

# Chapter 5

Patients and participants:  
governing the  
relationships

## Chapter 5 - Patients and participants: governing the relationships

### Chapter 5 - overview

The care of patients and research participants who undergo interventions using novel neurotechnologies presents the most immediate context in which to apply our ethical framework. Care does not only amount to administering safe interventions; it also entails promoting patients' and participants' autonomy and protecting them from psychological and social harms, minimising unrealistic expectations and guarding against privacy infringements.

Uncertainty about the long-term and unintended effects of intervening in the brain using novel neurotechnologies, a lack of alternative treatments for some neurological disorders, and the fact that many neurotechnologies address conditions that impair patients' decision-making capacities, all present challenges to responsible endeavours to support decision-making and informed consent by patients and participants and those close to them. Professional humility is particularly relevant here. Experimental therapies should not be characterised as offering a patient's 'last best hope' unless this is justified. We recommend that independent counselling, which acknowledges uncertainty, should be an essential part of treatment referral pathways (paragraph 5.9).

The lack of clear evidence of risks and benefits of some interventional techniques also presents challenges to responsible clinical decision-making. The National Institute for Health and Care Excellence's (NICE) Interventional Procedures Guidance (IPG) provides valuable advice to healthcare providers on clinical decision-making and oversight by drawing together the best available evidence. We recommend that compliance with NICE IPG should be mandatory (paragraph 5.24).

NICE guidance and the other oversight mechanisms operating in the NHS will not, however, extend to protecting the interests of patients who use private treatment services. There is a need for professional guidelines that require patients to undergo medical evaluation by a doctor before accessing neurostimulation treatment (paragraph 5.31).

Data concerning brain function and neurological health collected by devices such as those delivering deep brain stimulation (DBS) or using brain-computer interfaces (BCIs) may be sensitive and stigmatising. We suggest that this, combined with the health risks posed by malfunctions in neurodevices, provides grounds for the Medicines and Healthcare products Regulatory Agency (MHRA) to monitor the vulnerability of neurodevices to interference or data interception (paragraph 5.54).

Two important issues arise when considering the responsible protection of research participants' interests. The first is the prospect of sham neurosurgery being used as a placebo control in clinical trials of neural stem cell therapies. We recommend that research ethics guidance should be provided on this (paragraph 5.41). The second relates to the potentially serious impacts on participants from whom beneficial therapeutic or assistive neurodevices may be withdrawn at the end of a study. Where this is likely to be the case we recommend that submissions to research ethics committees must detail the information and support that will be provided to participants as part of consent procedures and at the conclusion of the study (paragraph 5.45).

It is not always possible to draw a neat line distinguishing therapy from research in a field where many novel applications of new technologies take place in the context of experimental treatments. Experimentation may be a necessary and valuable means of exercising inventiveness in this field, but it raises two concerns. First, there is a lack of clarity about whether interventions falling into this grey area should be governed as treatment or research. We recommend that this should be addressed by the provision of professional guidance on responsible conduct in experimental treatment (paragraph 5.60). Second, clinical experience gathered outside formal research studies may not be widely disseminated, thus perpetuating uncertainty. We suggest that publically accessible registers would provide a responsible approach to countering this risk (paragraph 5.63).

## Introduction

- 5.1 When addressing the ethical use of therapeutic applications of novel neurotechnologies, the first line of concern is the care of those individuals who undergo interventions using these. Care does not only amount to administering effective therapeutic interventions; it also entails protecting and promoting the autonomy of these individuals, safeguarding their health and well-being, protecting their privacy and refraining from building unsustainable hope. In this chapter we examine the role played by regulation and governance in shaping practices that protect these interests in the context of the relationships between patients or research participants, and the clinicians and researchers responsible for their care.

- 5.2 Many of these neurotechnologies are still under development, and even the more established technology of deep brain stimulation (DBS) is subject to exploration for new therapeutic applications. In these exploratory stages of a technology's development, there are often grey areas in which it is not possible to make a clear practical or ethical separation between research and treatment – although legal frameworks and professional guidance are sometimes premised on the assumption that this is possible. We return in the final section of this chapter to consider issues raised by this separation. Research participants will frequently be patients, and clinicians will usually be central to research teams. Many of the considerations dealt with here apply across the spectrum of users of neurotechnologies – from participants in clinical trials, through recipients of experimental treatment, to users of more established therapies – and pertain to the professional responsibilities of clinicians and researchers. For these reasons, in this chapter we are concerned with the care of both patients and research participants, and often talk of them together.
- 5.3 The care needs of individuals who use different technologies will be diverse and the exchanges and negotiations in their relationships with professionals will be shaped by the uncertainty inherent to many emerging applications of neurotechnologies. Our ethical framework supplies us with a normative map to guide our understanding and evaluation of professional practices in this area in light of individuals' interests and wider public benefits. This then assists in determining where ethically-informed governance can play a valuable role in engendering or enforcing these practices and outcomes. This allows us to assess where there may be gaps in current legal provisions or professional guidance and to make recommendations where we judge that there might be ethical grounds for different approaches or additional support.

## Decision-making, consent and autonomy

- 5.4 Obtaining consent from prospective patients or research participants for the use of novel neurotechnologies that intervene in the brain is one important aspect, although not the sole means, of respecting their autonomy. In law, consent is required for a clinician or a researcher to have physical contact with a patient or participant if it is not to constitute the common law offence of battery.<sup>475</sup> In health research contexts more widely, consent is an ethical requirement and may be a legal obligation, as in the regulations governing clinical trials in the UK.<sup>476</sup> In much professional guidance, such as that issued by the General Medical Council (GMC), the requirement is for 'valid consent', meaning that which meets all three criteria of being sufficiently informed, voluntary, and given by an individual with decision-making capacity.<sup>477</sup> Failure to obtain valid consent, especially in respect of ensuring the individual is sufficiently informed, may be grounds for a finding of negligence in law.<sup>478</sup>
- 5.5 As we observed in constructing our ethical framework, there are (to varying degrees) a number of impediments to meeting the criteria for valid consent in respect of current applications of novel neurotechnologies in treatment and health-related research. These arise chiefly from continued uncertainty – perhaps further clouded by hype in the popular media – about the efficacy and risks of some of these technologies, and the desperation and hope experienced by some patients (and those close to them) with neurological or mental health conditions that have proved resistant to other forms of treatment.<sup>479</sup> These factors present challenges to professionals' responsible efforts to ensure that, as far as possible, patients and participants have a sufficiently full and realistic understanding of proposed interventions and that they are

<sup>475</sup> See, for example, *Chatterton v Gerson* [1981] QB 432 and *Appleton v Garrett* [1995] 34 BMLR 23.

<sup>476</sup> Medicines for Human Use (Clinical Trials) Regulations 2004.

<sup>477</sup> General Medical Council (2010) *Good practice in research and consent to research*, available at: [http://www.gmc-uk.org/Research\\_guidance\\_FINAL.pdf\\_31379258.pdf](http://www.gmc-uk.org/Research_guidance_FINAL.pdf_31379258.pdf), at page 8.

<sup>478</sup> See, for example, *Chester v Afshar* [2004] UKHL 41, [2005] 1 AC 134.

<sup>479</sup> Bell E, Mathieu G and Racine E (2009) Preparing the ethical future of deep brain stimulation *Surgical Neurology* **72(6)**: 577-86, at page 580.

making choices free from external pressures, even where these pressures are well-meaning. In some instances, it might not be possible to achieve valid consent to the satisfaction of ethically or legally required standards. Securing valid consent cannot, however, mean eliminating all influences of desperation or hope. If the conditions of capacity, sufficient information, and absence of constraint can be achieved, professionals may have to exercise humility by stepping back from making paternalistic judgements about whether patients' or participants' choices are the 'right' ones. A further challenge to achieving consent that is especially marked (although not unique) in this field arises from the close link between many neurological disorders and impaired decision-making and decision-communicating capacities (we return to this issue in paragraphs 5.11 to 5.14).

- 5.6 Underlying these dilemmas is the practical question of whether a paradigm of decision-making and consent based upon a one-to-one clinician-patient or researcher-participant relationship and a single moment of consent is sufficient to protect the latter parties' wider interests in determining what happens to them and how they live their lives.<sup>480</sup> Despite an evolution over recent decades that has seen the kind of information provision required in the UK under common law evolve from what doctors would typically tell to what a reasonable patient would want to know,<sup>481</sup> consent to treatment is still largely equated with the moment when patients assent to a course of action proposed by their doctor. Similarly, the legal framework governing conduct in clinical research establishes a regulatory requirement for a signed consent form, thus focusing on professionals' responsibilities for the steps preceding its signing.<sup>482</sup> There are undoubtedly care teams that operate best practice procedures and engage patients in detailed discussions both before and after interventions, nevertheless, these legal frameworks reflect, and perhaps even perpetuate, models of practice that place chief emphasis upon securing and recording a *particular moment* of agreement.<sup>483</sup>
- 5.7 A 'one-off and one-to-one' model of consent as underscored by legal obligations may be unsuitable in contexts characterised by uncertainty, desperation and hype. This is perhaps particularly so where decision-making pertains to invasive novel neurotechnologies involving commitments to long-term interventions; where interventions may be accompanied by deeply personal unintended impacts upon identity, behaviour, and personal relationships (such as some patients experience with DBS);<sup>484</sup> or where interventions are experimental and of uncertain benefits (such as in the use of assistive brain-computer interfaces (BCIs)). The value of permitting prospective patients sufficient opportunity to explore in depth the possible implications of undergoing treatment with an invasive neurotechnology is underlined by the following perspective from one individual interviewed as part of the preparation of this report:

"When they [the clinicians] mention what the [DBS] operation involves it's very hard to understand exactly what it means, even though I would usually consider myself capable in this respect. I had asked all the questions that you would expect to ask

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<sup>480</sup> Cambridge University Press (2001) *Autonomy and trust in bioethics*, available at: <http://catdir.loc.gov/catdir/samples/cam033/2002073521.pdf>, pp.18-9; Manson NC and O'Neill O (2007) *Rethinking informed consent in bioethics* (Cambridge: Cambridge University Press).

<sup>481</sup> *Pearce v United Bristol Healthcare NHS Trust* (1999) 48 BMLR 118.

<sup>482</sup> Part 1 to Schedule 1(3) of the Medicines for Human Use (Clinical Trials) Regulations 2004. Although these regulations are not legally binding in research that is not a clinical trial, as a matter of policy they provide the benchmark for best practice in the ethical conduct of health research in the UK. See: NHS Health Research Authority (2012) *Standard operating procedures*, available at: <http://www.nres.nhs.uk/nres-publications/publications/standard-operating-procedures/>, v5.1, at page 14.

<sup>483</sup> For example, judgments such as that in *Chester v Afshar* [2004] UKHL 41; [2004] 3 W.L.R. 927 highlight that doctors may be found liable for negligence in failing to support patients' autonomy through information provision, but nevertheless make information provision prior to consent the focus of the standard of care on which this negligence is determined. See: Laurie G and Postan E (2012) Rhetoric or reality: what is the legal status of the consent form in health-related research? *Medical Law Review*.

