

Chapter 3

Economic drivers of
innovation

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Chapter 3 - overview

There are few effective treatments for many serious neurological and mental health disorders and therefore a significant degree of unmet need. Moreover, the high global incidence of these disorders generates considerable costs to national economies, not only through direct health care costs but also in lost productivity. The novel neurotechnologies we consider in this report offer potential routes to meeting these needs, but pathways to innovative and effective treatments must negotiate ethical and economic challenges.

Economic factors present both opportunities and constraints that shape the innovation pathways of novel neurotechnologies. This is especially so because even where initial research is publically funded, development of research into clinical products will often depend on commercial organisations with obligations to generate profits and shareholder value. For a number of reasons, therefore, it cannot be assumed that this putative area of economic opportunity will translate directly into the provision of therapeutic products where need is most pressing.

Private companies and investors are likely to focus on technologies that offer the greatest potential for financial return on investment, thus favouring those that target large or valuable markets. This threatens to divert investment away from potentially less profitable 'low tech' approaches to care, or treatments to address rarer neurological conditions. It may also leave the needs of those in less affluent parts of the world ill-served. Further challenges to equitable access arise from the fact that, even if the early production costs of the neurotechnologies fall, the wider costs of specialist care associated with their use will remain high in many cases. This raises the further risk that patients might travel to access more affordable treatment in countries with potentially less well-regulated systems of protection.

Large pharmaceutical companies might seem to be potential sources of investment in the field of novel neurotechnologies, when the limits of public funding are reached. However, their recent withdrawal from psychopharmaceutical research suggests that they have been discouraged by the complexity and costs of developing effective neurological interventions. The long, complex and costly development and regulatory pathways (associated with innovation in stem cell based technologies in particular) can be seen as economically too risky by private investors, such as venture capitalists, who look for swift returns on their investment. The development pathways of many novel neurotechnologies are, therefore, vulnerable to the 'valley of death' – where (often small) businesses fail due to a lack of funding to support them through the lengthy process of translating research into commercially viable products.

These kinds of challenges in obtaining funding can impose particular pressures on developers to pursue practices that secure greater market share and swifter returns on investment, but (in the field of medical devices in particular) they might also shape innovation pathways and practices in ways that do not best meet patients' needs for access to safe and effective therapies. These practices might include: exploiting regulatory routes that do not require manufacturers to conduct clinical investigations prior to placing their device on the market; developing therapeutically superfluous consumable elements of otherwise reusable devices; engaging in patent disputes to impede competitors; or offering incentives to clinicians to trial particular products, thus introducing potential conflicts of interest.

The economic drivers and constraints on the development of novel neurotechnologies highlight the ethical importance of proportionate regulatory oversight that encourages innovation, but which helps direct responsible research, development and investment towards the production of safe and effective products that meet genuine patient needs. However, effective regulation alone is unlikely to be sufficient to secure equitable access to affordable therapies; incentives for innovative and responsible research, and funding mechanisms to support lengthy development trajectories, will also be needed.

Background

- 3.1 This chapter describes some of the economic factors that shape the development and deployment of novel neurotechnologies for therapeutic purposes. We suggest that these economic factors produce both opportunities for, and constraints upon, the development of novel neurotechnologies, and can in some circumstances provide perverse incentives, directing the pathways of development in ways that do not match the needs of health services, or of patients.
- 3.2 We begin by locating these economic factors in relation to estimates of need, by considering the prevalence of those conditions that these new technologies might treat or ameliorate. These conditions clearly indicate the considerable degree of what is often termed 'unmet need', that is to say, the prevalence of many widespread neurological and mental health conditions that are not yet adequately addressed by available therapeutic options. This also suggests that there is

a potentially large market for innovative neurotechnologies to address these conditions, and that the kinds of technologies that we are considering in this report might have an important part to play although, as we discuss, it would be a mistake to think that this is simply a matter of providing better technological solutions. We consider the ways in which novel neurotechnologies might be brought from the laboratory – where research is often publicly funded – into therapeutic practice, a process of product development that is largely, if not exclusively, undertaken in the private and for profit sector.

- 3.3 After a general account of the ‘political economy’ of the neurotechnology industry, we consider three interrelated issues. First, do the characteristics of the market encourage or inhibit the development of innovative and effective neurotechnologies to the stage where they are available to those who need them? Here we suggest that there are major hurdles that have to be overcome if a truly innovative neurotechnology industry is to flourish. These differ among the various neurotechnologies considered in this report, and pose particular issues for the commercialisation of therapies involving neural stem cells. Second, are there characteristics of the market that drive the development of valuable neurotechnologies in ways that do not best meet the interests of prospective patients in receiving safe and effective therapies? We suggest that there are indeed a number of troubling practices, though many of these may not be unique to neurotechnological innovation. Third, we ask whether the market form itself generates ethical dilemmas concerning who will have access to the products of innovation. Here, we point in particular to the familiar gulf between promises and delivery that characterise this area, and highlight key issues of equity and justice.

Economic drivers and access to therapies

- 3.4 Why should a report on the ethical and social issues entailed in novel neurotechnologies that intervene in the brain give an important role to these economic considerations? There are a number of reasons, and we introduce them briefly in the following paragraphs.
- 3.5 Research and development in this area, as in the contemporary life sciences more generally, takes place within a global bioeconomy,²²⁹ where research and product development is shaped by decisions that are made by public and private actors about investment priorities.²³⁰ Given the “path dependent” character of knowledge production and product development, these decisions shape patterns of research and development in a quite fundamental way.²³¹ Such decisions are, of course, not based simply on an assessment of the scientific elegance or excellence of the research. They are made, explicitly or implicitly, on the basis of assumptions and expectations as to which problems are most important or exciting to explore (and which are either less important or less amenable to solution), which pathways are likely to be most productive, which outcomes are likely to be of most benefit, and so forth.²³² In the field of biomedical research, those expectations and anticipations could lead to public funding bodies giving priority to supporting the investigation of particular problems or diseases at the expense of others,²³³ and to particular solutions rather than others. Where research is funded by commercial companies or venture capitalists, decisions are shaped by expectations as to the research and development that will deliver products – or shareholder value – to ensure a return on capital

²²⁹ Rose quotes the OECD definition of the bioeconomy as ‘that part of economic activities “which captures the latent value in biological processes and renewable bioresources to produce improved health and sustainable growth and development.”’ Rose N (2007) *The politics of life itself: biomedicine, power, and subjectivity in the twenty-first century* (NJ: Princeton University Press), p32. Original can be found at <http://www.oecd.org/futures/long-termtechnologicalsocietalchallenges/thebioeconomyto2030designingapolicyagenda.htm>.”

²³⁰ Ibid, at page 80.

²³¹ See: Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf, pp.18-9.

²³² Rose N (2007) *The politics of life itself: biomedicine, power, and subjectivity in the twenty-first century* (NJ: Princeton University Press), pp 31-39.

²³³ Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf.

invested within a specific timeframe. These expectations may lead to an emphasis on high-tech, product-based solutions to tractable problems, where intellectual property rights (IPR) may be exploited and where the market is large and sufficiently resourced, rather than on low-tech, more affordable, but less profitable solutions; or, more complicated and risky explorations of potential solutions to more difficult problems.

- 3.6 Where investment is at stake, and potential profits are to be achieved, the emphasis on translation and commercialisation may generate the appetite for innovation that is needed if new products are to be created that would effectively address market demands; that is to say, the demands of those with needs for treatments that will alleviate their conditions.²³⁴ But it may also lead to premature claims about likely benefits, and this is especially significant where products are sold directly to consumers. Further, even where research in a laboratory situation seems to show that a particular invention may generate significant therapeutic benefits, and early stage finance is obtained to create a small commercial company to develop the product, there are many financial hurdles to overcome in bringing it to market. These include crossing the gulf between obtaining relatively small sums of short term funding for small scale research and development and obtaining much larger and longer term funding to scale up to commercial development (see paragraphs 3.41 to 3.47).²³⁵ Indeed, it has been suggested that private investors are increasingly interested in companies with products in later stage development, where the required funding may be greater but the risks are smaller.²³⁶
- 3.7 In this chapter, we also comment on a number of other potentially problematic issues arising from the political economy on novel neurotechnologies, which threaten the pursuit of responsible research and innovation practices. These issues include the incentive for manufacturers of devices to utilise any available means to speed products through the regulatory system and onto the market (see paragraphs 3.55 to 3.59), given the need to show a return on investment and the limited periods of market exclusivity afforded by many intellectual property rights. Other issues that have been raised in relation to medical devices in general, but which also may have implications for neurotechnologies specifically, include potential financial links and close relationships between manufacturers and clinicians who play a role in the uptake of technologies and in reporting on the results of their clinical use (see paragraphs 3.66 to 3.70).²³⁷
- 3.8 By exploring the nature of the economic drivers and constraints that operate on the development pathways of novel neurotechnologies, the kinds of challenges that must be confronted if innovation is to deliver access to safe, effective and affordable therapies can be appreciated. In order to understand more fully the ethical and social challenges posed by the aspects of the political economy outlined above, we first need to examine commercial imperatives that surround the development of novel neurotechnologies and the problems of securing sufficient investment to support their translation from basic research to marketable products, particularly where innovation trajectories entail uncertain risks and target markets may be small or otherwise less lucrative.

