responsibility for this, but both the clinician and manufacturer must complete forms that accompany the application (including the identity and medical details of the patient) which is then assessed by the MHRA. The clinician must also declare their opinion that the patient's condition will deteriorate without the use of the device and that the patient has given their explicit consent. The MHRA sets criteria and provides guidance to clinicians and manufacturers for the appropriate use of this exception, the essential criteria being that:

- There are no alternative CE-marked devices available for this treatment; and
- There is evidence that use of the device reduces significantly morbidity and/or mortality, compared with the use of alternative treatments that are available.⁷⁴⁷

7.75 The MHRA also has regulatory oversight of devices designed and built particularly for individual patients. To qualify as 'custom-made', a device must be "manufactured specifically in accordance with a written prescription of a qualified medical practitioner or a professional user" and be intended for the sole use of a particular patient.⁷⁴⁸ Manufacturers of these devices must ensure that their products meet the relevant requirements, including being clearly labelled as fulfilling a restricted purpose, and must register these products with the MHRA. It is unclear to what extent the 'custom-made' route is suitable, or has been used, for the supply of neurodevices.

7.76 These two regulatory mechanisms are not exhaustive of the routes available for individual or small numbers of patients to receive treatment using medical devices. Devices that are manufactured by health care establishments and only used on their own patients are currently exempt from compliance with the medical device regulations.⁷⁴⁹ Clinicians may use licensed devices 'off-label' (although manufacturers may not market devices on the basis of such off-label uses). Provided health care establishments or clinicians do not intend to utilise these as routes to market, the MHRA has no regulatory oversight of medical devices used in these ways. As we have already suggested (see paragraphs 7.49 to 7.51) these regulatory gaps give rise to some concerns about effective oversight. The interests of patients in accessing safe and effective therapies – and indeed the economic interests of manufacturers – are more likely to be best protected if rare neurological conditions can be addressed by devices that are approved for these conditions.

⁷⁴⁶ Regulation 12(5) of The Medical Devices Regulations 2002.

⁷⁴⁷ MHRA (2011) *Application for the exceptional use of non-complying devices*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007502.pdf>.

⁷⁴⁸ MHRA (2006) *Guidance notes for manufacturers of custom made devices*, available at: <http://www.mhra.gov.uk/home/groups/es-era/documents/publication/con007515.pdf>, at page 4.

⁷⁴⁹ MHRA (2010) *In house manufacture*, available at: <http://www.mhra.gov.uk/Howweregulate/Devices/Inhousemanufacture/index.htm>. As we have noted (see Box 7.1) there are EC proposals to end the 'in-house' exemption.

Box 7.6: Does the UK require an orphan devices regime?

The question may be raised as to whether the non-market routes described in this section are sufficient to meet unmet patient need or if more could be done to incentivise device manufacturers to develop devices for serious but rare neurological conditions. The economic challenges of bringing therapeutic products to market were discussed in Chapter 3: these are likely to be most acute where demand is low (in terms of numbers of patients) because conditions are rare. Demand in terms of the severity of unmet needs may, however, be significant.

In the pharmaceutical sector, the US and Europe have legislated to address precisely this problem of so-called ‘orphan’ conditions where, without incentives, it is unlikely that the revenue from marketing a medicinal product would cover the investment in its development. In Europe, these conditions must be classed as life-threatening or chronically debilitating and affect no more than five in 10,000.⁷⁵⁰ Incentives include assistance from the EMA in developing protocols, streamlined market authorisation, and ten years market exclusivity. The US also operates a Humanitarian Device Exemption (HDE) for devices addressing conditions affecting fewer than 4,000 people in the US per year.⁷⁵¹ The HDE offers the incentive of removing from the pre-market approval process the requirement to provide evidence of the device’s effectiveness for the intended purpose (although evidence of safety is a requirement).

This might suggest that both patients and manufacturers would benefit from the introduction of an orphan devices regime in the UK. However, this underestimates the significant differences between the regulatory requirements for marketing medical devices under European law and those for medicinal products in Europe, or medical devices in the US. As we have seen, in contrast to the latter two systems, pre-market regulation of devices in Europe is relatively ‘light touch’ – for example, there are no requirements for manufacturers to demonstrate efficacy. Furthermore, the MHRA *already* provides advice and support to device manufacturers, and the structure of the regulatory system does not permit market exclusivity provisions. It is difficult, therefore, to see how further incentives could be provided to manufacturers while exercising the virtue of responsibility. Moreover, the barriers to producing devices for small markets are much lower than for medicinal products, as research and development costs for devices are comparatively small and the life cycles of devices tends to be much shorter than those of drugs.