<sup>484</sup> Müller S and Christen M (2011) Deep brain stimulation in Parkinsonian patients: ethical evaluation of cognitive, affective, and behavioral sequelae *AJOB Neuroscience* 2(1): 3-13, at page 5.

relating to the risks and what was involved – but there are only so many questions you can ask.”<sup>485</sup>

- 5.8 Responsible professional practice and humility require clinicians to be open about the limits of current knowledge and the therapeutic benefits that a patient can expect. These virtues also require that clinicians recognise a distinction between those aspects of decisions for which their professional expertise provides the best guide, and where patients and participants would additionally benefit from the advice and support of non-clinical counsellors or from individuals who have undergone similar therapies. These sources of additional support could help in negotiating an uncertain landscape and decisions that may be more personal than clinical in nature. As we noted in Chapter 4, sometimes this may involve making difficult choices to prioritise health gains at the expense of other aspects of quality of life (see paragraph 4.31). The same interviewee we quoted in the previous paragraph also highlighted the potential value of talking to individuals with personal experience of these kinds of treatment:

“One way I felt I could give something back would be to talk to people and relatives before they have the [DBS] operation. Doctors can say what they have to say but it’s a totally different matter to have the operation. When I was in hospital for the first time this year there was a man in the bed next to me with cluster headaches who was waiting to have the operation. He overheard that I had had the operation and wanted to know more about it. I showed him my x-rays and I was able to explain a few things. One of the nurses said that it had made all the difference to the patient, to meet someone who was alive after the operation...”<sup>486</sup>

- 5.9 Given the uncertainty about the long-term unintended effects of some (particularly invasive) neurotechnologies, and the potential personal ramifications of these, prospective patients and those close to them are likely to benefit from counselling, which would complement information provided by clinicians. **We recommend that those responsible for commissioning specialised services for the NHS in each of the UK countries make it a requirement that, where treatments involving invasive neurostimulation (and, in the future, neural stem cell therapies) are provided, patients must be offered the opportunity to receive independent counselling from suitably qualified professionals about the implications of these treatments. Features of this counselling should include:**

- That it is offered as part of the referral pathway before consent is given; this would be in addition to, rather than a replacement for, the provision of clinical information supporting informed consent.
- It should also be distinguished from any parallel provision of therapeutic counselling for patients with mental health disorders.
- The counselling services recommended here would be analogous in delivery and aims to NHS genetic counselling services to the extent that they should: be delivered by a member of an interdisciplinary health care team; be non-directive; provide information suitable to patients’ individual circumstances and treatment options; and provide support to family members and others close to and caring for the patient.<sup>487</sup>
- Decision making is often a collective enterprise involving both patients and those close to them. Extending counselling to those close to the patient will be valuable in meeting these

<sup>485</sup> Factfinding meeting with Richard Smith, DBS patient, 20<sup>th</sup> November 2012.

<sup>486</sup> Factfinding meeting with Richard Smith, DBS patient, 20<sup>th</sup> November 2012.

<sup>487</sup> NHS Choices (2012) *What is genetic counselling and do I need a genetic counsellor?*, available at: <http://www.nhs.uk/chq/Pages/2370.aspx>; EuroGentest (2011) *What is EuroGentest?*, available at: <http://www.eurogentest.org/index.php?id=160>.

individuals' own support needs, and in helping to protect patients from pressures to undertake interventions, even where such pressures are well-intended.<sup>488</sup>

- 5.10 Obtaining legally valid consent for interventions using novel neurotechnologies is a key step in the conduct of ethically robust professional practice, but it is only the first step. It does not obviate the need for professional practices to respect individuals' autonomy throughout a treatment or research relationship, nor the need to safeguard parallel interests in, for example, safety and privacy. Ongoing discussion and information provision, beyond any initial consent process, would allow patients, participants and those close to them to adjust their expectations or reassess their participation in light of emerging understandings of the efficacy and risks of an intervention. This is illustrated, for example, by the significance of permitting users of DBS to be able to self-calibrate the levels of stimulation delivered,<sup>489</sup> or BCI users to control the way their device works,<sup>490</sup> in recognition of the role that these devices may play in users' concepts of their own bodies and their capacity to control their behaviour and express their identities.

## Decision-making and incapacity

- 5.11 Many of the therapeutic or assistive neurotechnologies we consider in this report are intended for use by patients with neurodegenerative disorders or brain injuries that affect their capacity to exercise their own autonomy. In the UK, several different legal regimes permit decisions to be made, and consent given, on the behalf of patients who lack capacity to make or to communicate their own decisions.<sup>491</sup> In this context it crucial to be able to distinguish whether an intervention constitutes research, routine treatment, or the kind of experimental intervention that is seen as an incapacitated individual's 'last best hope' for treatment, as different rights, responsibilities and potential liabilities follow as a result.
- 5.12 In the UK, the Mental Capacity Act 2005 and the Adults with Incapacity (Scotland) Act 2000 permit treatment decisions to be made on behalf of incapacitated adults, provided these are made in their 'best interests'.<sup>492</sup> Best interests are to be assessed by taking account of all considerations affecting the patient's condition, of which medical or carer perspectives are only two components.<sup>493</sup> In deciding what a patient's best interests might be, clinicians must consult those with a lasting power of attorney before treatment is given. Even if no such individual has been appointed, any prior expressed wishes of the patient must be taken into account and those with a legitimate interest in the patient's welfare must be consulted if practically possible.
- 5.13 Adults who lack capacity have the right in law to take part in research, provided stringent safeguards are in place.<sup>494</sup> The relevant legislation prescribes a risk-benefit analysis insofar as the research must be concerned with the treatment of the condition from which the person suffers, the research cannot be carried out on a consenting population, and that there must a potential to benefit the person without disproportionate burden (or, if the only outcome is generalisable knowledge about the condition, then there must be negligible risk and any

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<sup>488</sup> Bell E, Mathieu G and Racine E (2009) Preparing the ethical future of deep brain stimulation *Surgical Neurology* **72(6)**: 577-86, at page 581.

<sup>489</sup> Müller S and Christen M (2011) Deep brain stimulation in Parkinsonian patients: ethical evaluation of cognitive, affective, and behavioral sequelae *AJOB Neuroscience* **2(1)**: 3-13, at page 9.

<sup>490</sup> Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* **4(3)**: 1-22, pp. 14-5.

<sup>491</sup> In England and Wales Section 3 of the Mental Capacity Act 2005 applies and the law in Scotland is set out in Section 1(6) of the Adults with Incapacity (Scotland) Act 2000. In Northern Ireland decision-making about medical treatment is governed by the common law, though the Northern Ireland Assembly is currently considering the introduction of a Mental Capability Bill.

<sup>492</sup> Section 4 of the Mental Capacity Act 2005; Part 5 of the Adults with Incapacity (Scotland) Act 2000. The Scottish legislation does not use the terminology of 'best interests' but rather in terms of 'safeguarding or promoting' health and 'benefit'; the practical consequences of this are unlikely to be significant.

<sup>493</sup> See, for example, *Re A (medical treatment: male sterilisation)* [2000] 1 FLR 549 for a particularly clear articulation of the considerations.

<sup>494</sup> See, for example, sections 30-4 of the Mental Capacity Act 2005 and Section 51 of Adults with Incapacity (Scotland) Act 2000.

intrusion must not be unduly invasive or restrictive).<sup>495</sup> There are obligations to make reasonable attempts to consult family members and carers and any view they express that, in their opinion, the person would not want to be involved, must be respected. It is unlawful to proceed with research outside these parameters. The distinction between research and treatment is, however, not always clear in this context. For example, the Mental Capacity Act 2005 states that "...treatment that [the patient] has been receiving as part of the project [does not have to be] discontinued if [the researcher] has reasonable grounds for believing that there would be a significant risk to [the patient's] health if it were discontinued."<sup>496</sup>

- 5.14 It has been suggested that the only acceptable uses of invasive neurotechnologies are those in which there is a reasonable, evidence-based expectation of considerable benefit to the patient, and that this benefit clearly outweighs any risks.<sup>497</sup> However, as we have observed for some of the neurotechnologies we have considered – for example, the use of invasive BCIs by patients with locked-in-syndrome or in a minimally conscious state – it may be extremely difficult to give a straightforward assessment of benefit, therefore making any robust risk-benefit analysis impossible.<sup>498</sup> Applications of novel neurotechnologies such as these present a serious problem for all parties involved in making decisions on behalf of individuals who lack capacity, as it may not be clear whether and how the best interests test can be met. Where there is dispute about whether an experimental treatment would be in a patient's best interests, this will be referred to the courts where a decision will be made by a judge.<sup>499</sup> This route may be taken in instances of a patient's 'last best hope' – that is, where patients find themselves in desperate circumstances where the likely impacts of the few (or only) remaining options for therapeutic or assistive interventions are themselves unknown or doubtful.

### Experimental therapies and 'last best hope'

- 5.15 In the case of *Simms v Simms and Another*, the parents of two teenagers in advanced stages of variant Creutzfeldt-Jakob disease sought court authority for a 'treatment' that had never been tried in humans (though had shown moderate success in animal models). In this case, the High Court applied the best interests test to allow treatment on the basis that no medical witness would rule out the possibility that some benefit might accrue. It was relevant that there remained no other option but death and there was no significant risk of the intervention further harming the patients. This raises the question of the ethics of last best hope scenarios.<sup>500</sup> While, from a legal perspective, a court is the ultimate arbiter, this is often a pronouncement made retroactively.<sup>501</sup> This is not helpful to those facing decisions at the coalface on a daily basis. There is, nonetheless, a suggestion from this case that the desperate nature of the circumstances changes the ethical considerations and that desperation alone should not be taken as a reason to exclude highly experimental interventions. Perhaps the most important feature from a regulatory perspective is who should be responsible for taking such decisions if the court route is not practicable, and on what basis?<sup>502</sup> In *Simms*, the court relied on a "responsible body of medical opinion"; taking this benchmark from the criterion applied to determine medical negligence.<sup>503</sup> It may, however, be questioned whether such a decision

<sup>495</sup> These are the English and Welsh provisions. The Scottish position is similar but in some sense stricter; for example, the research must be "likely to produce a real and direct benefit" or if only generalisable knowledge can be generated, then there must be "no foreseeable risk, or only minimal foreseeable risk": section 51 of the Adults with Incapacity (Scotland) Act 2000.

<sup>496</sup> Section 33(6) of the Mental Capacity Act 2005.

<sup>497</sup> Haselager P, Vlek R, Hill J and Nijboer F (2009) A note on ethical aspects of BCI *Neural Networks* **22(9)**: 1352-7.

<sup>498</sup> *Ibid*, at page 1354.

<sup>499</sup> See, for example, *Simms v Simms and Another* [2003] 2 WLR 1465.

<sup>500</sup> See also: *An NHS Trust v HM* [2004] Lloyd's Reports Medical 207 and *EP v Trusts A, B and C* [2004] Lloyd's Reports Medical 211.

<sup>501</sup> Although not in the case of *Simms v Simms* since a declarator was sought about whether it would be lawful to proceed.

<sup>502</sup> Price D (2005) Remodelling the regulation of postmodern innovation in medicine *International journal of adaptive control and signal processing* **1(2)**: 122-41.