Assessing need

- 3.9 We argue here that there is a great and urgent need for innovative approaches to address the multiple problems of neurological disorders, and to develop better therapeutic approaches to tackle many mental health disorders that are currently inadequately treated by psychopharmaceuticals. Obtaining a clear picture of what this need looks like at a local and

²³⁴ In the area of pharmaceuticals, commercial incentives can stimulate imitation rather than innovation, as in the creation of 'me too' drugs to tap into a market that has already been opened by the products produced by a rival manufacturer.

²³⁵ House of Commons Science and Technology Committee (2013) *Bridging the valley of death: improving the commercialisation of research*, available at: <http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/348/348.pdf>.

²³⁶ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 374.

²³⁷ Wilmshurst P (2011) The regulation of medical devices *British Medical Journal* **342**:d2822.

global level and assessing to what extent novel neurotechnologies might realistically address the needs of various groups, however, can be difficult. In this section, we bring together the available evidence to outline the extent of need.

3.10 We begin by considering some recent estimates of the economic cost (conventionally termed ‘burden’) of brain disorders. The term ‘burden’ is used to describe not only the actual economic cost of treating those affected by these conditions but also other associated costs, for example those of welfare payments and loss of productivity. These figures should be treated with caution for a number of reasons:

- figures often include many conditions that are not currently considered as potentially treatable by novel neurotechnologies;
- the term brain disorders has come to be used by some bodies to cover both mental health and neurological disorders – misleadingly implying that the only pathway to therapy for conditions from anxiety to addiction²³⁸ lies in acting on the brain; and
- the estimates are often generated by organisations that have an interest in overestimation, because large numbers can be used rhetorically to stress the need for further investment in their own area of research. We observe below how such figures are deployed by neurotechnology market research companies (see paragraphs 3.18 to 3.20).

Indeed, without underplaying the significance of these estimates, we also note that they aim to have ‘performative’ consequences through shaping the direction of policy and investment. It is therefore unsurprising that, while some claim that these figures highlight the urgent need for action, others argue that they tend to overestimate necessary levels of public investment.²³⁹

3.11 Estimates of the economic cost of neurological diseases and mental health disorders vary widely. In 2001, the World Health Organization (WHO), perhaps set the pattern for subsequent estimates of previously under-recognised worldwide prevalence of mental health disorders in its report *Mental health: new understanding, new hope*. The report stated:

“By the year 2020, if current trends for demographic and epidemiological transition continue, the burden of depression will increase to 5.7 per cent of the total burden of disease, becoming the second leading cause of DALYs (disability adjusted life years) lost. Worldwide it will be second only to ischemic heart disease for DALYs lost for both sexes. In the developed regions, depression will then be the highest ranking cause of burden of disease.”²⁴⁰

Furthermore, in 2007, the WHO estimated that 6.8 million people die every year as a result of a neurological disorder, and that up to one billion people worldwide are affected.²⁴¹

3.12 There have also been a series of other reports by NGOs, professional organisations and commercial companies, many of which attempted to estimate the cost of such disorders. For example, in 2002, the Society for Neuroscience estimated that the annual direct cost of

²³⁸ Gustavsson A, Svensson M, Jacobi F *et al.* (2011) Cost of disorders of the brain in Europe 2010 *European Neuropsychopharmacology* **21(10)**: 718-79, at page 720.

²³⁹ Estimates of the size and burden of psychiatric disorders have been particularly controversial, with disputes focused on the methodology of generating estimates. See: Regier DA, Kaelber CT, Rae DS *et al.* (1998) Limitations of diagnostic criteria and assessment instruments for mental disorders: implications for research and policy *Archives of General Psychiatry* **55(2)**: 109-20.

²⁴⁰ World Health Organization (2001) *The world health report 2001: mental health: new understanding, new hope*, available at: http://www.who.int/whr/2001/en/whr01_en.pdf, at page 30.

²⁴¹ World Health Organisation (2007) Neurological disorders affect millions globally, available at: <http://www.who.int/mediacentre/news/releases/2007/pr04/en/index.html>

neurological and mental health disorders in the US exceeded \$548 billion.²⁴² According to data compiled by the market research organisation NeuroInsights and the lobbying body Neurotechnology Industry Organization, the annual economic burden of brain-related illness in the US exceeds \$1.4 trillion.²⁴³ To put this into perspective, the American Cancer Society estimated the overall costs of cancer in the US in 2010 to be \$263.8 billion,²⁴⁴ while the economic burden of pre-diabetes and diabetes in the US in 2007 has been estimated at \$218 billion.²⁴⁵

- 3.13 A report by the European Brain Council (EBC) recently estimated the total cost of brain disorders in Europe to be €798 billion in 2010. Direct healthcare costs constituted 37 per cent (€295 billion) and 23 per cent (€183.5 billion) for direct non-medical costs. The remaining 40 per cent (€319 billion) were indirect costs associated with patients' production losses.²⁴⁶ Analogous estimates have been made in the US:²⁴⁷ according to estimates made in 2007, migraine was the most common neurological disorder in the US population affecting 35 million people. Stroke was the second most common neurological disorder and affected a total of 541,000 people each year (75% of whom were aged 65 or over) with a prevalence in the US population of 2,956,000. The next most common disorder was Alzheimer's disease with an annual incidence of 468,000, and almost 2.5 million people living with the disorder. Parkinson's disease affected 349,000 people, with 59,000 new cases each year.²⁴⁸
- 3.14 The figures for migraine are just one element in the more general 'empire of pain' that seems to affect so many in advanced industrial societies: thus the Medical Expenditure Panel Survey (MEPS) estimated that approximately 100 million adults in the US are affected by chronic pain, including joint pain or arthritis. The survey also estimated that persistent pain costs the US economy between \$560 and \$635 billion annually.²⁴⁹ Statistics published by the National Institutes of Health (NIH) state that the costs of persistent pain exceed the economic costs of the six most costly major diagnoses, namely cardiovascular diseases (\$309 billion), neoplasms (\$243 billion), injury and poisoning (\$205 billion), endocrine, nutritional and metabolic diseases (\$127 billion), digestive system diseases (\$112 billion), and respiratory system diseases (\$112 billion).²⁵⁰

²⁴² NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 35.

²⁴³ *Ibid.*, at page 35.

²⁴⁴ Christakis P (2011) Bicentennial: the birth of chemotherapy at yale: bicentennial lecture series: surgery grand round *Yale Journal of Biology and Medicine* **84(2)**: 169-72, at page 169.

²⁴⁵ Dall TM, Zhang Y, Chen YJ *et al.* (2010) The Economic burden of diabetes *Health Affairs* **29(2)**: 297-303.

²⁴⁶ Gustavsson A, Svensson M, Jacobi F *et al.* (2011) Cost of disorders of the brain in Europe 2010 *European Neuropsychopharmacology* **21(10)**: 718-79, at page 720.

²⁴⁷ The research was carried out by US National Institutes of Neurological Disorders and Stroke/National Institutes of Health and the National Center for Chronic Disease Prevention and Health & Promotion/Centers for Disease Control and Prevention.

²⁴⁸ Hirtz D, Thurman D, Gwinn-Hardy K *et al.* (2007) How common are the "common" neurologic disorders? *Neurology* **68(5)**: 326-37, at page 332.

²⁴⁹ Gaskin DJ and Richard P (2012) The economic costs of pain in the United States *The Journal of Pain* **8(13)**: 715-24, p715

²⁵⁰ *Ibid.*, at page 723.

Box 3.1: UK estimates for people affected by neurological and mental health conditions

We can make some rough estimates of the numbers of people in the UK that might benefit from the novel neurotechnologies that we discuss in this report.