It should also not be overlooked that in the US, the HDE has been subject to criticism. One group of commentators has expressed concern that this simpler, cheaper, and faster approval process – such as that used to approve DBS for the suppression of symptoms of severe OCD – means that devices are not subject to sufficiently rigorous clinical investigation, potentially risking patient safety.⁷⁵² Further concerns arise regarding the potential commercial motivations for manufacturers to pursue the HDE, and that “the humanitarian device exemption is being used to give the device manufacturer access to patients, rather than giving researchers access to subjects, or patients access to sound scientific evidence.”⁷⁵³ Any hypothetical reductions to the (already light) pre-market evidence requirements under European regulations could be vulnerable to a similar criticism that commercial interests have obscured patient interests.

The challenge to device manufacturers operating in the UK, who seek to make economic returns on devices, is more likely to stem from their securing market share when there might be competition from innumerable licensed devices fulfilling similar purposes and where there are only a small number of potential patients. Such challenges will not be solved by regulatory incentives. Instead, the opportunities for manufacturers are likely to come from exercising inventive routes to identify the kinds of devices that would best address unmet therapeutic needs and, working with NICE and the NHS National Institute for Health Research (NIHR), to provide the kinds of evidence of efficacy that would encourage uptake by health care providers. For example, the NIHR Healthcare Technology Co-operatives (HTCs) aim to encourage collaborations between industry, patients, charities, and academic researchers to develop new medical devices and technology-dependent interventions to address areas of serious illness and unmet need for NHS patients.⁷⁵⁴

ATMPs: the hospital exemption and ‘Specials’

7.77 The development of stem cell therapy for a particular patient is possible under the so-called ‘hospital exemption scheme’ which applies to all ATMPs, and which is provided for under the ATMP Regulation and Directive 2001/83/EC. The UK legislation regarding this – an d implementing the ATMP Regulation in general – came into force on 19 August 2010. The MHRA has regulatory oversight for the hospital exemption in the UK.

⁷⁵⁰ European Medicines Agency (2010) *Committee for orphan medicinal products: overview*, available at: http://www.emea.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000123.jsp&mid=WC0b01ac0580028e32.

⁷⁵¹ FDA (2010) *Humanitarian device exemption*, available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm>.

⁷⁵² Fins JJ, Mayberg HS, Nuttin B *et al.* (2011) Misuse of the FDA Humanitarian Device Exemption in deep brain stimulation for obsessive-compulsive disorder *Health Affairs* **30**(2): 302-11, at page 305.

⁷⁵³ *Ibid.*, at page 306.

⁷⁵⁴ NIHR (2008) *Healthcare technology co-operatives*, available at: <http://www.nihr.ac.uk/infrastructure/Pages/HTCs.aspx>.