<sup>503</sup> This is the 'Bolam test', *Bolam v Friern Hospital Management Committee* [1957] 1 WLR 582. See: Laing J (2003) Incompetent patients, experimental treatment and the 'bolam test' *Medical Law Review* **11(2)**: 237-41.

ought to be left to the medical profession alone, given that best interests may be construed differently by different parties and that it seems desirable that input is received from as many quarters as possible.

- 5.16 While the *Simms* case did not concern one of the novel neurotechnologies we discuss in this report, the circumstances of last best hope are exemplified by instances where patients with locked-in syndrome have already lost, or fear losing, the ability to move and are offered experimental invasive BCIs in an effort to restore or preserve their only opportunity for communication.<sup>504</sup> However, not all neurological disorders present such stark choices. The best interests test may be welcomed to the extent that it does not preclude individuals – whose neurological disorders have severely impaired their consciousness, cognitive capacities or motor skills – from partaking in potentially beneficial interventions. Nevertheless, humility warns against applying this test in a short-termist or cavalier way. This is particularly true where the absolutism implied by ‘last best hope’ itself may be questionable. Many conditions for which therapeutic or assistive neurotechnologies are indicated are chronic but not fatal, so it may be inappropriate to talk in terms of *last* best hope. It is also relevant to consider to what ‘best hope’ refers, when we are not in the tragic circumstances of imminent death with which the *Simms* case was concerned. Moreover, exercising responsibility and humility entails recognising that extending hope by offering treatment options of uncertain value (even if these delay death) may itself be contrary to the interests of patients and those close to them. This is particularly important in view of the desperate circumstances in which some patients and their families might find themselves, as illustrated by the Dementia Services Development Centre’s response to the Working Party’s public consultation:

“...we recognize how desperate some of the families and individuals with dementia are, and we can see that they might be tempted to undertake risky or dangerous interventions to escape from the horror of their situation.”<sup>505</sup>

- 5.17 In order to protect and uphold trust by ensuring that risks and benefits are appropriately understood by those with delegated legal responsibility for making care decisions on behalf of incapacitated patients, responsibility and humility require that clinicians draw a distinction between experimental therapies that genuinely represent someone’s last best hope, and those that might better be characterised as the ‘*latest new hope*’, in the absence of other effective interventions. It is no less important that clinicians also avoid the inappropriate presentation of novel, experimental therapies as last best hope in situations where patients are competent to make their own treatment decisions.

## Protection from harm to health and well-being

- 5.18 In Chapter 2, we outlined the potential unintended risks to health associated with therapeutic applications of novel neurotechnologies. These technologies do not share a single profile in terms of potential risks, but rather occupy a broad spectrum from the least invasive, such as electroencephalography-based (EEG) BCIs, to the most, such as DBS, invasive BCIs and neural stem cell therapies, which require neurosurgery, with attendant risks of infection, bleeding and unintentional damage to, or stimulation of, neural tissue and neural functions. Though the risks of these invasive technologies may be considered relatively low compared with other kinds of more drastic neurosurgery (for example, surgery to remove brain tumours), the special status of the brain nevertheless means that protecting against harm arising from treatment and research uses of these technologies is particularly important. Given the role of the brain not only in the healthy functioning of our minds as well as our bodies, this encompasses not only physical impacts but also those affecting behaviour and individuals’ experiences of themselves.

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<sup>504</sup> Haselager P, Vlek R, Hill J and Nijboer F (2009) A note on ethical aspects of BCI *Neural Networks* **22(9)**: 1352-7.

<sup>505</sup> Dementia Services Development Centre, University of Stirling, responding to the Working Party’s consultation.

## Treatment contexts

- 5.19 In treatment relationships, the protection of patients from harm is secured by the fundamental ethical principle of non-maleficence, corresponding to the principle of caution in our ethical framework (see paragraph 4.22), and by the common law of medical negligence. An approach to pursuing novel interventions that exemplifies all three virtues of responsibility, humility and inventiveness is not one that seeks to avoid risks at any cost, but strives for a proportionate balance between potential risks and benefits. Nevertheless, clinicians must proceed with great caution in pursuing experimental therapies where there are evidence gaps regarding their safety and efficacy. The law regarding medical negligence in the UK is founded upon the legal duty of care that doctors owe to their patients. Broadly speaking, treatment is negligent where it departs from the standard of care expected by “a responsible body of medical opinion” (the so-called ‘Bolam test’)<sup>506</sup> and causes the patient a legally recognised form of physical or psychiatric harm. This last element could mean that redress under negligence law might not be available if unwanted behavioural or cognitive effects are not classed as psychiatric harms.
- 5.20 As we have seen in the *Simms* case discussed in the previous section, the Bolam test does not necessarily preclude the pursuit of more experimental therapeutic interventions where there might not yet be an established opinion.<sup>507</sup> This is significant, given the investigative status of many interventions involving novel neurotechnologies. Decisions about whether to pursue experimental therapies will be a matter for clinicians’ professional judgement, although they can also draw on good practice guidance from the GMC,<sup>508</sup> the advice of local ethics committees within their hospital or health authority<sup>509</sup> and *Interventional Procedures Guidance* (IPG) issued by the National Institute for Health and Care Excellence (NICE).<sup>510</sup> There is an irony here that the most experimental interventions are likely to be carried out on some of the most vulnerable patients. This places all the more emphasis on professionals exercising the virtue of responsibility in deciding whether interventions can be justified in terms of being of genuine benefit to the patient.<sup>511</sup> As we discuss in the final section of this chapter, distinguishing when experimental treatment crosses over into what should be more properly regarded as ‘clinical research’ (to which different governance measures apply) may not always be a straightforward matter.

### **NICE Interventional Procedures Programme**

- 5.21 The National Institute for Health and Care Excellence (NICE) is charged, *inter alia*, with reviewing the evidence and approving new interventional procedures for use in the NHS under the *Interventional procedures programme* (IPP).<sup>512</sup> The aim of guidance issued under the IPP is to assess the safety and efficacy of a procedure, whether it works well enough for routine use or whether special arrangements are needed for patient consent, clinical governance and research when it is used in the NHS.<sup>513</sup> This safety dimension makes the IPP’s focus distinct from NICE’s role in evaluating the cost-effectiveness of health technologies, for example under the *Technology appraisals and medical technologies evaluation* programmes. It also means that

<sup>506</sup> *Bolam v Friern Hospital Management Committee* [1957] 1 WLR 582.

<sup>507</sup> *Simms v Simms and Another* [2003] 2 WLR 1465.

<sup>508</sup> GMC (2013) *Good medical practice*, available at: [http://www.gmc-uk.org/guidance/good\\_medical\\_practice.asp](http://www.gmc-uk.org/guidance/good_medical_practice.asp).

<sup>509</sup> For example, Imperial College Healthcare NHS Trust (2012) *Clinical ethics committee*.

<sup>510</sup> For example, NICE (2003) *Deep brain stimulation for Parkinson's disease*, available at: <http://egap.evidence.nhs.uk/deep-brain-stimulation-for-parkinsons-disease-ipg019>.

<sup>511</sup> In December 2012 Lord Saatchi, as a member of the House of Lords, introduced a proposal for a ‘Medical Innovation Bill’ that would aim to codify ‘responsible innovation’ to offer protection to doctors pursuing innovative treatment in the absence of evidence-based treatments: House of Lords (2012) *Medical Innovation Bill*, available at:

<http://www.publications.parliament.uk/pa/bills/lbill/2012-2013/0061/20130061.pdf>.

<sup>512</sup> NICE (2013) *Interventional procedures*, available at: <http://www.nice.org.uk/guidance/ip/index.jsp>.

<sup>513</sup> NICE (2011) *About interventional procedures*, available at:

[http://www.nice.org.uk/aboutnice/whatwedo/aboutinterventionalprocedures/about\\_interventional\\_procedures.jsp](http://www.nice.org.uk/aboutnice/whatwedo/aboutinterventionalprocedures/about_interventional_procedures.jsp).

NICE does not recommend that procedures *must* be used, but instead gives the conditions under which innovative procedures can be introduced safely for patients and clinicians.

- 5.22 Although anyone may notify NICE of a procedure for assessment, it is most often clinicians who do so. The process for gathering evidence to produce an IPG involves specialist advisors, an independent advisory committee and public consultation.<sup>514</sup> Many of the procedures considered will be new, but where these involve medical devices they will only be assessed by NICE where such a device is licensed to be marketed for that purpose in the UK. Several novel neurotechnologies have been considered under the IPP.<sup>515</sup> One example of this is the IPG on DBS for refractory epilepsy, which was considered in January 2012. The guidance states that:

“The evidence on the efficacy of deep brain stimulation (DBS) for refractory epilepsy is limited in both quantity and quality. The evidence on safety shows that there are serious but well-known side effects. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.”<sup>516</sup>

In view of these caveats, the guidance lays out procedures to be followed by clinicians, including: informing clinical governance leads in the NHS trust; patient selection and management by multidisciplinary teams; ensuring that patients and their carers understand the uncertainty about the procedure’s safety and efficacy; and auditing and reviewing clinical outcomes of all patients. The IPG also encourages the pursuit of further research.<sup>517</sup>

- 5.23 The NICE IPP reflects the virtue of responsibility in that it embodies a step-by-step precautionary approach while laying out clearly the duties of practitioners when involving patients in such procedures. Evidence of efficacy and of adverse or negative outcomes (including inefficacy) must be gathered and shared as robustly as possible. The IPP also embodies inventiveness in that it seeks to encourage innovation by welcoming all appropriate forms of evidence as to the efficacy and safety of procedures. While the quality of this evidence is crucial for NICE, its sources are not limited to the results of randomised controlled trials (RCTs). Observational data such as case studies and registers will often form a more appropriate evidence base for identifying features such as device failure or other longer term adverse events that would not arise during the normally limited time period of an RCT. Specialist advisors’ knowledge of the use of procedures in clinical practice is also an important component of the assessment by the NICE IPP, as are patients’ own experiences and views on the relative benefits and risks of the procedure. The resulting guidelines are reviewed as new evidence emerges.

- 5.24 The role of a centralised body such as NICE in considering evidentiary and consent issues, and in providing uniform guidance on how to proceed with appropriate caution, is clearly to be welcomed. However, while the practical application of its guidance is largely down to local level decision-makers such as commissioners and clinicians, it can only go so far in ensuring good patient outcomes. **It is essential that NICE continue to work with stakeholders, including patients, to maximise usefulness of *Interventional procedures guidance (IPG)* and its application in real life settings. At present, compliance with NICE IPG is voluntary. We recommend that compliance with NICE IPG should be made compulsory within the NHS and that the Care Quality Commission (CQC) is assigned the role of inspecting NHS trusts (and boards) to ensure compliance.**

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<sup>514</sup> NICE (2012) *Developing NICE interventional procedures*, available at: [http://www.nice.org.uk/aboutnice/howwework/developingniceinterventionalprocedures/developing\\_nice\\_interventional\\_procedures.jsp](http://www.nice.org.uk/aboutnice/howwework/developingniceinterventionalprocedures/developing_nice_interventional_procedures.jsp).

<sup>515</sup> NICE (2013) *Published interventional procedures*, available at: <http://www.nice.org.uk/guidance/ip/published/index.jsp?p=off>.