- There are more than one million stroke survivors in the UK, 300,000 of which are living with moderate or severe disabilities.²⁵¹
- In the UK, 127,000 people are thought to have Parkinson's disease.²⁵²
- 800,000 are living with Alzheimer's disease and other forms of dementia.²⁵³
- 100,000 people have multiple sclerosis (MS).²⁵⁴
- Dystonia is thought to affect at least 70,000 people.²⁵⁵
- Epilepsy affects around 600,000 people. However, approximately one third of patients do not respond to medication, continuing to experience seizures.²⁵⁶
- Around 500,000 people (aged 16-74) live with long term disabilities as a result of traumatic brain injury.²⁵⁷
- Approximately 40,000 individuals in the UK are living with a traumatic spinal cord injury.²⁵⁸
- Four adults in every 100 over the age of 40 are affected by essential tremor.²⁵⁹
- One in 100 people are affected by Tourette's syndrome.²⁶⁰
- OCD affects approximately 12 people in 1,000.²⁶¹
- Approximately one in 1,000 experience cluster headaches.²⁶²
- About 12 people per 100,000 are affected by Huntington's disease.²⁶³
- 5,000 people are thought to have motor neurone disease.²⁶⁴
- Anorexia is thought to affect approximately 2,000 people in the UK.²⁶⁵
- In 2008-2009 4,211 weight loss procedures were carried out on the NHS.²⁶⁶
- It has been estimated that treatment-resistant depression – usually defined as when at least two trials with antidepressants from different pharmacologic classes do not produce a significant clinical improvement – occurs in 15-33 per cent of people with depression.²⁶⁷
- Neuropathic pain occurs in three to eight per cent of individuals in industrialised countries.²⁶⁸
- Chronic pain “of moderate to severe intensity” occurs in 13 per cent of adults in the UK and seriously affects the quality of their social and working lives.²⁶⁹

²⁵¹ BBC News Health (1 May 2012) *Stroke survivors "being denied best recovery chance"*, available at: <http://www.bbc.co.uk/news/health-17893433>.

²⁵² Parkinson's UK (2013) *What is Parkinson's?*, available at: <http://www.parkinsons.org.uk/about-parkinsons/what-is-parkinsons.aspx>.

²⁵³ Alzheimer's Society (2013) *What is dementia?*, available at: http://alzheimers.org.uk/site/scripts/documents_info.php?documentID=106.

²⁵⁴ NHS Choices (2012) Multiple sclerosis, available at: <http://www.nhs.uk/conditions/Multiple-sclerosis/Pages/Introduction.aspx>.

²⁵⁵ The dystonia society (2012) *About dystonia*, available at: <http://www.dystonia.org.uk/index.php/about-dystonia>.

²⁵⁶ Central Manchester University Hospital (2012) *Surgery boost for children with drug-resistant epilepsy*, available at: <http://www.cmfh.nhs.uk/media-centre/latest-news/surgery-boost-for-children-with-drug-resistant-epilepsy.aspx>.

²⁵⁷ The United Kingdom Acquired Brain Injury Forum (2004) *Prevalence*, available at: <http://www.ukabif.org.uk/information/data/55-prevalence>.

²⁵⁸ National Guidelines (2008) *Chronic spinal cord injury: management of patients in acute hospital settings*, available at: http://www.spinal.co.uk/userfiles/Professionals_Portal/RCP_SCI_Guidelines.pdf, at page 1.

²⁵⁹ NHS Choices (2011) *Tremor (essential)*, available at: [http://www.nhs.uk/conditions/Tremor-\(essential\)/Pages/Introduction.aspx](http://www.nhs.uk/conditions/Tremor-(essential)/Pages/Introduction.aspx).

²⁶⁰ NHS Choices (2011) *Tourette's syndrome*, available at: <http://www.nhs.uk/conditions/Tourette-syndrome/Pages/Introduction.aspx>.

²⁶¹ NHS Choices (2012) *Obsessive compulsive disorder*, available at: <http://www.nhs.uk/Conditions/Obsessive-compulsive-disorder/Pages/Introduction.aspx>.

²⁶² NHS Choices (2011) *Cluster headaches*, available at: <http://www.nhs.uk/conditions/cluster-headaches/Pages/Introduction.aspx>.

²⁶³ NHS Choices (2012) *Huntington's disease*, available at: <http://www.nhs.uk/conditions/Huntingtons-disease/Pages/Introduction.aspx>.

²⁶⁴ Motor Neurone Disease Association (2013) *Journalist's guide to MND*, available at: <http://www.mndassociation.org/news-and-events/news-room/journalists-guide-to-mnd>.

²⁶⁵ House of Commons Hansard (9 March 2009) *Parliamentary questions: eating disorders*, available at: <http://www.publications.parliament.uk/pa/cm200809/cmhansrd/cm090309/text/90309w0028.htm>.

²⁶⁶ National Institute of Clinical Excellence (2012) *New weight-loss operation: NICE encourages more research*, available at: <http://www.nice.org.uk/newsroom/pressreleases/NewWeightLossOperationNICEEncouragesResearch.jsp>. As noted at paragraph 2.54 above, there are studies investigating the use of DBS to treat obesity.

²⁶⁷ See, for example, Little A (2009) *Treatment-resistant depression* *American Family Physician* **80(2)**: 167-72.

²⁶⁸ Ashton JC and Milligan ED (2008) *Cannabinoids for the treatment of neuropathic pain: clinical evidence* *Current opinion in investigational drugs (London, England: 2000)* **9**: 65.

²⁶⁹ Based on 46,394 people within 15 European countries and Israel who took part: Breivik H, Collett B, Ventafridda V, Cohen R and Gallacher D (2006) *Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment* *European Journal of Pain* **10(4)**: 287-333.

- 3.15 The figures we cite in Box 3.1 above can give only approximate figures for the numbers of people in the UK who are in need of access to effective treatments to ameliorate neurological and psychiatric disorders. These disorders are, at the very least, disruptive to their lives and the lives of their families and, at the most, are severely disabling, leading to incapacity and death. It is also clear that these conditions have major social and economic consequences, although as we have noted, estimates of the costs of such disorders should be treated with caution.
- 3.16 The conditions aggregated in assessments of need such as those cited above are of different orders, with different causes. One EBC report has argued that “[b]oth lay persons and professionals are typically unaware of the commonalities and the shared mechanisms of ‘brain disorders’”²⁷⁰ in which it includes depression, schizophrenia, anxiety disorders, drug dependence, dementia, epilepsy and multiple sclerosis (MS). However, framing these diverse conditions in this way, could be misleading to the extent that it implies that the pathway to understanding and treating all of them lies in solely the brain, hence accentuating the potential role for technologies that intervene directly in the brain. While some disorders, such as Parkinson’s disease, clearly arise from neurological damage located in the brain, the causal pathways for others, such as obesity, are more complex, and the centrality of the brain as the key target for intervention is less certain, and often disputed. Similarly, while some of these conditions have no available and effective treatments, others (for example, several mental health disorders), respond to available pharmaceuticals in various degrees, and may respond even better to cognitive therapy or social interventions.
- 3.17 Two points remain clear, however. The first is that the perceived size of the potential market for products to address these disorders provides significant financial incentives for companies to develop products to meet these needs. The second is that these companies have to engage in and understand the complex process required to turn developments that work in laboratory situations or in small-scale medical interventions into products that are available on the market, that will be accepted by medical practitioners, and will be purchased by those who commission health services, or, in some circumstances, by patients themselves. The processes of how these aims may be achieved, and the difficulties in achieving them, are discussed below.

Estimating neurotechnology markets

- 3.18 Assessments of the value of biotechnology markets – specifically the revenue generated by biotechnology companies – are produced by a number of organisations, including governments, international organisations and private market research companies. According to one estimate, the value of the global biotechnology market in 2011 was \$281.7 billion, which will rise by over 60 per cent by 2016 to an estimated \$453.3billion.²⁷¹ The majority of the biotechnology industry is based in the US, but China, India, Japan, Brazil, and EU countries are also developing biotechnology markets.²⁷²
- 3.19 It is generally held that the most lucrative part of the global biotechnology market is that concerned with medicine and health care. According to one estimate, in 2008 this section generated 69 per cent of the market’s overall value.²⁷³ Another forecast concluded that “[t]he medical technology market is estimated to be worth £150-70 billion worldwide with growth rates

²⁷⁰ Wittchen HU, Jacobi F, Rehm J *et al.* (2011) The size and burden of mental disorders and other disorders of the brain in Europe 2010 *European Neuropsychopharmacol* **21(9)**: 655-79, at page 656.

²⁷¹ Biotechnology: Global Industry Guide (2012) *Biotechnology: global industry guide*, available at: http://www.researchandmarkets.com/reports/41522/biotechnology_global_industry_guide.

²⁷² Abuduxike G and Aljunid SM (2012) Development of health biotechnology in developing countries: can private-sector players be the prime movers? *Biotechnology Advances* **30(6)**: 1589-601; Neurotechnology Industry Organization (2009) *Neurotech clusters 2010: leading regions in the global neurotechnology industry 2010 - 2020*, available at: http://www.neurotechindustry.org/images/Neurotech_Clusters_2010_Report.pdf.