- 7.78 The hospital exemption was included in the ATMP Regulation in recognition of the fact that some non-routine development, preparation and use of ATMPs occur as a continuation of, or as part of, treatment at hospital level in accordance with a medical prescription for an individual patient. The exemption also aims to incentivise development of treatments for ‘orphan’ conditions: those for which the potential patient population is too small for the operation of the market alone to deliver the necessary treatment. The exemption applies to manufacturers and their supply of medicinal products to clinicians, and it frees non-routine products from the central European authorisation procedure. However, the *manufacture* of ATMPs under this exemption is still subject to authorisation by the MHRA. ATMPs manufactured under the hospital exemption must comply with the principles of Good Manufacturing Practice (GMP).⁷⁵⁵ When a licence is being sought by the manufacturer from the MHRA, the MHRA will consider whether a plan to mitigate risks is necessary.
- 7.79 Various conditions apply under the hospital exemption,⁷⁵⁶ particularly that the ATMP must be prepared and used in the same Member State and cannot be used to circumvent core features of regulation and enter a wider market. Other conditions are that:
- the ATMP must be commissioned by a medical practitioner;
 - the ATMP must be custom-made to meet an individual prescription;
 - the ATMP must have been prepared on a ‘non-routine basis’;⁷⁵⁷ and
 - the ATMP must be used in a hospital.
- 7.80 Guidance from the MHRA on the application of the hospital exemption stipulates that standards for traceability, quality, and pharmacovigilance must be equivalent to those for a centralised market authorisation. With regards to reporting, manufacturers operating under the hospital exemption are required to record any adverse reactions and notify ‘serious adverse reactions’ to the MHRA. The manufacturer is also required to provide an annual report to the MHRA concerning activities carried out under the hospital exemption.⁷⁵⁸ However, it is unclear how rigorously the guidance on incident reporting is enforced.
- 7.81 In addition to hospital exemptions, Member States may set up their own arrangements to allow individual patients access to non-licensed medicinal products on a named-patient basis. This process is called ‘Specials’ in the UK and it is currently embodied in the 2012 Regulations.⁷⁵⁹ This is to be contrasted with off-label prescribing which involves products that *do* have a licence but the use is *not* one for which this was originally granted. It has been deployed to allow cell and gene therapy in individual circumstances.⁷⁶⁰
- 7.82 It is not clear to what extent the hospital exemption or the Specials arrangements have been used in the UK to govern the manufacture of products to be used in neural stem cell therapies.

Ethical issues raised by exceptional and non-routine provision

- 7.83 The regulatory measures permitting access to novel neurotechnologies under the regulatory routes outlined above are sound in their motivation as they provide routes for unmet therapeutic

⁷⁵⁵ MHRA (2010) *Guidance on the UK’s arrangements under the hospital exemption scheme*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf>, pp. 4-5.

⁷⁵⁶ *Ibid.*, at page 2.

⁷⁵⁷ ‘Non-routine’ means that the product is not being produced for a mass market. The MHRA takes the position that it is not possible to provide a simple numerical formula to distinguish routine from non-routine, instead this is determined by the scale and frequency of the production of the product.

⁷⁵⁸ MHRA (2010) *Guidance on the UK’s arrangements under the hospital exemption scheme*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf>, pp. 5-6.

⁷⁵⁹ MHRA (2012) *Medicines that do not need a licence (exemptions from licensing)*, available at: <http://www.mhra.gov.uk/Howweregulate/Medicines/Doesmyproductneedallicence/Medicineshatdonotneedallicence/index.htm>

⁷⁶⁰ See, for example, King’s College London (2012) *Rayne cell therapy suite*, available at: <http://www.kcl.ac.uk/medicine/research/divisions/cancer/research/sections/haematooncology/celltherapysuite.aspx>.

needs to be addressed even when the market has not delivered the necessary product. Regulators are alert to protecting these targeted arrangements from abuse by manufacturers or researchers seeking a more rapid route to the wider market – which has been raised as a concern with respect to the US HDE. For example, sanctions and penalties are applicable if the individual or organisation places an ATMP manufactured for non-routine use on the market without market authorisation.⁷⁶¹