<sup>516</sup> NICE (2012) *Deep brain stimulation for refractory epilepsy*, available at: <http://www.nice.org.uk/nicemedia/live/12775/57916/57916.pdf>.

<sup>517</sup> *Ibid.*

5.25 The NICE IPP fulfils an important function by providing a framework for clinicians and commissioners to refer to when using novel neurotechnologies. Even so, IPGs cover procedures in *general* terms; they do not address the efficacy or safety of devices made by particular manufacturers, nor can they reflect the significant differences to patient outcomes that may be made by the techniques of individual clinicians. As we discuss in paragraphs 5.61 to 5.66 and further in Chapter 7, there is a broad need, particularly in respect of neurodevices, to encourage better collection and sharing of information on clinical experiences of using novel neurotechnologies.

**Private provision of treatment services**

5.26 It might be assumed from our discussion thus far that therapeutic uses of novel neurotechnologies will be administered by clinicians or other health care professionals working for the NHS. However, this will not always be the case; treatments may, of course, be provided through private medical care. They might also be offered outside the formal healthcare sector, by private therapists without medical training. Unlike prescription drugs, there are no regulatory restrictions upon who can administer treatment using licensed neurodevices and where these treatments can be sold.<sup>518</sup>

5.27 The NICE IPG on the use of TMS in severe depression advises that, in view of uncertainty about the clinical efficacy of this treatment (at the parameters of delivery that have been studied thus far) TMS for depression should be only performed in *research* to investigate its efficacy using different parameters of neurostimulation.<sup>519</sup> In accordance with this guidance, there appear to be no NHS hospitals which formally offer TMS services for depression in the UK. However, several TMS devices are licensed for this purpose in Europe, and it is possible that treatment is being offered where equipment and expertise are available in research institutes and at the request of private practitioners. There are indications that private businesses are operating to meet a demand for provision of TMS and rTMS<sup>520</sup> to treat depression.<sup>521</sup> As we discuss further in Chapter 8, at least one private company offers TBS services directly to consumers with the suggestion that this “can help” in depression, stroke and migraine.<sup>522</sup> Box 5.1 below provides one example rTMS being offered in a private healthcare setting.

**Box 5.1: The London Psychiatry Centre<sup>523</sup>**

The London Psychiatry Centre website claims that it is only clinic in the UK offering rTMS for depression. The website describes rTMS as “a highly effective and safe intervention to help overcome treatment-resistant Depression” and “safe middle step in cases which do not respond to antidepressants, but before considering ECT”. The information provided by their website notes that there is a “very small” risk of suffering a seizure, but it also includes the potentially obfuscatory claim that “since the only thing entering your body is pure energy, rTMS is free from the many side effects associated with antidepressant medications”.

The treatment plan outlined by the centre offers five sessions of just over half an hour per week and the Centre’s website suggests that an average treatment will last four weeks – the total cost of which is given as six thousand pounds.

<sup>518</sup> The Medicines Act 1968 and Prescription Only Medicines (Human Use) Order 1997 cover the sale, use and production of medicines, including prescribing rights. Neurodevices are not medicines and are not covered by these statutes.

<sup>519</sup> NICE (2007) *Transcranial magnetic stimulation for severe depression* available at: <http://www.nice.org.uk/nicemedia/live/11327/38391/38391.pdf>.

<sup>520</sup> rTMS, refers to a variant of TMS, repetitive transcranial magnetic stimulation.

<sup>521</sup> The London Psychiatry Centre (2011) *rTMS*, available at: <http://www.psychiatrycentre.co.uk/our-services/repetitive-transcranial-magnetic-stimulation-rtms/>; Neuradaptix (2012) *Using TMS to treat depression*, available at: <http://www.neuradaptix.com/>.

<sup>522</sup> Biofeedback & Neurofeedback in York (2012) *Transcranial direct current stimulation*, available at: <http://www.york-biofeedback.co.uk/neurofeedback/tcds.aspx>.

<sup>523</sup> The London Psychiatry Centre (2011) *rTMS*, available at: <http://www.psychiatrycentre.co.uk/our-services/repetitive-transcranial-magnetic-stimulation-rtms/>.

- 5.28 The use of rTMS and TMS in private settings raises clear issues regarding the regulation and protection of patients' interests. In considering what kinds of restrictions should be placed on the private provision of services involving non-invasive neurotechnologies, it is important to attend to the need for proportionate oversight. Whether existing oversight is adequate is likely to depend on what categories of provider are involved. Private doctors are bound by professional ethical norms and principles of common law and those who are licensed by the GMC will also be bound by associated guidance. However, oversight of safe and ethical practice may be less stringent than that entailed by the codes of practice applying to NHS employees. The oversight and accountability of private practice, for example in respect of the long-term follow-up of patients or reporting an adverse event, is unclear. If interventions are administered by, or under the instructions of, a doctor or in a health care setting, the GMC and the CQC could use their powers to sanction fraudulent or unsafe use by the professionals or services that fall within their respective remits.<sup>524</sup> If, for example, a doctor were to use a licensed medical device 'off-label'<sup>525</sup>, the GMC would be concerned to know that this was based on honest beliefs of sound evidence that this was in the 'patient's' best interests and that the patient had been provided with sufficient information to support informed consent. However, where an intervention is non-invasive and considered low risk, the GMC would be unlikely to sanction doctors offering poorly evidenced interventions.<sup>526</sup>
- 5.29 Where services are delivered wholly outside the medical sphere, the restrictions on what service providers can and cannot do becomes even less clear. For example, many of the guarantees that patients can expect within medical settings regarding standards of diagnosis, information provision, and consent procedures cannot be assumed to apply. It is not clear from the website of the private clinic described in Box 5.1 above what category of practitioner will actually *deliver* treatment, what training they have received to carry out these procedures, and what referral route(s) would be accepted. These omissions raise questions about ensuring that this kind of treatment is safe and suitable for individual patients. The website of one UK-based company reflects a responsible approach by stating that patients will only be able to access their services on the referral of a medical professional, that treatment will be discontinued if "there are any adverse experiences or there is no discernible improvement", and that the "referring physician" must confirm that the prospective patient does not have other risk factors.<sup>527</sup>
- 5.30 Where there are no other effective treatments available for severe conditions such as depression, it might be disproportionate to outlaw the private provision of neurostimulation services – especially while providers of more poorly evidenced alternative therapies are permitted to operate. However, harm to *physical* health is not the only category of potential risk that is relevant for the users of such services. For example, fraudulent (or even unknowingly useless) provision of interventions may also exploit vulnerable individuals and irresponsibly sustain hope. As we note above, service providers who are not doctors will not be bound by the same professional duties as clinicians to protect privacy and confidentiality. The potential risks are also not restricted to individual harm. Whilst public awareness and understanding of these technologies is still evolving, poorly performed or poorly explained uses may also undermine trust in therapies that, when delivered under appropriate protocols, could deliver valuable outcomes.
- 5.31 In view of these considerations, we judge that the greatest risk to patients' health and well-being arises from the provision of services by private providers without medical qualifications who operate outside the governance structures of the health service or professional medical ethics.

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<sup>524</sup> CQC (2010) *Essential standards of quality and safety*, available at: [http://www.cqc.org.uk/sites/default/files/media/documents/gac\\_-\\_dec\\_2011\\_update.pdf](http://www.cqc.org.uk/sites/default/files/media/documents/gac_-_dec_2011_update.pdf).

<sup>525</sup> The expression 'off-label' is most commonly used in relation to prescription drugs where it refers to the practice of prescribing drugs for conditions, in categories of patients, or at doses other than those for which it has been licensed. Here it is used to refer to analogous practice in respect of medical devices. The regulations governing medical devices in Europe prohibit manufacturers *marketing* devices for uses other than those for which approval has been obtained, but do not prohibit these 'off-label' uses. For further discussion, see Chapter 7.

<sup>526</sup> Fact-finding meeting with the GMC, 20 September 2012.

<sup>527</sup> Neuradapix (2012) *Using TMS to treat depression*, available at: <http://www.neuradapix.com/>.

We recommend that the relevant professional bodies, including the Association of British Neurologists and the Royal College of Psychiatrists, should work together to issue a set of guidelines to establish a benchmark for responsible professional standards in the delivery of non-invasive neurostimulation treatments. These guidelines should state those categories of neurostimulation treatment that should only be provided by a suitably qualified professional, following clinical evaluation of a patient by a doctor. The aim is to ensure that neurostimulation treatments are provided only where there are appropriate clinical indications and where individual risk factors have been assessed.

### *Direct-to-consumer advertising*

- 5.32 A final issue to consider where neurotechnologies such as TMS are offered by private providers is that of direct-to-consumer (DTC) advertising. The websites referenced in paragraph 5.27 are written in a style that suggests their target market is prospective patients themselves, indicating that DTC marketing of services using neurotechnologies is an emerging area of commerce. This raises the question of what regulation in this arena might look like and who would regulate it. It is noteworthy that none of the EU Directives regulating the entry of medical devices onto the market (which we consider in more detail in Chapter 7) covers advertising. It is also worthwhile observing that companies could offer their treatment services from bases anywhere in the world, and as such their advertising efforts might fall under a different jurisdiction.
- 5.33 The issues raised here are similar to those addressed by the Nuffield Council's 2010 report on *Medical profiling and online medicine*, which considered the regulatory challenges relating to DTC marketing of, amongst other services, body scanning.<sup>528</sup> In that context the Council concluded that harms did not appear sufficiently serious to justify a restriction on sales of these services. Rather, what was required was more *accurate* information for consumers on their utility and value. With regards to a DTC body scan, the Council recommended: i) independent research on the impact and effects on individuals of DTC body imaging performed as a health check; ii) appropriate regulation of services; iii) better provision of information; and iv) good professional medical practice in the public healthcare system.<sup>529</sup> There are clear parallels here with the direct marketing of TBS and TMS services. As far as these non-invasive neurotechnologies are understood, the health risks are not sufficient to seek to prohibit the advertising of private services, but there *is* a need for greater efforts to inform potential customers and professionals alike. The level of action that is most likely to have a beneficial effect is that targeted at the professional or service provider and which emphasises the importance of accessing these services via the appropriate medical referral routes. The virtue of responsibility suggests that, while efforts to develop a better evidence base and to inform users are necessary, it is not clear that efforts to go beyond this in an attempt to control DTC marketing would be effective or practical.

### **Research contexts**

- 5.34 It is a central principle of ethical research practice, as established by international guidelines such as the Declaration of Helsinki, that the well-being of the individual research subject takes precedence over other interests.<sup>530</sup> This does not mean that research involving novel neurotechnologies must be risk-free, but that potential harm to participants must be

<sup>528</sup> Nuffield Council on Bioethics (2010) *Medical profiling and online medicine: the ethics of 'personalised healthcare' in a consumer age*, available at: [http://www.nuffieldbioethics.org/sites/default/files/Medical%20profiling%20and%20online%20medicine%20-%20the%20ethics%20of%20personalised%20healthcare%20in%20a%20consumer%20age%20\(Web%20version%20-%20reduced\).pdf](http://www.nuffieldbioethics.org/sites/default/files/Medical%20profiling%20and%20online%20medicine%20-%20the%20ethics%20of%20personalised%20healthcare%20in%20a%20consumer%20age%20(Web%20version%20-%20reduced).pdf).