²⁷³ Highbeam Business (2009) *Global - biotechnology (industry overview)*, available at: <http://business.highbeam.com/437189/article-1G1-206253164/global-biotechnology>.

forecast at ten per cent per annum over the next five to six years and a market size approaching £300 billion by 2015.”²⁷⁴

3.20 NeuroInsights has stated that the 2011 market for neurodevices for therapeutic use generated estimated revenues of \$8.63 billion (8.1% growth). “This compares to \$7.98 billion (13% growth) in 2010, \$7.06 billion (15% growth) in 2009, and \$6.1 billion (18.6% growth) in 2008.”²⁷⁵

3.21 In light of these estimates, the belief in the potential value that can be generated by neurotechnologies has consequences for the direction of research and development. A significant amount of basic research is conducted in universities and funded with grants from research councils and charitable foundations. Even this area is now subject to requirements to realise value in terms of intellectual property,²⁷⁶ and to have an ‘impact’, by translating research into treatments or products to enhance health and generate wealth.²⁷⁷ There are partnerships between universities and industry,²⁷⁸ with industry playing a role in funding basic research and training of neuroscientists,²⁷⁹ as well as supporting research into products that are closer to being launched on the market.

3.22 When public bodies estimate the ‘burden’ of brain disorders, they frequently couple this estimate of ‘costs’ with potential ‘benefits’ (the economic returns that can be generated by fulfilling unmet medical needs). For example, the Department for Business, Innovation and Skills, in a report published jointly with the Department of Health, argues that:

“The expected ageing of the UK’s population will continue to boost market opportunities for regenerative medicine products as well as increase cost pressures on health care providers. There are also large and growing unmet medical needs, for example neurodegenerative diseases (including Parkinson’s disease), stroke and heart failure that currently have no significant therapeutic options and are therefore only managed palliatively.”²⁸⁰

3.23 The Nuffield Council on Bioethics’ report on *Emerging biotechnologies* draws attention to the ‘growth agenda’ that dominates publicly funded research, noting that the promotion of economic growth has featured centrally in the aims of research councils for a number of years.²⁸¹ The Council’s report cites a number of examples, including the Treasury’s *Science and innovation framework 2004-2014* which begins by stating that “[h]arnessing innovation in Britain is key to improving the country’s future wealth creation prospects.”²⁸² This focus on economic motivation is echoed in the *Strategy for UK Life sciences* which, as the Council’s *Emerging biotechnologies*

²⁷⁴ Department for Business Innovation and Skills, UK Trade and Investment and Department of Health (2011) *Strength and opportunity 2011: the landscape of the medical technology, medical biotechnology, industrial biotechnology and pharmaceutical sectors in the UK*, available at: <http://www.bis.gov.uk/assets/biscore/innovation/docs/s/11-p90-strength-and-opportunity-2011-medical-technology-sectors.pdf>, at page 10.

²⁷⁵ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 18

²⁷⁶ 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, at page 47.

²⁷⁷ HM Treasury (2006) *A review of UK health research funding*, available at:

<https://www.bioin.or.kr/upload/industry/1192426342312.pdf>, pp.3-4; UK Evaluation Forum (2006) *Medical research: assessing the benefits to society*, available at:

http://www.wellcome.ac.uk/stellent/groups/corporatesite/@msh_publishing_group/documents/web_document/wtx031817.pdf, at page 5.

²⁷⁸ For example: NIHR Imperial BRC (2011) *Industry partners*, available at: <http://imperialbrc.org/our-partners/industry-partners>.

²⁷⁹ Amara SG, Grillner S, Insel T, Nutt D and Tsumoto T (2011) Neuroscience in recession? *Nature Reviews Neuroscience* **12(5)**: 297-302, pp.297-8.

²⁸⁰ Department of Health and Department for Business Innovation and Skills (2011) *Taking stock of regenerative medicine in the United Kingdom*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32459/11-1056-taking-stock-of-regenerative-medicine.pdf, at page 7.

²⁸¹ Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf, pp.117-20.

²⁸² HM Treasury (2004) *Science and innovation investment framework 2004-2014*, available at: http://www.hm-treasury.gov.uk/d/spend04_sciencedoc_1_090704.pdf, at page 5.

report observes, is notable for the way in which it “corrals the whole area of medical research (on which it is almost exclusively focused) into the guiding objective of generating economic benefit.”²⁸³ The Council’s report also argued that priorities have become excessively narrowed by economic considerations which are inevitably tied to speculations about future benefits which are themselves shaped by the promises and predictions that are encouraged by public research funding systems.²⁸⁴ Research, whether conducted in the public or the private domain or in partnerships between these, may increasingly be viewed as ‘promissory’ in nature: the policy and funding environments place increasing expectations on researchers to promise benefits, and research is increasingly shaped by these promises.²⁸⁵

Promises and problems in neurotechnology markets

3.24 In the promissory political economy of neurotechnologies, expectations of the potential for developments in neurotechnologies play a crucial role in developing the market. Hence market scoping companies such as IMS and NeuroInsights, claim to help commercial companies identify and estimate key potential markets for their products.²⁸⁶ Such estimates are ‘performative’ as they help to bring these new markets into existence by encouraging their commercial exploitation. For example, NeuroInsights estimates that almost half the global patient population is “unserved” and that “The unserved market represents neurotechnology’s enormous, long-term market opportunity. Examples of indications in this segment include cures for Alzheimer’s disease, chronic addiction and age-related sensory disorders (such as hearing loss).”²⁸⁷ We can see echoes in these commercial forecasts of the kind of foresight activities, estimating the prevalence and costs of disease, conducted by the public bodies such as the WHO (see paragraph 3.11).

Box 3.2: Neuro-lobbying in the US

In the US, the neurotechnology industry forms a powerful lobby group. For example, the National Neurotechnology Initiative, which comprises over 100 companies, was formed to coordinate and accelerate neurotechnology research, support entrepreneurship, and improve the effectiveness and efficiency of the FDA neurotechnology approval process.²⁸⁸ In 2009, it lobbied Congress for incentives for the neurotechnology industry in the form of a National Neurotechnology Initiative Act.²⁸⁹ It argued that “[f]or \$200 million – three percent of the current NIH brain and nervous system research and development budget – the NNTI Act will dramatically increase the speed and number of treatments and cures for brain and nervous system illnesses, disorders and injuries. It coordinates research for increased efficiency, and leverages private sector innovation.” The Initiative also proposed the establishment of “a research center to conduct studies on the ethical, legal and social implications of neurotechnology, addressing issues such as its appropriate use in the criminal justice system, or enhancement of soldier and civilian mental capabilities (\$10 million).”²⁹⁰ The legislation failed to gather sufficient support and did not proceed, but lobbying continues with hopes for success at a future session.²⁹¹

3.25 If incentives to innovate in this field are framed purely in terms of likely financial return on investment, it is clear that economic considerations – such as the capacity of health care organisations or individuals to afford to purchase products – will steer development towards the

²⁸³ Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf, at page 120.

²⁸⁴ Ibid.

²⁸⁵ Hedgecoe A (2004) *The politics of personalised medicine: pharmacogenetics in the clinic* (Cambridge: Cambridge University Press), at page 17.

²⁸⁶ NeuroInsights (2012) *The neurodiagnostics report 2012: brain imaging, biomarkers and neuroinformatics*, available at: <http://www.neuroinsights.com/marketreports/neurodiagnosticsreport.html>. These reports often cost several thousand dollars to purchase, indicating their potential value to their target audience of investors,

²⁸⁷ NeuroInsights (2010) *Neurotechnology industry reports revenues of \$143.1 billion in 2009*, available at: <http://www.neuroinsights.com/neurotech2010release.html>, at page 21.

²⁸⁸ Neurotechnology Industry Organization (2011) *Neurotechnology Industry Organization: homepage*, available at: <http://www.neurotechindustry.org/>.

²⁸⁹ Neurotechnology Industry Organisation (2012) *About the Neurotechnology Industry Organization*, available at: <http://www.neurotechindustry.org/aboutnio.html>.

²⁹⁰ NeuroInsights (2010) *Neurotechnology industry reports revenues of \$143.1 billion in 2009*, available at: <http://www.neuroinsights.com/neurotech2010release.html>, at page 39.

²⁹¹ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights)

health care needs of the developed world, and within that, to specific population groups. Such market-based shaping of technology development raises particular issues of equity and justice. For example, Alzheimer's disease and other age-related conditions offer tempting potential markets, and the development of effective treatments promises significant benefits for both industry and national economies; however, there is significant unmet need for people with rare and complex neurological conditions, such as motor neurone disease, locked-in syndrome and end-stage Parkinson's disease. In the case of medicines for rare conditions, various options have been tried. For example, some companies create successful business models for rare conditions, based on setting very high costs for their products,²⁹² although a more familiar route is via the designation of 'orphan disease' status for conditions affecting fewer than five per 10,000 (in Europe).²⁹³ For such conditions, EU legislation seeks to encourage innovation with incentives including ten years of market exclusivity; protocol assistance and access to centralised procedure at the European Medicines Agency; reduction in fees such as those for pre-authorisation activity; and free scientific advice.²⁹⁴ Neurological devices for smaller populations face less costly manufacturing and regulation (see Box 7.6), but may struggle to demonstrate efficacy to potential buyers without larger clinical trials, an issue which is compounded by small patient populations.