- 7.84 There is, however, a dearth of evidence about the operation of the hospital exemption and Specials arrangements, and how far these assist in the development of therapies for rare conditions. The European industry group, the Alliance of Advanced Therapies, has welcomed the aims of the hospital exemption to encourage innovation to address the needs of small patient groups, but expressed the view that it is implemented inconsistently in Member States and may, in fact, “impede the development of new safe and effective treatments”.⁷⁶²
- 7.85 Questions may also be raised about whether provision of therapies via these routes is sufficiently well grounded in the regulatory or professional systems that support them. The regulatory oversight of the MHRA extends to the *manufacture* of ATMPs for non-routine use, but not to their uses in treatment. Anecdotal reports from practitioners working in the field of neurostimulation also reflect concerns that there is very little regulatory oversight with regards to patient-by-patient development of interventions.⁷⁶³ This raises important questions about gaps in the oversight and control of the use (in what might be seen as experimental contexts) of products approved in this way. These gaps are, of course, not unique to neurodevices or neural stem cell therapies, but are brought into sharp focus by the observations we have made in our ethical framework about the special status of the brain and continued uncertainty about the benefits and unintended effects of some novel neurotechnologies. In the absence of regulatory prescription, there is a greater onus upon those responsible for care in clinical settings to protect the safety and well-being of patients. This confronts the kinds of ethical challenges we considered in Chapter 5, including the difficulties of obtaining informed consent under conditions of uncertainty and constrained choices, and of assessing whether a treatment genuinely offers a patient their only ‘current best hope’.
- 7.86 It may be questioned whether there is currently sufficient guidance for actors to navigate relevant ethical matters in the context of more experimental uses of neurotechnologies with single patients. For example, the MHRA guidance states that, with regards to ethical issues presented by non-routine uses of ATMPs in clinical practice, there is no need to seek a favourable opinion from a REC if the ATMP is administered as part of treatment (provided it does not involve xenotransplantation and is not administered in the context of research).⁷⁶⁴ The guidance holds that these ethical matters would be covered by NHS trusts’ clinical governance arrangements. This implies that a clear line can be drawn between treatment, experimentation, and research. As we have noted at several points in this report, this does not reflect the reality. The risk is that this leaves a gap whereby experimental interventions are classified as treatment and, perhaps, inappropriately governed. We recall here our recommendation in Chapter 5 (at paragraph 5.60) for the provision of guidance to clinicians pursuing experimental treatment using novel neurotechnologies.
- 7.87 Regulatory provisions that permit small numbers of patients to access otherwise unavailable therapies are welcome insofar as they foster inventiveness to meet the needs of patients in rare and difficult circumstances. However, we suggest there is some doubt whether they sufficiently embody the virtue of responsibility by providing effective and proportionate protection of the safety and well-being of patients. The irony is that *precisely* because these regulatory routes will

⁷⁶¹ MHRA (2010) *Guidance on the UK's arrangements under the hospital exemption scheme*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf>, at page 6.

⁷⁶² AFAT (2013) Focus hospital exemption on developing innovative and safe treatments for patients *Regenerative Medicine* **8(2)**: 121-3, at page 121.

⁷⁶³ Factfinding meeting with clinicians, 16 February 2012.

⁷⁶⁴ MHRA (2010) *Guidance on the UK's arrangements under the hospital exemption scheme*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf>, at paragraph 23.

be used in exceptional circumstances, these patients are likely to be amongst the most vulnerable, due to the inevitable lack of evidence and practical clinical or research experience to inform professionals as to how to proceed in unusual or highly individual circumstances. These uncertainties coexist with the possibility that single-patient interventions are used chiefly with the most desperate, for whom all other therapeutic options are not available or have failed. Humility demands that their care and safety must be a principal consideration when the territory is so uncharted; it emphasises further the need for caution and for sharing of clinical experiences.

7.88 The requirement for responsible innovation in this field to proceed upon, generate, and disseminate robust evidence is, therefore, particularly pertinent in this context. However, the problem of the collection and dissemination of valuable evidence of the safety and efficacy of interventions (that we have noted at a number of points in this chapter) is particularly marked in respect of the permitted uses of non-licensed medical devices and ATMPs for non-routine or individual treatment. This is due, in part, to the inherent lack of transparency in the regulatory regimes that precludes the development of a realistic picture of how widely and for what kinds of conditions these regulatory routes are used. The regulatory mechanisms for capturing the outcomes of treatments delivered via these exceptional routes also lack teeth. Although the MHRA requires manufacturers operating under the hospital exemption to report any adverse events, it is unclear how well the guidance on incident reporting is enforced. There is no legal requirement for post-market surveillance or reporting to the MHRA for adverse events arising from the use of bespoke or in-house manufactured devices. These factors join the more general challenge of an absence of mechanisms to capture and share clinical (including patient reported) outcomes of these kinds of single-patient interventions that we have noted in earlier chapters.