<sup>529</sup> Ibid, at page 166.

<sup>530</sup> See, for example, World Medical Association (2008) *WMA declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/>, Principle 6.

proportionate to the benefits and carefully managed.<sup>531</sup> In the UK this principle is reflected in the combination of practice guidance, statutory regulation, and ethical oversight that governs health research involving, or impacting upon the care of, NHS patients. Each of the countries in the UK has published a research governance framework for health and social care (or ‘community care’ in Scotland).<sup>532</sup>

- 5.35 The scientific value of all proposed health research involving or impacting on the care of NHS patients is subject to scrutiny and research proposals are assessed by Research Ethics Committees (RECs).<sup>533</sup> Protection of the health and well-being of participants in clinical trials of medicines is regulated in the UK by the Medicines for Human Use (Clinical Trials) Regulations 2004 under the authority of the responsible licensing body, the Medicines and Healthcare products Regulatory Agency (MHRA). Though most research involving neurodevices will not take place as clinical trials, but rather small studies, the clinical governance requirements of these regulations applies to all research involving patients – although as a matter of policy rather than strict law.<sup>534</sup> Novel neurotechnologies do not present any particular challenges to the application of these governance measures that seek to secure the safety and well-being of research participants, except in one area: the ethical status of sham neurosurgery as placebo in the control arm of clinical trials.

### ***Sham surgery as placebo control***

- 5.36 The purpose of sham surgery is to provide a control arm for double-blinded RCTs of medical interventions involving surgery. These are clinical research trials in which neither the participants nor the investigators are told which of the participants have received the active treatment under investigation or a ‘control’ against which the effects of this will be compared. Sham surgery is used as a control in some trials to exclude the possibility that any observed benefits (or harms) are attributable to the placebo effects of surgery alone.<sup>535</sup> A number of clinical neurosurgical trials for Parkinson’s disease in the US have used this form of placebo control.<sup>536</sup> The research protocol for the control group has commonly been to drill holes in the outer layer of the skull, but not to inject cells into the brain itself.<sup>537</sup>
- 5.37 In the context of this report, the issue of sham neurosurgery arises particularly in the context of RCTs of neural stem cell therapies.<sup>538</sup> The only clinical trial of neural stem cells in the UK to

<sup>531</sup> Department of Health (2005) *Research governance framework for health and social care: second edition*, available at: [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_4108962](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962), at page 8.

<sup>532</sup> Ibid; Scottish Executive Health Department (2006) *Research governance framework for health and community care*, available at: <http://www.cso.scot.nhs.uk/publications/ResGov/Framework/RGFEdTwo.pdf>; Welsh Assembly Government (2012) *Research and governance framework for health and social care in Wales: second edition*, available at: <http://wales.gov.uk/docs/dhss/publications/governance/090929researchen.pdf>; Research & Development Office (2006) *Research and governance framework for health and social care* available at: [http://www.dhsspsni.gov.uk/research\\_governance\\_framework.pdf](http://www.dhsspsni.gov.uk/research_governance_framework.pdf).

<sup>533</sup> Department of Health (2005) *Research governance framework for health and social care: second edition*, available at: [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_4108962](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962), at pages 13 and 41.

<sup>534</sup> Ibid, at page 13; NHS Health Research Authority (2012) *Standard operating procedures*, available at: <http://www.nres.nhs.uk/nres-publications/publications/standard-operating-procedures/>, at page 14.

<sup>535</sup> In the context of surgery, the term ‘placebo’ has slightly different connotations from its use in drug trials. In the latter a placebo will be inactive – for example involving a sugar pill, any effects of which can be assumed to be psychological (though no less significant for this). However, in surgery, the sham procedures are in a sense *real* surgery with associated physiological effects. The control is therefore not strictly against a wholly inactive procedure, but rather one that is active, but which omits the element of the treatment under investigation.

<sup>536</sup> Swift T and Huxtable R (2011) The ethics of sham surgery in Parkinson’s disease: back to the future? *Bioethics*: 1-11.

<sup>537</sup> Ibid, at page 1.

<sup>538</sup> In the case of sham-controlled DBS research, the considerations are somewhat different. Participants are unlikely to be subject to the risks of surgery without the possibility of gaining any therapeutic benefit from receiving the active intervention. There may be a control arm of the research protocol, in which the neurostimulation is sham, but the surgery itself will be real. Barring unforeseen complications, a functioning DBS device will be implanted and a cross-over research protocol will be used so that participants who do not receive stimulation will do so later in the study. Galpern WR, Corrigan-Curay J, Lang AE *et al.* (2012) Sham neurosurgical procedures in clinical trials for neurodegenerative diseases: scientific and ethical considerations *The Lancet Neurology* 11(7): 643-50, at page 644.

date has not involved sham surgery.<sup>539</sup> However, as more trials progress to Phase II, at which efficacy is tested with larger cohorts, the greater the chance that this method of placebo control could be considered.

- 5.38 The Declaration of Helsinki permits placebo controlled trials, provided there is no current proven intervention that may be used as control, or a placebo is needed to assess efficacy.<sup>540</sup> Sham controlled trials of neural stem cells, for example to restore damaged neural tissue in stroke or Parkinson's disease patients, may fulfil these criteria. This methodology nevertheless raises a profound ethical dilemma.<sup>541</sup> On one hand, it could be the most robust method of ascertaining efficacy of invasive interventions for serious conditions. Even though alternative control methods exist, these may fail to distinguish which effects are due to the surgery rather than the active treatment.<sup>542</sup> On the other hand, it has been suggested that sham surgery is "arguably the riskiest and most invasive type of active placebo".<sup>543</sup> As such, its use runs contrary to the Declaration's further provisions that participants' well-being takes precedence over other considerations and that "extreme care" should be taken to ensure that the control group are not be subject to "serious or irreversible harm".<sup>544</sup> This possible harm arises not only from incisions or drilling. Participants in the sham control group may also be subject to brain scans, anaesthesia, immunosuppressant drugs and other interventions associated with surgery and follow-up.<sup>545</sup>
- 5.39 Decisions about whether sham surgery is an ethically defensible part of the development of novel neurotechnologies in the UK will be made by Research Ethics Committees and there is unlikely to be one straightforward answer. The virtue of responsibility – to participants or to the wider public interest in delivering effective therapies – occupies each side of this dilemma. The acceptability of sham surgical controls will therefore be distilled into an assessment of the risks and benefits in any particular study and whether participants can be said to give valid consent for exposure to risks that cannot be eliminated.
- 5.40 Patients may exhibit both altruism and the virtue of inventiveness by participating in RCTs, but it is important to consider whether those with few or no therapeutic options outside the chances offered by participating are truly making a free choice. It has been suggested that the prevalence and tenacity of the therapeutic misconception amongst research participants (that irrespective of what they are told, they will receive beneficial treatment) also threatens informed consent. Similarly, active attempts by surgical teams to conceal the sham nature of control procedures may be viewed as an unethical degree of deception of participants.<sup>546</sup>
- 5.41 Recommendations have been made as to how the risk-benefit ratio of sham surgery may be improved, including permitting it to be used only when a trial has a sufficiently strong scientific

<sup>539</sup> A summary of the protocol for the PISCES trial may be found on the NIH clinical trials database: ClinicalTrials.gov (2013) *Pilot Investigation of Stem Cells in Stroke (PISCES)*, available at: <http://clinicaltrials.gov/ct2/show/NCT01151124?term=stem+cells+and+stroke&rank=6>.

<sup>540</sup> World Medical Association (2008) *WMA declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/>, Principle 32.

<sup>541</sup> For further discussion, see, for example, Macklin R (1999) The ethical problems with sham surgery in clinical research *The New England journal of medicine* **341(13)**: 992-6; Dekkers W and Boer G (2001) Sham neurosurgery in patients with Parkinson's disease: is it morally acceptable? *Journal of Medical Ethics* **27**: 151-6; Galpern WR, Corrigan-Curay J, Lang AE *et al.* (2012) Sham neurosurgical procedures in clinical trials for neurodegenerative diseases: scientific and ethical considerations *The Lancet Neurology* **11(7)**: 643-50.

<sup>542</sup> Galpern WR, Corrigan-Curay J, Lang AE *et al.* (2012) Sham neurosurgical procedures in clinical trials for neurodegenerative diseases: scientific and ethical considerations *The Lancet Neurology* **11(7)**: 643-50, at page 646.

<sup>543</sup> Swift T and Huxtable R (2011) The ethics of sham surgery in Parkinson's disease: back to the future? *Bioethics*: 1-11, at page 8.

<sup>544</sup> World Medical Association (2008) *WMA declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/>, Principles 6 and 32

<sup>545</sup> Swift T and Huxtable R (2011) The ethics of sham surgery in Parkinson's disease: back to the future? *Bioethics*: 1-11, at page 1.

<sup>546</sup> Macklin R (1999) The ethical problems with sham surgery in clinical research *The New England journal of medicine* **341(13)**: 992-6.

rationale; when the sham procedure is the least invasive possible while maintaining uncertainty; where information provision is thorough; and when participants will have opportunities (all being well) to receive active interventions after the trial.<sup>547</sup> It is notable that no professional bodies in the UK have issued guidance on the consideration and weighing of criteria such as these. We suggest that this represents a significant gap and that the production of such guidance ought to be prepared in time to inform the progression of UK clinical trials of neural stem cell therapies to Phase II in which efficacy is assessed. **We recommend that – to support decision-making by clinical investigators, sponsors and Research Ethics Committees – the Health Research Authority (HRA) should develop guidance on the kinds of circumstances in which sham neurosurgery may, or may not, be an appropriate part of clinical investigations, and what post-trial obligations should hold in respect of participants assigned to the sham arm of trials.**

## Managing wider psychological, behavioural and social impacts

5.42 The goals of minimising harm to patients and participants, and providing them with the best advice about the likely impacts of undertaking neurotechnological interventions rely on the presumption that the information necessary to achieve this will be available. One area in which this poses a particular problem is in the assessment of the unintended cognitive, emotional and behavioural consequences of treatment, which could have significant effects on individuals' conception of themselves and relationships with people close to them. These kinds of effects are currently of greatest concern in relation to the use of DBS. As we have noted, these effects are poorly understood and present a complex picture, in part because their incidence varies between patients and also because disease progression and pharmacological therapies can contribute similar effects (see paragraphs 2.53 and 4.31).<sup>548</sup> A further crucial factor is that objective measures of these consequences fail to capture arguably the most important element; not simply whether these effects occur, but whether they are experienced as welcome or unwelcome by patients themselves. The following personal account was received in response to the Working Party's public consultation.

"I have been pulled up by the DBS...My mood has improved from base-line but I think I have a way to go yet, I experience a lot more anxiety (usually over silly little things) now than before. I usually only get about 3 hours sleep a night, my short term memory is bad and I lack concentration which makes reading very difficult... I am not sure whether these were totally pre-existing but I am sure there are ways around them... DBS has given me the most important thing – HOPE."<sup>549</sup>

The view expressed by this respondent, an individual who had received DBS to treat depression, illustrates the multifaceted nature of a patient's own experience of the outcomes and unintended effects of treatment. It has been argued that, where it is possible to obtain them, qualitative patient-reported outcome measures (those that patients rather than clinicians judge to be most significant) provide an essential part of the evidence puzzle.<sup>550</sup> For this reason, we suggest that capturing patient reported outcome measures should be one important aim of the registers of clinical experiences that we recommend at paragraph 5.63.