- 3.26 Even though some novel neurotechnologies such as deep brain stimulation (DBS) have proven effective for relatively common conditions such as Parkinson's disease, the question remains whether they will be available to the majority of patients who have such conditions. Considerations such as cost and the need for ongoing skilled medical attention and surveillance bring into question whether the widespread use of such novel neurotechnologies will be possible in the foreseeable future. For example, while stroke is a major global health problem, the WHO recommends that stroke is best addressed in primary care settings as this is the only point of access the majority of sufferers have to medical treatment.²⁹⁵ It is, of course, possible that as efficacy of a particular neurotechnology product is demonstrated and production volume increases, its price will fall and the size of the market will increase, as evidenced by conventional economics. By definition, the 'novel' neurotechnologies that we discuss in this report have not reached this point. However, even when those technologies are mature, the realities of health care systems and funding in the global south may well mean that, for the vast majority, these treatments will remain out of reach, and that in developing countries, the availability of these treatments will follow a familiar and inequitable path.

Securing funding to pursue innovation

- 3.27 The dilemma we are faced with is this: emphasising the global incidence of neurological disease, the very large numbers of persons affected and the high personal, familial and national costs they entail, may help to raise the profile of these disorders, and therefore opportunities for commercial exploitation. It may also stimulate those who, aware of unmet needs, seek to exploit desperate patients. The challenge for those seeking to develop such neurotechnologies in clinically appropriate ways remains that of seeking funds for research and development of neurotechnologies that, in the short term at least, are unlikely to be widely available. It is in this light that we can consider whether the current political economy of neurotechnologies encourages the development of devices that address unmet needs, both in relation to common conditions such as stroke and Parkinson's disease, and in relation to rarer conditions. We will

²⁹² Novas C (2008) Patients, profits and values, in *Biosocialities, Genetics and the Social Sciences: Making Biologies and Identities*, Gibbon S, and Novas C (Editors) (London: Taylor Francis), pp 136-152.

²⁹³ Taruscio D, Capozzoli F and Frank C (2011) Rare diseases and orphan drugs *Annali dell'Istituto Superiore di Sanità* **47(1)**: 83-93.

²⁹⁴ *Ibid*, at page 85. The introduction of value-based pricing (VBP) may also provide further incentives for the development of products for smaller patient populations in the future. VBP is a proposal for changing the way that the UK prices and reimburses new medicines. Price will be linked to an assessment of the value of a new medicine to the NHS.

²⁹⁵ World Health Organization (2007) *Neurological disorders: a public health approach*, available at: http://www.who.int/mental_health/neurology/chapter_3_a_neuro_disorders_public_h_challenges.pdf, at page 178.

see that even where market incentives appear to be significant because potential demand is high, it is often difficult to obtain funding of an appropriate scale and duration to bring products to market. This challenge is even more pronounced in relation to rarer conditions, although there are examples of investors or companies who focus on relatively small market opportunities where it is commercially viable.²⁹⁶

Public and third sector funding

- 3.28 In the case of stem cell therapies and regenerative medicine, funding from public sources and third sector organisations has been particularly significant in Europe and North America. They are viewed by some national governments, including the UK government, as key areas of opportunity for economic growth.²⁹⁷ However the practical considerations associated with the regulation and production of products based on living cells may be perceived as investment risks that present challenges to private funding models.²⁹⁸
- 3.29 In the UK, regenerative medicine generally has seen significant public funding over the last ten years (over £200 million since 2003).²⁹⁹ A joint report by the Department for Business, Innovation and Skills and the Department of Health entitled *Taking stock of regenerative medicines in the United Kingdom*, argues for investment in the development of regenerative medical techniques, especially therapies for stroke and Parkinson's disease in light of potential economic savings which could offset growing costs of public health care for an ageing population.³⁰⁰ In the US in 2004, Californian voters approved *Proposition 71: the California stem cell research and cures initiative*, which meant that \$3 billion (funded by the sale of public bonds) would be made available over 10 years for the creation of the California Institute for Regenerative Medicine (CIRM) and the funding of stem cell research.³⁰¹
- 3.30 However, much of the burden for funding research into regenerative medicine has fallen on third sector organisations. It has been argued by Rare Diseases UK that “[m]ajor national funders do not include research into rare disease as a priority and are often reluctant to support such research because of a perceived lack of impact on the burden of disease and expected limited cost-effectiveness due to the small number of affected people.”³⁰² It has often fallen to charities to fund research into rare diseases that offer less attractive markets to commercial companies, and do not have the economic impact to attract large amounts of public funding. For example, the Association of Medical Research Charities (AMRC) estimates that in 2008-9 UK charities invested approximately £3.6 million in rare disease research.³⁰³ According to the AMRC the third sector invested approximately £38 million in regenerative medicine research from 2005-2009.³⁰⁴ Indeed, of the £60 million of grants made by Parkinson's UK,³⁰⁵ it has invested over

²⁹⁶ Genzyme (2012) *Our treatment areas*, available at: <http://www.genzyme.co.uk/treatment-areas.aspx>.

²⁹⁷ Gov.UK (2012) *Speech by the Chancellor of the Exchequer, Rt Hon George Osborne MP, to the Royal Society*, available at: <https://www.gov.uk/government/speeches/speech-by-the-chancellor-of-the-exchequer-rt-hon-george-osborne-mp-to-the-royal-society>; Department of Health and Department for Business Innovation and Skills (2011) *Taking stock of regenerative medicine in the United Kingdom*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32459/11-1056-taking-stock-of-regenerative-medicine.pdf.

²⁹⁸ Department of Health and Department for Business Innovation and Skills (2011) *Taking stock of regenerative medicine in the United Kingdom*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32459/11-1056-taking-stock-of-regenerative-medicine.pdf, at page 22.

²⁹⁹ *Ibid*, at page 22.

³⁰⁰ *Ibid*, at page 7.

³⁰¹ Adelson JW and Weinberg JK (2010) The California stem cell initiative: persuasion, politics, and public science *Journal of Information* **100**(3): 446-51.

³⁰² Rare Disease UK (2011) *Improving lives optimising resources: a vision for the UK Rare Disease Strategy*, available at: <http://www.raredisease.org.uk/documents/RD-UK-Strategy-Report.pdf>, at page 23.

³⁰³ *Ibid*, at page 23.

³⁰⁴ Department of Health and Department for Business Innovation and Skills (2011) *Taking stock of regenerative medicine in the United Kingdom*, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/32459/11-1056-taking-stock-of-regenerative-medicine.pdf, at page 27.

³⁰⁵ Parkinson's UK (2012) *Our plan to cure Parkinson's*, available at: http://www.parkinsons.org.uk/research/our_plan_to_cure_parkinsons.aspx.

£1.7 million in stem cell research.³⁰⁶ Figures provided by the Medical Research Council (MRC), show that approximately £500,000 has been invested in neural stem research between 2007 and 2012.³⁰⁷ A further search for “neural stem cells” via the European PubMed Central “Grant lookup tool”³⁰⁸ identifies that the Wellcome Trust have registered research projects that amount to over £2.5 million in this area. However, even the significant public and third sector investments outlined here have not yet been sufficient to bring neural stem cell therapies to market.³⁰⁹ While these are significant sums for public and charitable organisations, they are very small compared to the historical investments of large pharmaceutical companies in the development of drugs which target the central nervous system.

- 3.31 The public sector has also invested in neurotechnological devices though these sums are very small compared with those invested in research and development by commercial companies. Figures provided by the MRC show that approximately £3 million and £1 million have been invested in DBS and TMS/TDS respectively. The European PubMed Central “Grant Lookup Tool” also indicates that Wellcome Trust has invested close to £1.5 million in TMS/TDCS. The European Commission spent approximately €38 million on ten projects based on BCI-related systems between 2007 and 2013,³¹⁰ and in the US the Department of Defense and the Department of Veterans’ Affairs have invested in BCI with the hope that research in this area will improve the quality of life for war veterans who have lost limbs.³¹¹

Large pharmaceutical and medical technology companies

- 3.32 Historically, large pharmaceutical and medical technology companies have been relied on to bring new therapies to market. However, recent withdrawal of multinational pharmaceutical companies such as GlaxoSmithKline and AstraZeneca³¹² from research into the brain suggests that there needs to be a paradigm shift away from such funding and development models for neurotechnologies. High hopes were placed in the therapeutic possibilities that would be opened up by the emergence of the field of neuroscience in the 1960s. However, while some new pharmaceuticals for mental health and neurological conditions have proved to be effective, few new drug targets or therapeutic mechanisms of real significance have been identified for more than four decades.³¹³ According to Steven Hyman, former Director of the US National Institute of Mental Health, despite the large unmet need and the growing markets for treatments for mental health disorders, these financial drivers have not proved sufficient to overcome the “very difficult scientific terrain.”³¹⁴
- 3.33 One major problem that has been experienced by pharmaceutical companies in developing their drug pipeline has been that compounds that appear promising in laboratory experiments – often with animal models – have not proved successful in clinical trials with humans.