7.89 We suggest, therefore, that (in addition to the broad recommendation we made in Chapter 5 for the establishment of registers for evidence of clinical experience), there is a need to capture and make accessible information on *all* instances for which regulatory approval is given for the use of medical devices and ATMPs under regulatory routes. This includes the supply of products for single patients or on exceptional or non-routine bases. **We recommend that the MHRA should record anonymised data on when, and for what purpose(s), approval has been given for the supply of neurodevices under exceptional use or custom made arrangements⁷⁶⁵ and for non-routine supply of ATMPs under the hospital exemption or Specials arrangements. In addition, we recommend that the MHRA establishes mandatory schemes by which manufacturers and clinicians report data on patient outcomes, and adverse events of resultant interventions.** The aim of this will be to enhance understanding the extent to which use is made of these routes, will help to assess the value of these regulatory mechanisms, and support dissemination of valuable evidence of efficacy and risks to promote further learning. Even though regulatory responsibilities for oversight of these exceptional and non-routine supply routes are devolved the Competent Authorities in Member States, it would nonetheless be valuable if data regarding when they are utilised and patient outcomes were also coordinated at a European level: by the EMA (for ATMPs) and through Eudamed (for medical devices). These data should be accessible by both health care providers and the public.

Concluding remarks

7.90 Novel neurotechnologies do not raise truly exceptional regulatory concerns. Nevertheless, we have identified several priority areas for attention. The regulatory regimes that apply to neurodevices are quite distinct from those that apply to neural stem cell therapies. For this reason, and for the most part, the concerns we have identified in this chapter differ, depending on the category of novel neurotechnology.

⁷⁶⁵ This should include in-house usage if EC proposals to bring these within the scope of regulatory compliance requirements are adopted.

- 7.91 In the case of neurodevices, the three most significant features are the fact that medical devices may be marketed without manufacturers being required to provide evidence of efficacy; secondly, the regulatory routes by which devices reach patients militate (albeit unintentionally) against the generation and dissemination of a robust body of evidence about their effects more generally; and thirdly, that the opaque system of Notified Bodies compounds questions about the adequacy of the evidence on which devices are licensed for sale. These factors are of particular concern in light of the ethical imperative, underscored by the virtue of humility, that we should *not* intervene in the brain unnecessarily – even if the known risks of doing so are low.
- 7.92 While the regulation of neurodevices chiefly raises questions about whether there may be gaps in regulatory oversight, the framework that applies to stem cell technologies raises the opposite concern: that in some circumstances, the layers of regulatory oversight may have (until recent changes) been disproportionately burdensome. In the context of effective and proportionate regulation, the virtue of responsibility requires achieving proportionate position that not only protects patients from harm, but also seeks to avoid impeding the development of much-needed therapeutic interventions without good cause. This is a particular threat where innovation in this sector is pursued to such a large degree by SMEs with limited resources. The regulatory landscape that applies to neural stem cells is currently undergoing significant changes and it is too soon for us to comment on the proportionality of any new approaches.
- 7.93 Our recommendations for addressing the evidence requirements in the field of neurodevices are equally constructed with acute awareness of avoiding detrimental regulatory burdens. Blanket requirements to conduct large-scale pre-market RCTs of devices would be disproportionate. Instead, we have recommended that, on as many fronts as possible (including, but not limited to, those mechanisms within the control of regulators) it is essential that data on how well these devices do or do not function are collected – both before and after devices enter the market – and widely shared. These concerns regarding transparency and dissemination of information are not limited to the medical device sector. Where either devices or cell-based therapies are developed to treat single patients, or on exceptional or non-routine bases, we have noted that there is a risk of valuable information about the risks and benefits of novel neurotechnologies being lost in the absence of formal tracing and collection mechanisms.
- 7.94 The value of this information goes beyond helping to underpin decision-making by regulators. The regulatory system is in a position to play an important role in addressing the persistent uncertainty that defines the ethical landscape in the field of novel neurotechnologies. Access to more, and better, evidence will equip professionals to make the most appropriate decisions regarding patients' and participants' care, and to support truly informed decision-making by those undergoing these interventions. However, improved transparency of evidence available to regulators can only fill this gap to a partial extent. Complementary collaborative efforts to improve information governance and data linkage by manufacturers, practitioners and other stakeholders such as NICE are also needed.
- 7.95 This chapter concludes our three part discussion of the governance and oversight of therapeutic neurotechnologies (see also chapters 5 and 6). We turn now to consider the ethical, social and regulatory challenges posed by their application for *non-therapeutic* purposes. As we note in Chapter 8, the actors and rules governing these uses are in many respects quite different from those we have discussed hitherto, although it is instructive to carry with us the understanding of the promises, risks and uncertainties of these technologies that we have developed over the previous chapters.