5.43 Patient and participant selection is a central element of the responsible conduct of treatment and research involving invasive neurotechnologies such as DBS; for example, to ensure that those involved are those best equipped to tolerate surgery and manage their own postoperative

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<sup>547</sup> Galpern WR, Corrigan-Curay J, Lang AE *et al.* (2012) Sham neurosurgical procedures in clinical trials for neurodegenerative diseases: scientific and ethical considerations *The Lancet Neurology* **11**(7): 643-50, at page 646.

<sup>548</sup> Müller S and Christen M (2011) Deep brain stimulation in Parkinsonian patients: ethical evaluation of cognitive, affective, and behavioral sequelae *AJOB Neuroscience* **2**(1): 3-13, at page 6.

<sup>549</sup> An anonymous respondent, responding to the Working Party's consultation.

<sup>550</sup> Mathieu G, Bell E and Racine E (2011) Subjective Outcomes Measurement and Regulatory Oversight for Deep Brain Stimulation in Parkinson's Disease *AJOB Neuroscience* **2**: 16-8.

care. Neuropsychological factors may be particularly important in making such assessments,<sup>551</sup> and considerations such as supportive home environments are also relevant. Securing the psychological well-being of individuals post-intervention will also depend on the efforts of professionals to manage the expectations of patients, participants and those close to them through the kind of counselling to which we refer above (see paragraph 5.9). This requires transparency about the therapeutic limits of the intervention, for example that a neurotechnology offers alleviation of symptoms rather than a cure and also about the possibility (when participating in research) of being assigned to a placebo control group.

- 5.44 One area of particular concern is the ‘non-abandonment’ of patients and research participants following treatment, or at the conclusion of a study.<sup>552</sup> The removal of beneficial therapeutic technologies at the end of research studies could impact significantly on the health and quality of life of participants who may have come to depend on them.<sup>553</sup> This is particularly true where there are no effective alternative therapeutic or assistive options available, as is so often the case with the neurotechnologies that are the subject of this report. This problem may be particularly acute for assistive BCIs which are currently only available in research contexts.

#### Box 5.2: The experience of a family participating in BCI research

The following extracts are from an interview conducted with the parents of a young man, whose official diagnosis is the minimally conscious state although recent evidence from BCI based awareness assessment (along with his family’s own observations over 12 years) would suggest that the young man is more than just minimally conscious and perhaps in a total locked-in state. The young man has been participating in a follow on (post assessment) BCI research programme to determine if he can learn to modulate brain activity to produce a communication channel through BCI. The extracts below highlight the generosity and commitment of individuals who participate in research and that of their families, as well as the difficult circumstances that might arise at the conclusion of the research:

“BCI is our huge hope really... This is our only hope of informed communication with [our son]... So it’s hugely important... and, as such, we would pay towards funding of it if we thought it was going to help.”

“I’ve told [our son] “this is your life’s work now. You have the opportunity to work with [the scientist] to advance this technology which hopefully will be of benefit to you and to a lot of other people as well. This is your work. [The scientist] needs you as much as you need [the scientist].” I just keep saying those kinds of things to him. What effect that has – I don’t know. But hopefully he can take some kind of benefit from it, some worth and some self esteem.”

Fact finding meeting with Eoin, Eddie and Karen O’Mahony, 7 December 2012

- 5.45 The Declaration of Helsinki states that ethical research practice entails offering participants access to treatments identified as beneficial by the study.<sup>554</sup> However, neurodevices such as assistive BCIs present particular challenges to securing continued access. Unlike many pharmaceuticals, neurodevices may require significant support for their continued use. Even if resources for such support were available, the continued use of devices may be precluded by intellectual property rights, or regulatory approval that extends to only to non-research uses.<sup>555</sup> Nevertheless, the virtue of responsibility requires that researchers have in place appropriate arrangements to protect participants’ quality of life at the end of a study. The HRA currently provides framework guidelines for NHS RECs on ethical and practical issues of care after research.<sup>556</sup> These refer to the position of the 2005 Nuffield Council on Bioethics report *The*

<sup>551</sup> Bell E, Mathieu G and Racine E (2009) Preparing the ethical future of deep brain stimulation *Surg Neurol* **72**: 577-86, at page 579.

<sup>552</sup> Fins JJ (2009) Deep brain stimulation, deontology and duty: the moral obligation of non-abandonment at the neural interface *Journal of Neural Engineering* **6**(5): 1-4.

<sup>553</sup> Hildt E (2010) Brain-computer interaction and medical access to the brain: individual, social and ethical implications *Studies in Ethics, Law and Technology* **4**(3): 1-22, at page 10.

<sup>554</sup> World Medical Association (2008) *WMA declaration of Helsinki - ethical principles for medical research involving human subjects*, available at: <http://www.wma.net/en/30publications/10policies/b3/>, Principle 33.

<sup>555</sup> For example, in the UK a device that has been notified to the Medicines and Healthcare products Regulatory Agency for use in a clinical investigation need not have a CE mark, without which it cannot be placed on the market: MHRA (2013) *Clinical trials for medical devices*, available at: <http://www.mhra.gov.uk/Howweregulate/Devices/Clinicaltrials/index.htm>.

<sup>556</sup> HRA (2012) *Care after research*, available at: [http://www.nres.nhs.uk/applications/guidance/guidance-and-good-practice/?1307152\\_entryid62=148568](http://www.nres.nhs.uk/applications/guidance/guidance-and-good-practice/?1307152_entryid62=148568).

*ethics of research related to healthcare in developing countries*, that “researchers should endeavour before the initiation of a trial to secure post-trial access for effective interventions for participants in the trial and that the lack of such arrangements should have to be justified to a research ethics committee.”<sup>557</sup> We reiterate here our position from this earlier report and **recommend that researchers should provide, as part of their submissions to RECs, exit strategies for circumstances in which they are unlikely to be in a position to provide patients with continued use of neurodevices beyond the conclusion of the study.** These strategies should be proportionate to the harm (or loss of benefit) to participants from withdrawal of the device. At minimum, these submissions should include what participants will be told as part of consent procedures about access to treatment beyond the study’s duration, and details of arrangements to offer appropriate counselling and support at the study’s conclusion. **We further recommend that the HRA guidance on care after research includes explicit recognition of the issues raised by the withdrawal of access to assistive technologies.**

## Privacy and data protection

### Protection of personal information

- 5.46 Clinical care teams or researchers have legitimate reasons for accessing or sharing data collected from neurodevices and wider health information about those using novel neurotechnologies in order to deliver good care, or to support health research in the public interest. However, as we observed in our ethical framework, this raises concerns about the collection and handling of such information in order to protect the privacy of the patients and research participants from whom it is obtained (see paragraphs 4.37 to 4.39).
- 5.47 In the UK, there are a number of legal frameworks that, *inter alia*, offer protection to individuals’ personal health information. These include: the common law regarding confidentiality of patient information; the protection of privacy and autonomy under the right to respect for ‘private life’ under Article 8 of the Human Rights Act 1998;<sup>558</sup> and the Data Protection Act 1998 (DPA).<sup>559</sup> These are underpinned by professional guidance from bodies such as the GMC,<sup>560</sup> MRC<sup>561</sup> and, within NHS trust or boards, by the Caldicott Guardians.<sup>562</sup> We do not suggest here that identifiable personal information pertaining to, or obtained from, the use of novel neurotechnologies is exceptional in the context of these legal frameworks which provide sound protection for individuals’ informational privacy – it is, and should be, treated like any other sensitive health-related information. However, there are some aspects relating to their collection and use that warrant attention.
- 5.48 Doctors have a professional duty of confidence, which extends to other professionals in health care environments. Confidentiality and privacy may also be ascribed in law on the basis of an individual’s reasonable expectations, given the nature of the information in question and the circumstances in which it is divulged.<sup>563</sup> Under the DPA 1998, certain principles must be observed with respect to the processing (which includes storage, use and disclosure)<sup>564</sup> of personal data. Personal data are those from which a living person to whom they relate (the ‘data subject’) can be identified either directly, or in combination with “other information which is in

<sup>557</sup> Nuffield Council on Bioethics (2002) *The ethics of research related to healthcare in developing countries*, available at: <http://www.nuffieldbioethics.org/sites/default/files/Ethics%20of%20research%20related%20to%20healthcare%20in%20developing%20countries%20I.pdf>, at paragraph 9.31.

<sup>558</sup> See, for example, *Campbell v Mirror Group Newspapers* [2004] 2AC 457, [2004] 2 All ER 995.

<sup>559</sup> Data Protection Act 1998.

<sup>560</sup> General Medical Council (2009) *Confidentiality*, available at: [http://www.gmc-uk.org/static/documents/content/Confidentiality\\_0910.pdf](http://www.gmc-uk.org/static/documents/content/Confidentiality_0910.pdf).

<sup>561</sup> Medical Research Council (2011) *Data and tissues tool kit*, available at: <http://www.dt-toolkit.ac.uk/home.cfm>.

<sup>562</sup> NHS (2013) *Caldicott guardians*, available at: <http://www.connectingforhealth.nhs.uk/systemsandservices/infogov/caldicott>.

<sup>563</sup> *Campbell v Mirror Group Newspapers* [2004] 2AC 457, [2004] 2 All ER 995 and Mason J and Laurie G (2011) *Law and medical ethics*, 8th Edition (Gosport, Hampshire: Oxford University Press), at page 182 (paragraph 6.22).

<sup>564</sup> Section 1(1) of the Data Protection Act 1998.

possession of, or is likely to come into the possession of, the data controller”.<sup>565</sup> These include restrictions on how these are obtained, the duration and security of their retention, and how they will be used.<sup>566</sup> Health-related personal data are classed as ‘sensitive’ under this legislation, meaning that certain further restrictions to apply its lawful storage and use.<sup>567</sup>

- 5.49 Under the DPA 1998, sensitive personal data may be used lawfully for research purposes, including those beyond any research for which they were originally collected. This use is permitted provided that this does not underpin decisions regarding particular individuals or risk substantial damage or distress to them, and that individuals will not be identifiable from the research outputs.<sup>568</sup> The need to build a robust body of evidence about efficacy and risks of neurotechnologies to address ongoing uncertainty in the field of novel neurotechnologies means that research uses of patient data (including linkage between data sets held by different organisations) are likely to be of particular value. However, vigilance to protect patients’ informational privacy is warranted here as the relatively small numbers of individuals being treated with some categories of novel neurotechnologies at present mean that they may be more readily identifiable, even from anonymised data. This risks exposing individuals to distress or discrimination and also potentially exposes researchers to liability for unlawful data processing.<sup>569</sup> There is a need for particular attention where data are shared internationally (as would be particularly valuable in creating rich multinational registry resources), as the DPA 1998 requires that personal data are not shared outside the European Economic Area unless an adequate level of protection can be ensured in those jurisdictions.<sup>570</sup>
- 5.50 Distinct issues are raised by neurodevices that collect sensitive health information directly from patients. The automated nature of collection, storage or transmission of data by devices presents difficulties for identifying a single definitive point or purpose of ‘data collection’ at which it can be confirmed that the patient has understood and agreed to potential uses. This could pose a challenge to obtaining sufficiently informed and specific consent to processing these data.<sup>571</sup> Although consent is not always required for the lawful processing of sensitive personal data under the DPA 1998, it may nevertheless be the means by which its privacy or confidentiality can be determined.<sup>572</sup> If patients or participants have not clearly understood, or agreed to, particular uses of automatically collected personal data – for example, the extent to which these might be shared within care or research teams – not only could their privacy be undermined, but professionals could be liable for unlawful disclosures. This has particular salience in the context of BCIs where it has been noted that research teams are large and represent diverse professions.<sup>573</sup> Where data collection is automated and clinical care or research teams are large, there is an additional challenge in identifying the data controller, who

<sup>565</sup> Section 1(1) of the Data Protection Act 1998.