³⁰⁶ Data on file at NCOB received from Parkinson’s UK. Parkinson’s UK, personal communication, 19.19.2012.

³⁰⁷ Data on file at NCOB received from Medical Research Council MRC *personal communication*, 16.01.2013.

³⁰⁸ European PubMed Central (2013) *Grant lookup tool*, available at: <http://europepmc.org/GrantLookup/>.

³⁰⁹ Economic factors are of course not the only constraints on complex biological products reaching the market. In Chapter 2 (paragraph 2.80) we review some of the scientific issues that must first be resolved and in Chapter 7 (paragraphs 7.60 to 7.72) we review the regulatory framework that determines the marketability of these products.

³¹⁰ Future BNCI (2012) *Future BNCI: A Roadmap for Future Directions in Brain / Neuronal Computer Interaction Research*, available at: http://future-bnci.org/images/stories/Future_BNCI_Roadmap.pdf, at page 24.

³¹¹ Brown University (2012) *People with paralysis control robotic arms using brain-computer interface*, available at: <http://news.brown.edu/presreleases/2012/05/braingate2>.

³¹² The Guardian (13 June 2011) *Research into brain disorders under threat as drug firms pull out*, available at: <http://www.guardian.co.uk/science/2011/jun/13/research-brain-disorders-under-threat>.

³¹³ Hyman SE (2012) Revolution stalled *Science Translational Medicine* **4(155)**: 1-5, at page 1.

³¹⁴ *Ibid*, at page 3. Both the EU and the US have recently announced major long term investments in human brain mapping programmes, designed, in part, to provide alternative approaches to the use of animal models in the trialling of therapeutic interventions into the brain, which may provide effective alternatives able to capture these complex neural properties and explore mechanisms of action in ways that facilitate translation.

“The best recognized obstacles to effective clinical translation in psychiatry include the complexity of the brain and the associated challenge of connecting levels of analysis from molecules to cells, synapses, circuits, and thence to higher cognition, emotion, regulation, and executive function.”³¹⁵

These difficulties in translation from the laboratory to clinical application in psychopharmaceuticals illustrate a general problem for the funding and longer term support of neurotechnology. Investment in psychopharmaceuticals from the 1960s was based on widely accepted hypotheses as to the mode of action of the drugs, linked to hypotheses about the neurobiological basis of the conditions that they sought to treat.³¹⁶ These hypotheses – even if they now appear partial, at best – guided research and development. However, there is still little understanding of how some neurotechnological interventions achieve their intended therapeutic effects (for example, see paragraph 2.49) and this has consequences for the development and refinement of the technologies.

- 3.34 Nonetheless, it has been suggested that the difficulties encountered in the development of novel psychopharmaceuticals opens new opportunities for those developing devices.³¹⁷ Historically, neurodevices have been better supported by bigger companies than stem cells. Several major companies – including Medtronic,³¹⁸ St. Jude Medical,³¹⁹ and Boston Scientific³²⁰ – have made significant investments in start-ups and have successfully brought products to market, including those used in DBS. In 2009 it was estimated that over 60,000 people worldwide had received DBS.³²¹ DBS accounts for about one sixth of the neuromodulation devices market with an estimated global volume of \$3 billion in 2010.³²² There are indications that pharmaceutical companies are beginning to consider increasing investment in neurotechnologies of the sort that we are discussing in this report.³²³
- 3.35 In the context of stem cells, some pharmaceutical companies have, to date, begun to invest in cell-based therapies, although not yet in the neurological area.³²⁴ However large companies have, for the most part, shown a reluctance to invest in stem cell research and have, instead, preferred to observe the field to monitor if any potentially viable products emerge.³²⁵ While successful developments in neural stem cell therapies may lead to lucrative buy-outs from these companies later in development pathways, this does not address the initial costs of basic research and development or those of transitional research.

³¹⁵ Ibid, at page 3.

³¹⁶ Healy D (1997) *The antidepressant era* (Harvard: Harvard University Press).

³¹⁷ Neurotech Business Report (2011) *Drop in pharma R&D for CNS opens door for devices* available at: http://www.neurotechreports.com/pages/CNS_Pharma_R&D_Funding_Decline.html.

³¹⁸ Medtronic (2013) *Deep brain stimulation for movement disorders*, available at: <http://professional.medtronic.com/pt/neuro/dbs-md/index.htm#.UbG3H-dwprR>.

³¹⁹ At a conference organised by J. P. Morgan in 2011, “St. Jude Medical CEO Dan Starks touted the company’s 11% top-line growth. In neuromodulation, Starks said the company has a leadership position in Japan with its Eon Mini device [a very small implantable pulse generator (IPGs) for chronic pain management] and that SJM would be first to market with neuromodulation system to treat migraine.” Neurotech business report (2011) *Neurotech executives report progress at J.P. Morgan healthcare conference* available at: http://www.neurotechreports.com/pages/2011_JP_Morgan_Healthcare_Conference_Neurotech.html.

³²⁰ In 2011, Boston Scientific CEO Ray Elliott reported that his company “had lots of IP and two opportunities to compete in the hypertension neuromodulation space, which he sees as a \$5 billion business by 2020. The approaches include stimulation of baroreceptors and renal nerves... he touted the company’s Vercise DBS system, which is currently undergoing clinical trials in Cologne...”. See: Ibid.

³²¹ Ponce FA and Lozano AM (2010) Chapter 16 - Deep brain stimulation: state of the art and novel stimulation targets, in *Progress in brain research*, Anders B, and Cenci MA (Editors) (Elsevier).

³²² Christen M and Müller S (2012) Current status and future challenges of deep brain stimulation in Switzerland *Swiss Medical Weekly* **142(w13570)**: 1-8, at page 2.

³²³ Gewin V (2008) Brain work *Nature* **426**: 276-7; The Lundbeck Foundation (2011) *The Lundbeck Foundation 2011 annual report*, available at: <http://www.lundbeckfoundation.com/media/LF11-12UK.pdf>, at page 30.

³²⁴ See, for example, Bloomberg (8 December 2010) *Cephalon buys mesoblast stake, drug rights in potential \$2 billion deal*, available at: <http://www.bloomberg.com/news/2010-12-08/cephalon-buys-20-stake-in-mesoblast-rights-to-adult-stem-cell-therapies.html>.

³²⁵ Parson A (2006) The long journey from stem cells to medical product *Cell* **125(1)**: 9-11.

Venture capital

- 3.36 Venture capital (VC) is a key source of funding for the development of novel neurotechnologies.³²⁶ There has already been significant investment from venture capitalists in this field, and it has been estimated that in 2011, this amounted to over \$1.63 billion.³²⁷ Approximately \$646 million (52%) of this neurotechnology funding was in neurodevice companies at the late stages of development.³²⁸ However, during a factfinding meeting, it was suggested to the Working Party that the large amount of VC investment in this area is due to smaller companies – in which venture capitalists had already invested – lacking exit capability, and thus retaining their dependence on VC funding, rather than due to an increase in the number of ideas or companies in which to invest.³²⁹ The standard route for the progress of novel neurotechnological products from early stage research to scaled-up production and marketing is via acquisition by a large company. It was suggested that the reason VC investment remains high may be explained by, in these cases, the difficulty of establishing intellectual property meaning that they were not attractive acquisition targets for large medical device companies.³³⁰
- 3.37 While VC investment – with its willingness to take risks in the hope of large returns – can potentially play a key role in addressing unmet need, it can also make developers highly dependent on the decisions of the investor. Investors may wish to steer developments into areas with which they are more familiar, or where they consider that the market is more mature or offers more opportunities; if the scientists and researchers who initiate the start-up company are unable or unwilling to move in this direction, future investment may be curtailed.³³¹ Such decisions, in favour of a developed and established market rather than a new and risky one, may undermine the need for innovation in this area, and instead focus development on small improvements in familiar technologies, rather than on novel approaches.
- 3.38 Investment in non-therapeutic products could potentially have positive repercussions for the development of BCI technologies that might also be applied to therapeutic or assistive purposes. BCI companies Neurosky and Emotiv, both of whom focus on entertainment and performance BCIs, in 2010, received over \$10 million in VC funds.³³² The prospects for the therapeutic market could grow significantly as more capable and practical systems are developed.³³³ However, in the near future, assistive BCIs are likely to remain available to only a small number of people³³⁴ meaning that companies developing assistive BCIs may find it difficult to attract VC funding.
- 3.39 In contrast to neurodevices, private and VC investment has been deterred by the particular challenges of bringing stem cell based therapies to market.³³⁵ In addition to general problems associated with translating advances in brain research into therapeutic applications, neural stem cell products, unlike novel neurodevices, have to satisfy stringent regulatory criteria that apply to ‘advanced therapeutic medicinal products’ (ATMPs), which are similar to those that

³²⁶ Ernst & Young (2012) *Beyond borders: global biotechnology report 2012*, available at: [http://www.ey.com/Publication/vwLUAssets/Beyond_borders_2012/\\$FILE/Beyond_borders_2012.pdf](http://www.ey.com/Publication/vwLUAssets/Beyond_borders_2012/$FILE/Beyond_borders_2012.pdf), at page 39.

³²⁷ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 22.

³²⁸ *Ibid.*

³²⁹ Factfinding meeting on industry and investment, 16 February 2012.

³³⁰ Factfinding meeting on industry and investment, 16 February 2012; NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 256.

³³¹ Factfinding meeting on industry and investment, 16 February 2012.

³³² Future BNCI (2012) *Future BNCI: A Roadmap for Future Directions in Brain / Neuronal Computer Interaction Research*, available at: http://future-bnci.org/images/stories/Future_BNCI_Roadmap.pdf, at page 107.

³³³ Frances J. R. Richmond and Gerald E. Loeb (2012) Dissemination: getting BCIs to people who need them, in *Brain-Computer Interfaces: Principles and Practice*, Wolpaw J, and Wolpaw EW (Editors) (New York: Oxford University Press), at page 349.

³³⁴ *Ibid.*

³³⁵ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 377. See also footnote 309 above.

apply to traditional pharmaceuticals.³³⁶ Furthermore, the need to satisfy the assessment by the specialised ethics committee, the Gene Therapy Advisory Committee (GTAC). These factors have, historically, had the potential to cause delays for product research and development (see paragraphs 7.70 to 7.71 for further discussion).

- 3.40 In comparison to pharmaceutical products and most neurodevices, investors are also confronted by the prospect of high costs of manufacturing neural stem cell therapies. Laborious manufacturing processes, batch testing, shipping costs, shelf life, staff turnover and patentability of products all contribute to a rise in production costs which effectively reduce profit margins.³³⁷ Venture capitalists are also reluctant to invest in technologies that have extended development trajectories³³⁸ (for example, those extending over more than ten years); this category of investor rarely sees a product through to market and is far more likely to seek a trade sale, an option which is currently limited due to factors such as the financial crisis and lower budgets in the pharmaceutical industry.³³⁹

The valley of death

- 3.41 A major problem that affects start-up companies has become known as the ‘valley of death’. This term refers to the difficulty of carrying through research and development from spun-out academic research to commercially-viable innovation.³⁴⁰ In part, these difficulties result from the significant escalation of costs involved in developing, scaling-up and trialling biomedical products, combined with high attrition rates for new products. The problem typically occurs when small spin-out companies find themselves unable to fund further development and potential investors are unwilling to bear the substantial risk involved for the anticipated returns. These potential investors may be large firms who wish to acquire stock or smaller companies with valuable intellectual property in the same field, or they may be venture capitalists. The Nuffield Council’s earlier report on *Emerging biotechnologies* (referring to pharmaceutical companies) noted that:

“It is possible, in principle, for venture capital to bridge this gap but it is hard and/or unacceptable in practice, because venture capitalists demand a very large stake in return for their investment. There may be specific reasons for the limitations of venture capital in the UK, but the problem is clearly worldwide. The exorbitant terms of venture capital funding arise from their perception of risk (which depends on their understanding of the technology and the market).”³⁴¹

- 3.42 Venture capitalists may also show increasing reluctance to invest in biotechnologies owing to historically poorer-than-expected returns and external economic conditions. In particular, they may perceive earlier translational stages of development to be too risky and prefer to invest at a later stage, when products are closer to market and the risks are perceived as lower.³⁴²

³³⁶ MHRA (2013) *How we regulate advanced therapy medicinal products*, available at: <http://www.mhra.gov.uk/Howweregulate/Advancedtherapymedicinalproducts/Aboutadvancedtherapymedicinalproducts/index.htm>.

³³⁷ Parson AB (2008) Stem cell biotech: seeking a piece of the action *Cell* **132(4)**: 511-3; Working Knowledge: Harvard Business School (2011) *Funding unpredictability around stem-cell research inflicts heavy cost on scientific progress*, available at: <http://hbswk.hbs.edu/item/6601.html>; Malik N (2012) Allogeneic versus autologous stem-cell therapy *BioPharm International* **25(7)**: 36-40

³³⁸ Parson AB (2008) Stem cell biotech: seeking a piece of the action *Cell* **132(4)**: 511-3, at page 511.

³³⁹ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 394.

³⁴⁰ House of Commons Science and Technology Committee (2013) *Bridging the valley of death: improving the commercialisation of research*, available at: <http://www.publications.parliament.uk/pa/cm/201213/cmselect/cmsctech/348/348.pdf>, at paragraph 9.

³⁴¹ Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf, at page 164.

³⁴² NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), p374.

3.43 Recently, the problem posed by the valley of death has been discussed by the UK Parliament's Science and Technology Select Committee.³⁴³ The Committee heard evidence from several people, including Sir David Cooksey, author of the Cooksey Report.³⁴⁴ In his evidence, he remarked:

“[I]n order to make the valley of death crossable you need to have finance to do it in the first place... If you look today at the successful venture capital firms, they are the ones that are investing at the later stages of the process, as the company comes up the other side of the valley of death, and the real problem is getting from there to where you see the growth beginning to take place.”³⁴⁵

3.44 In a well-known example from the US, Geron (a US-based biopharmaceutical company) sought permission from the FDA to begin a clinical trial of a therapy using human embryonic stem cells (hESCs) to treat spinal cord injury. The process of gaining approval for the trial took several years,³⁴⁶ with Geron required to submit a 21,000-page application to the FDA.³⁴⁷ This trial aimed only to test the *safety*, rather than the *efficacy* of the therapy, and involved injecting cells into the spinal cord of between eight and ten individuals.³⁴⁸ The trial began in October 2010, but by July 2011, after treating just four patients, Geron announced that it had abandoned the trial on financial grounds:³⁴⁹ the projected returns from investment in stem cell research – which was high risk, at early stages, and therefore quite distant from the market – were less than those anticipated from investing the same resources in therapies that were closer to market applications. This decision was understandable in the context of the company's obligations to its shareholders, however it resulted in the termination of a potentially important clinical application.

3.45 As the Geron example shows, costs incurred at the preclinical/clinical interface can be vast, especially for companies which, like Geron, seek to develop genuinely innovative technologies in a heavily-regulated field such as stem cells. In other areas of neurotechnology research, however, some small neurodevice companies have had success in bridging the gap. For example Neuronetics developed the first repetitive transcranial magnetic stimulation³⁵⁰ (rTMS) device (NeuroStar TMS Therapy[®]) to be licensed by the FDA in 2008 for use to treat depression in the US. So far, 270 of these devices, each of which is worth \$70,000, have been sold.³⁵¹ In the UK the NHS National Institute for Health Research's Healthcare Technology Co-operatives operates with the specific aim of encouraging collaborations between industry, patients, charities and academic researchers to develop new medical devices and technology-dependent interventions to address areas of serious illness and unmet need for NHS patients.³⁵²

3.46 As the problems of translation at the preclinical/clinical interface have been increasingly recognised, measures have been introduced in the UK to try to alleviate this situation. These include the £180 million Biomedical Catalyst funding programme operated by the Medical

³⁴³ House of Commons Science and Technology Committee (2013) *Bridging the valley of death: improving the commercialisation of research*, available at:

<http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/348/348.pdf>.

³⁴⁴ HM Treasury (2006) *A review of UK health research funding*, available at:

<https://www.bioin.or.kr/upload/industry/1192426342312.pdf>

³⁴⁵ House of Commons Science and Technology Committee (2011) *Bridging the valley of death: improving the commercialisation of research*, available at:

<http://www.publications.parliament.uk/pa/cm201213/cmselect/cmsctech/348/348vw.pdf>, at Ev40.

³⁴⁶ The New York Times (23 January 2009) *FDA approves a stem cell trial* available at:

http://www.nytimes.com/2009/01/23/business/23stem.html?_r=0.

³⁴⁷ Nature Newsblog (18 October 2012) *Former Geron execs bid for abandoned stem cell programme*, available at:

<http://blogs.nature.com/news/2012/10/former-geron-execs-bid-for-abandoned-stem-cell-program.html>.

³⁴⁸ The New York Times (23 January 2009) *FDA approves a stem cell trial* available at:

http://www.nytimes.com/2009/01/23/business/23stem.html?_r=0.