<sup>566</sup> Schedule 1 to the Data Protection Act 1998.

<sup>567</sup> Section 2 of the Data Protection Act 1998.

<sup>568</sup> Section 33 of the Data Protection Act 1998.

<sup>569</sup> See, for example, *Common Services Agency v Scottish Information Commissioner* [2008] UKHL 47.

<sup>570</sup> Principle 8, Schedule 1 to the Data Protection Act 1998.

<sup>571</sup> The data subject’s consent is only one of the possible grounds for the lawful processing of sensitive personal data under the Data Protection Act 1998. It is not necessary for the data to be used for ‘medical purposes’, including medical research, when undertaken someone bound a duty of confidentiality equivalent to a health professional (Schedule 3 to the Data Protection Act 1998). Under the terms of the proposed reforms to European data protection law, however, a requirement has been added for consent to be both ‘specific’ and ‘explicit’ (Regulation of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation) 2012/0011 (COD) draft Article 4.8. See further: Recitals 25, 38 and 41 on the requirement that consent be ‘explicit’).

<sup>572</sup> For example, establishing what a patient was told about how their data would be handled, and what they agreed to, could be key to determining whether there has been an unlawful breach of confidentiality, or if their right to respect for private life under Article 8 of the HRA 1998 has been infringed. Broadly speaking, under the common law of confidentiality, it is unlikely to be lawful for clinicians or researchers to share health information about which there is a reasonable expectation of privacy or confidentiality, unless the individual has assented to its wider disclosure or it this is otherwise authorised or justified – for example, by a Court holding that the disclosure is in the public interest, or because there is appropriate ethical and statutory oversight for its use in research.

<sup>573</sup> Haselager P, Vlek R, Hill J and Nijboer F (2009) A note on ethical aspects of BCI *Neural Networks* **22(9)**: 1352-7, at page 1355.

holds responsibility for ensuring the lawful processing of data under the DPA 1998, and ensuring they understand the extent of their legal responsibilities.<sup>574</sup>

- 5.51 In practical terms, a lack of clarity about the potential liabilities of professionals for unauthorised disclosure of information could impact upon the care of patients and participants. The virtues of inventiveness and responsibility both point to the value of sharing health data amongst those responsible for ensuring patients' safety and well-being and in the wider public interest in using these as part of health-related research. Yet if clinical teams or researchers are unsure about what they may lawfully do with patient data, or are deterred from sharing them by fear of legal liability, this may infringe the interests of current and future users of novel neurotechnologies by inhibiting the optimal flow of information and placing unnecessary obstacles in the way of much needed research.

### Securing neurodevices against interference

- 5.52 Personal information might, as suggested in our ethical framework, not only be collected from neurodevices for legitimate reasons, there is a possibility – albeit somewhat speculative at present – that sensitive information may be vulnerable to unauthorised interception through hacking or wireless transmission. This is related to a potential parallel problem of accidental or malicious interference with the functioning of neurodevices. Inventiveness would suggest that one means of preventing these kinds of infringements of privacy would be for manufacturers to respond by designing technical protections (such as user-authorisation checks) into medical devices.<sup>575</sup> However, responsibility also requires weighing up the risks and benefits of technical solutions for users of these technologies. For example, greater encryption of data might enhance information security, but use more power, thus requiring more frequent surgery (with its attendant risks) to replace battery packs.<sup>576</sup> Obligations to improve the protection against unauthorised interference should be proportionate to how critical a device's safe functioning is to patients' well-being.<sup>577</sup> DBS and assistive BCI technologies might not be life-preserving in a literal sense, but their safe functioning could be critical to the quality of life of individuals with debilitating movement disorders or paralysis.
- 5.53 Since it is not yet clear how serious or widespread the potential threats from unauthorised access to devices might be to the private lives of those using them, it is challenging to assess how pressing the need is for regulators to act to address any gaps in protection from potential risk. Expert advice provided to the US Government Accountability Office about the informational security of active implantable medical devices (although not specifically neurodevices) is that the threat is sufficiently plausible and serious that the US Food and Drug Administration (FDA) ought to develop a plan for “enhancing its review and surveillance of medical devices as technology evolves [to] incorporate the multiple aspects of information security”.<sup>578</sup> It was suggested this should include increasing the FDA's focus on manufacturers' role in mitigating security risks and the role of post-market surveillance to identify possible information security problems.
- 5.54 At present, the European Directive which governs the marketing of active implantable medical devices requires that devices must not compromise the safety or health of patients or other users.<sup>579</sup> The safety considerations listed in the Directive include “risks connected with

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<sup>574</sup> Section 1(1) of the Data Protection Act 1998.

<sup>575</sup> Maisel WH and Kohno T (2010) Improving the security and privacy of implantable medical devices *New England Journal of Medicine* **362**(13): 1164-6, at page 1165.

<sup>576</sup> United States Government Accountability Office: Report to Congressional Requesters (2012) *Information security of active medical devices*, available at: <http://www.gao.gov/assets/650/647767.pdf>, at page 21.

<sup>577</sup> Maisel WH and Kohno T (2010) Improving the security and privacy of implantable medical devices *New England Journal of Medicine* **362**(13): 1164-6, at page 1165.

<sup>578</sup> United States Government Accountability Office: Report to Congressional Requesters (2012) *Information security of active medical devices*, available at: <http://www.gao.gov/assets/650/647767.pdf>, at page 35.

<sup>579</sup> Article 2 of the Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of Member States relating to active implantable medical devices (AIMD).

reasonably foreseeable environmental conditions such as magnetic fields, external electrical influences, [and] electrostatic discharge”, which covers some sources of accidental interference, and instructions for use must also include advice about such risks.<sup>580</sup> Particular attention is also required for the proper functioning of the device’s software.<sup>581</sup> The Directive does not, however, address directly the risks of malicious hacking or of unauthorised data interception. **We recommend that the MHRA monitors the vulnerability of neurodevices to accidental, unauthorised or malicious interference, especially where these could impair health, undermine patients’ confidence in their devices, or lead to the interception of sensitive personal data about health or neural activity. Appropriately anonymised records of any such incidents should be made publically accessible.**

## Experimental treatment

- 5.55 Underlying the discussion in this chapter thus far is an assumption that, where the governance frameworks, or professional norms, underlying treatment and research relationships diverge, it will be possible to determine which of these applies in any particular instance. In truth, this may not always be a straightforward matter. Many of the investigational uses of novel neurotechnologies take place as experimental interventions with patients.<sup>582</sup> This, rather than larger or more formal research studies, may often be the more appropriate approach, given the small numbers of individuals eligible to participate in investigations for rare conditions (for example, identification of cognitive activity in patients in minimally conscious states), where there is uncertainty about risks, or where there is limited evidence on which pursue the kind of hypothesis-driven research protocol needed for an RCT. Nevertheless, this raises a question, namely: what is the appropriate dominion in which to regulate investigation occupying this intermediate area of investigation: treatment or research?
- 5.56 It is questionable whether all such exploratory activities occupy the realm of research. Research implies a predetermined protocol, with a clearly defined end-point and which results in generalisable knowledge and understanding.<sup>583</sup> Experimentation, by contrast, is a more *ad hoc*, speculative endeavour, usually calibrated by a particular subject’s responses and not beholden to a rigid protocol.<sup>584</sup> The difference may also be reduced to a question of *intention*. Research in general is not chiefly concerned with the research participant’s own health and is instead about improving the wider scientific knowledge base. Experimental treatment, in contrast, is usually more concerned with the therapeutic benefits to the person upon whom the experiment is being conducted. In its recent judgment in the case of *Walker-Smith v GMC* the High Court confirmed that establishing the clinician’s intention is key to determining whether they have strayed beyond the boundaries of treatment into research.<sup>585</sup> The court further acknowledged that:

“[W]hen a clinician departs in a significant way from standard or accepted practice entirely for the benefit of a particular individual patient, and with consent, the

<sup>580</sup> Annex 1, Part 1 (8-15) of the Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of Member States relating to active implantable medical devices.

<sup>581</sup> Article 16(9) of the Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of Member States relating to active implantable medical devices. For example, claims that a device is compliant with the essential requirements of the Directive must be supported by descriptions of how the software is protected from accidental or unauthorised change.

<sup>582</sup> See, for example, Synofzik M, Fins JJ and Schlaepfer TE (2012) A neuromodulation experience registry for deep brain stimulation studies in psychiatric research: rationale and recommendations for implementation *Brain Stimulation* 5(4): 653-5, at page 653. This is particularly apparent for the medical devices sector: Factfinding meeting with clinicians, 16 February 2012.

<sup>583</sup> Department of Health (2005) *Research governance framework for health and social care: second edition*, available at: [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_4108962](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962), at page 3.

<sup>584</sup> Mason J and Laurie G (2011) *Law and medical ethics*, 8th Edition (Gosport, Hampshire: Oxford University Press), at page 611(19.05).

<sup>585</sup> *Walker-Smith v General Medical Council* [2012] EWHC 503 (Admin), at paragraph 186.

innovation need not constitute research, though it may be described as an experiment in the sense that it is novel and un-validated.”<sup>586</sup>

If highly experimental interventions “need not constitute research”, this exposes a possible regulatory lacuna whereby investigatory procedures are governed under the legal and professional frameworks that set the standards for which appropriate and lawful clinical care – which, in the UK, are chiefly a matter of common law – that are quite distinct from the protocols that apply to research. Clinical trials in the UK are subject to statutory regulation which is increasingly providing the benchmark for all health-related research involving patients.<sup>587</sup>

- 5.57 It might seem unsatisfactory that the question of which regulatory framework applies in particular situation is determined solely by the subjective intention(s) of the clinician. While proposed health research involving or impacting on the care of NHS patients must not only be approved by a REC, but also exposed to peer review,<sup>588</sup> decisions about treatment depend on the judgements and professional norms of clinicians without any prior requirement for external scrutiny. This disparity raises particular concerns where there are potential conflicts of interest that might remain unexposed in a treatment paradigm, but must be declared according to the research ethics standards established by the Clinical Trials Regulations.<sup>589</sup>
- 5.58 Financial interests are not the only possible source of conflicts of interest to which clinicians might be subject. They might equally have intellectual or reputational investment in gathering evidence through pursuing new and experimental applications of neurotechnologies. Therefore while the inventiveness of researchers and clinicians is essential to the development of novel therapies, this needs to be qualified by the virtue of responsibility, lest the pursuit of innovation and knowledge threaten to overshadow clinicians’ obligation first to protect the health and well-being of the patient. Clinicians are likely to be found guilty of serious professional misconduct and struck off if, while purporting to offer *treatment*, their intention is actually to undertake *research*.<sup>590</sup> Corresponding concerns might also arise where investigations of therapeutic or assistive technologies are categorised as research. In particular, these may arise in relation to ambiguities in the extent of the duty of care owed to research participants by researchers – for example regarding their responsibilities to promote participants well-being beyond the scope of the a research protocol (as discussed at paragraph 5.44 to 5.45).
- 5.59 It seems inappropriate that so much should rest on category allocation when the core interests at stake remain the same, particularly from the perspective of the person who is subject to intervention.<sup>591</sup> While so much of the development of the therapeutic applications of novel neurotechnologies takes place in the realm of experimental treatment, our ethical framework suggests that there is a need for clear and specific ethical guidance on how clinicians and investigators should navigate this difficult boundary in a way that is responsible, without stifling inventiveness. The MRC has developed an *Experimental medicine toolkit* for use in small-scale, academic-led studies in humans.<sup>592</sup> This provides valuable sources of advice on the development of protocols, risk assessment and the dissemination of findings. However, as its focus is on academic studies, it may not be seen to apply to, or capture, the full range of

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<sup>586</sup> Ibid, at paragraph 12. This passage from the judgment directly quotes the Royal College of Physicians’ guidance (January 1990) “Research involving patients”.

<sup>587</sup> 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; NHS Health Research Authority (2012) *Standard operating procedures*, available at: <http://www.nres.nhs.uk/nres-publications/publications/standard-operating-procedures/>, v5.1.

<sup>588</sup> Department of Health (2005) *Research governance framework for health and social care: second edition*, available at: [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_4108962](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962), at page 13.

<sup>589</sup> Part 1(1) of Schedule 3 to the Medicines for Human Use (Clinical Trials) Regulations 2004.

<sup>590</sup> GMC (2013) *Good practice in research and Consent to research*, available at: [http://www.gmc-uk.org/static/documents/content/Good\\_practice\\_in\\_research\\_and\\_consent\\_update\\_17\\_4\\_13.pdf](http://www.gmc-uk.org/static/documents/content/Good_practice_in_research_and_consent_update_17_4_13.pdf).

<sup>591</sup> Compare with the observations in Oberman M and Frader J (2003) Dying children and medical research: access to clinical trials as benefit and burden *American Journal of Law and Medicine* 29(2-3): 301-17.

<sup>592</sup> MRC (2012) *Experimental medicine tool kit*, available at: <http://www.em-toolkit.ac.uk/home.cfm>.

experimental interventions conducted with single, or very few, patients in treatment rather than academic contexts.

5.60 **We recommend that the GMC, the HRA and the MRC work together to produce guidance for clinicians pursuing experimental therapies. This would address lacunae between the regulation of research and treatment, with the aim of ensuring that experimental interventions are pursued in a responsible way that protects patients' interests, while supporting inventiveness through the generation of new knowledge in the public interest.** The recommended guidance would adopt the best features of each of the treatment and research governance paradigms, while seeking to eliminate the worst. What this might mean in practice is that:

- the primacy of patient interests is imported from the treatment paradigm, entailing a duty of care that persists beyond the period of experimentation.
- Unlike clinical trials, experimental treatments taking place in this middle-ground cannot be expected to meet the requirements for large numbers of participants, control groups, or double blinding of participants and investigators.
- They can, however, be expected to be grounded in an evidence base that is appropriate to the (necessarily) exploratory context.
- The pursuit of an intervention solely because it putatively represents a patient's 'last best hope' is likely to be too cavalier to justify an experimental intervention.
- A responsible approach imported from the clinical research paradigm would, therefore, recommend adopting clear investigatory protocols, including means of assessing efficacy and risk, as well as methods of recording and sharing findings.
- Humility recommends independent ethical oversight of these protocols and practices.

We suggest that this guidance might usefully build on the MRC's *Experimental medicine toolkit*.

## Registers of clinical experiences

5.61 A further implication of many investigatory applications of novel neurotechnologies taking place in treatment settings rather than as part of formal research is that clinical experience of the efficacy and risks of these technologies, and the benefits and adverse events associated with their use, is lost. There is an absence of mechanisms to capture and share the outcomes of single-patient interventions or small observational or pilot studies. As we explore further in Chapter 7, the regulatory systems operating in the UK are ill-equipped to capture information on (or simply do not require reporting of) the kinds of experimental or single-patient uses of medical devices and stem cell therapies with which we are concerned here, or their outcomes. The outcomes from these kinds of interventions, particularly negative or non-positive findings, are also less likely to be published in peer reviewed journals.<sup>593</sup> The risk is that, if clinical experiences are shared only in *ad hoc* ways through, for example, journals or professional networks such as conferences, the reach of this information will remain narrow and elite. There is an addition risk that outcomes could be misleading or meaningless when taken out of context.

5.62 This report recognises that uncertainty about the efficacy, unintended effects and mechanisms of action of many of the novel neurotechnologies discussed here is a key ethical issue. There is a need for greater transparency and accessibility of evidence to ensure the safety and well-

<sup>593</sup> Schlaepfer TE and Fins JJ (2010) Deep brain stimulation and the neuroethics of responsible publishing *The Journal of the American Medical Association* **303**(8): 775-6, at page 775.

being of patients and research participants, and to also make the best use of existing knowledge to underpin robust research practices and support innovation. The exercise of all three virtues, responsibility, humility, and inventiveness, requires that the professions conducting experimental and investigational treatments adopt new means for capturing and sharing their own clinical experiences. There are a number of calls in the academic literature for registers to be established to capture this kind of evidence – particularly where it is generated outside of formal clinical trials.<sup>594</sup> Many of these focus upon DBS, but we suggest that the value of registers would extend to the other categories of neurotechnologies we discuss in this report.

5.63 Therefore, **we recommend that professional bodies, such as the Association of British Neurologists and the Society of British Neurological Surgeons and the Royal College of Psychiatrists, work with each other and with relevant patient groups and charities to establish registers (where these do not already exist), or to improve the quality, accessibility and profile of those which already exist. These registers would gather data on clinical experiences of treatments using novel neurotechnologies, record the outcomes of these interventions, and make these publically available.**

5.64 As these registers would potentially encompass a range of different technologies and clinical uses, it is not possible to be prescriptive about their exact form or scope. However, we suggest that essential features would include:

- independent oversight to ensure the impartiality of registered data;
- robust mechanisms for protecting patient confidentiality;
- academic involvement to ensure the quality of data;
- dedicated curatorship, to ensure that the data collected is of a kind that is useful and informative to the intended users of the register, and collected and presented in ways that facilitates comparisons and meta-analyses of aggregate data;
- recording negative or inconclusive findings as well as positive treatment outcomes;<sup>595</sup> and
- capturing patient-reported outcomes as part of building a comprehensive picture of benefits and risks that includes subjective experiences (see paragraph 5.42 above).<sup>596</sup>

5.65 We anticipate that registers of this kind will not only be useful to clinicians and researchers seeking to give the best advice to their patients or participants and to avoid pursuing futile or disproportionately risky interventions (and thus unnecessary interventions to individuals' brains), but will also be valuable to patients (or their family and carers) in making treatment decisions and thus also to those delivering counselling services we recommended at paragraph 5.9. Other users of these registers might include NICE, regulators and ethical review committees, each of whom have an interest in providing effective oversight, proportionate to the best current understanding of risks and benefits. This wide range of potential users should inform decisions regarding the information collected and the presentation of outputs. In accordance with recent recommendations by the Royal Society for the pursuit of open science, the aspiration should be for these registers to provide outputs that, wherever possible, are “accessible, intelligible, assessable and usable” to a non-specialist public audience, with patients' needs particularly in

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<sup>594</sup> Mathieu G, Bell E and Racine E (2011) Subjective outcomes measurement and regulatory oversight for deep brain stimulation in Parkinson's disease *AJOB Neuroscience* **2(1)**: 16-8; Schermer M (2011) Ethical issues in deep brain stimulation *Frontiers in Integrative Neuroscience* **5(17)**: 1-5; Synofzik M, Fins JJ and Schlaepfer TE (2012) A neuromodulation experience registry for deep brain stimulation studies in psychiatric research: rationale and recommendations for implementation *Brain Stimulation* **5(4)**: 653-5.

<sup>595</sup> Synofzik M, Fins JJ and Schlaepfer TE (2012) A neuromodulation experience registry for deep brain stimulation studies in psychiatric research: rationale and recommendations for implementation *Brain Stimulation* **5(4)**: 653-5.

<sup>596</sup> Mathieu G, Bell E and Racine E (2011) Subjective outcomes measurement and regulatory oversight for deep brain stimulation in Parkinson's disease *AJOB Neuroscience* **2(1)**: 16-8.

mind.<sup>597</sup> These might initially cover data collected in the UK, but an aspiration to create connections with international registers would be valuable.

- 5.66 We recognise that the establishment and maintenance of data repositories of this kind are resource-intensive and that adequate resourcing is essential to their utility and longevity.<sup>598</sup> In view of the potential breadth of their utility in research, innovation, regulation, and health care delivery, costs might appropriately be met by a number of organisations including the research councils or the Wellcome Trust in the UK, or by European research and innovation funds. Financial support might also be sought from commercial partners in the neurodevice and regenerative medicine industries, provided there is robust independent oversight.

## Concluding remarks

- 5.67 Therapeutic applications of novel neurotechnologies do not present unique or exceptional concerns for the ethical conduct of relationships of care in treatment and research contexts. However, examination of the governance mechanisms that apply to these relationships through the filter of our ethical framework highlights some areas of concern which, while not unique to this field, are nonetheless important in protecting the interests of patients and participants. These include the limits of legally required consent procedures and the assessment of patients' best interests in light of the limits of current knowledge of efficacy and risks – which is particularly pressing in relation to delegated decision-making, determinations of when experimental treatment is justified when few other options are available, and sham neurosurgery. There is also a need for greater attention to harm beyond impacts on physical health, including impacts on wider well-being, privacy and autonomy. As befits a context in which approaches must remain responsive to individual patients' and participants' different needs and experiences, our recommendations relate to the provision of professional guidance rather than more rigid regulatory measures. Although these recommendations are necessarily directed at the organisations responsible for the governance of clinical care and health research respectively, we suggest that while so much investigation in this field takes place in the realm of experimental treatment, it is essential that there is uniformity between professional practices in these domains, wherever possible.
- 5.68 Having considered the 'frontline' of the use of novel neurotechnologies in this chapter, in Chapter 7 we turn to consider the regulatory frameworks that license these technologies for use. Before we do so, however, in Chapter 6 we address broader questions of *where* priorities lie for governance in this context by offering a definition of what constitutes 'responsible research and innovation' (RRI) when framed specifically with novel neurotechnologies in mind.

<sup>597</sup> 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](http://royalsociety.org/uploadedFiles/Royal_Society_Content/policy/projects/sape/2012-06-20-SAOE.pdf), at page 14

<sup>598</sup> 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 page 32(73).