³⁴⁹ The Guardian Online (15 November 2011) *Geron abandons stem cell therapy as treatment for paralysis*, available at:

<http://www.guardian.co.uk/science/2011/nov/15/geron-abandons-stem-cell-therapy>.

³⁵⁰ rTMS, refers to a variant of TMS, repetitive transcranial magnetic stimulation.

³⁵¹ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 283.

³⁵² NIHR (2008) *Healthcare technology co-operatives*, available at: <http://www.nihr.ac.uk/infrastructure/Pages/HTCs.aspx>.

Research Council (MRC) and the Technology Strategy Board (TSB) with the aim of helping small and medium sized enterprises (SMEs) and academics with innovative products to bridge the translational gap.³⁵³ The similarly aimed Cell Therapy Catapult has a core grant of £70 million from the TSB.³⁵⁴ While these funds are significant, are not sufficient to cover the funding gap that currently faces biomedical initiatives that are unable to obtain private funding to take them through this stage in the translation process. Hence, in the current situation, it is likely that many potentially useful novel neurotechnologies at the research stage, or in development by start-up companies, will fail because they cannot negotiate ‘the valley of death’. This seems particularly true in the field of stem cell research, where costs are high, and the risks for investors are often perceived as formidable.

- 3.47 The ability for companies to bridge the valley of death is a source of concern in the context of this report not because of the survival of these enterprises themselves, but because the failure of promising therapeutic innovations to translate into marketable products affects the well-being of patients who lack other therapeutic products. Despite the expectations and anticipations that characterise the market for novel neurotechnologies, it is by no means clear that the market, as it is currently structured, has proved the best mechanism for bringing therapeutic technologies to the clinic. We suggest that the combined effects of the complexity of the brain, lack of incentives where patient populations are small, the perceived risks of investment in stem cell technologies, navigating regulatory requirements, the focus of public investment on economic benefit and the short-termism of VC, mean that the market mechanism runs the risk of combining exaggerated promises with failure to deliver.

Market-driven development and the need for safe and effective treatment

- 3.48 So far in this chapter, we have looked at different approaches to characterising unmet need and at how the novel neurotechnology market strives, to varying degrees of success, to address this need. Where funding *is* secured, there is usually an associated imperative to make a profit in a specific timeframe. A number of familiar techniques are used to monetise innovations in neurotechnology, some of which have significant social and ethical implications; it is to these that we now turn. While our main geographical focus in this report is on the UK, it is relevant here to discuss some US examples, given the key role that the US plays in the research and development of novel neurotechnologies.

Intellectual property

- 3.49 One of the main ways that commercial companies may derive revenue from a product or process, by protecting market share from potential competitors, and displaying a product’s viability to potential funders, is through exercising intellectual property rights (IPR).³⁵⁵ Mechanisms of protection include patents, trade secrets, design rights, regulatory data protection or marketing exclusivity.³⁵⁶ There are significant differences between different intellectual property (IP) regimes in different regions. For example, in Europe, surgical, therapeutic or diagnostic instruments or devices can be patented, but novel methods for

³⁵³ The £180 million Biomedical Catalyst is operated jointly by the MRC and TSB, with the intention of providing support to life science opportunities arising in the UK. See: Medical Research Council (2012) *Biomedical catalyst: developmental pathway funding scheme (DPFS)*, available at: <http://www.mrc.ac.uk/Fundingopportunities/Grants/DPFS/index.htm>.

³⁵⁴ Cell Therapy Catapult (2013) *The cell therapy catapult: the UK’s initiative to accelerate the development of cell therapies*, available at: http://www.cirm.ca.gov/sites/default/files/files/about_cirm/04_Mount_CriticalPathWorkshop.pdf, at page 8.

³⁵⁵ For example CellFactors, a UK biotechnology company founded in 1997 had IP in both the US and in Europe on its method to produce and immortalise human neural stem cell lines. It raised a total of £7 million to develop this work over seven years, and passed a number of pre-clinical milestones, but was unable to attract further funding, and went into administration in 2004. See: BioSpace (2005) *CellFactors plc enters administration*, available at: <http://www.biospace.com/News/1-enters-administration/16873420>.

³⁵⁶ IP issues relating to biotechnologies are discussed in more detail in Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice and the public good*, available at: http://www.nuffieldbioethics.org/sites/default/files/Emerging_biotechnologies_full_report_web_0.pdf, pp.156-61.

treatment cannot. However, in the US, it is possible to patent a procedure, thus associating neurotechnology with a medical application.³⁵⁷

- 3.50 Stem cell therapies again pose specific issues, distinct from neurodevices, that may deter investors and thus hinder the pathway to clinical applications. In 2011, the Court of Justice of the European Union ruled that patenting products derived from human embryos was prohibited in Europe, and this would apply to neural stem cells derived from such material, although not to those developed by other means (such as iPS).³⁵⁸ However, the German Federal Court has already narrowed this prohibition (within its own jurisdiction) to products that *directly* entail the destruction of embryos.³⁵⁹ Further, there may be more effective options than patents by which developers can protect market share. The chief purpose of a patent is to prevent competition from generic products, but it will be virtually impossible for a stem cell therapy to receive regulatory approval as a 'generic' due to the near impossibility of showing that the second product is bioequivalent to the original.³⁶⁰ In addition, the valuable intellectual assets in this field are as likely to be located in the processes of manufacturing products as in the cell lines themselves. Aspects of these processes could themselves be patentable, but much of the value may well be the technical 'know-how' which is amenable to protection as confidential trade secrets and regulatory exclusivity afforded by statute to new medicinal products.³⁶¹ Finally, the originator of a cell line should be able to exert control as a result of appropriate terms of access of the physical cell line itself. It is thus too early to evaluate the effect of the European Court of Justice ruling on the development of neurotechnologies based on stem cells.
- 3.51 In contrast, where neurodevices are concerned, patents are likely to remain a relevant form of protection of IPR. In the UK, patent rights last for up to 20 years and make it illegal for anyone except the owner or someone operating under licence from the owner, to use, make, import or sell the invention in the country where the patent is in force.³⁶² Unlike ATMPs, medical devices are likely to have shorter development periods and be subject to rapid incremental modifications. This can be both a boon and a limitation for the use of patent rights. Shorter development periods mean that rights may be secured more quickly; in contrast, mere incremental modifications might not meet the stringent requirements for patentability which include the need to show that an invention is 'novel' and embodies an 'inventive step', that is, it is an advance in the field that would be a non-obvious advance to a relevant expert.³⁶³ For

³⁵⁷ In *Mayo v Prometheus* 132 S Ct 1289 (2012), the Supreme Court ruled that a patent for a method of drug delivery was non-patentable as an example of natural law: "[T]he claims inform a relevant audience about certain laws of nature; any additional steps consist of well-understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately. For these reasons we believe that the steps are not sufficient to transform un-patentable natural correlations into patentable applications of those regularities." Jeffer Mangels Butler & Mitchell LLP (2012) *Mayo collaborative services, , dba mayo medical laboratories, et al., petitioners v. prometheus laboratories, Inc*, available at: <http://www.jmbm.com/docs/mayovprometheus.pdf>, at page 11.

³⁵⁸ InfoCuria: Case-law of the Court of Justice (2011) *Oliver Brüstle v Greenpeace e.V. (C-34/10)*, available at: <http://curia.europa.eu/juris/document/document.jsf?text=&docid=111402&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&part=1&cid=1520913>. This decision does not impact the patentability of therapies based on autologous cells or other allogeneic cells, nor does it affect the patentability of hESC therapies outside Europe. See: Harmon SH, Laurie G and Courtney A (2013) Dignity, plurality and patentability: the unfinished story of *Brüstle v Greenpeace* *European Law Review* 92-106.

³⁵⁹ BioNews (3 December 2012) *German court upholds Brüstle patent as valid*, available at: http://www.bionews.org.uk/page_222080.asp.

³⁶⁰ House of Lords Select Committee on Science and Technology (2012) *Regenerative medicine*, available at: <http://www.parliament.uk/documents/lords-committees/science-technology/RegenerativeMedicine/ucST271112ev8.pdf>, at page 3.

³⁶¹ These may include regulatory data exclusivity. See: Article 10 of the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. For orphan drug designation, see: European Medicines Agency (2010) *Orphan incentives*, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000393.jsp.

³⁶² Intellectual Property Office (2011) *Patents: basic facts*, available at: <http://www.ipo.gov.uk/p-basicfacts.pdf>, at page 6.

³⁶³ *Ibid*, at page 8.

these reasons, design rights (which do not have such exacting requirements) might be more effective for neurodevice developers.³⁶⁴

- 3.52 Some of the limits of patent law can be seen, for example, with TMS and TDCS, which are underpinned by simple physics, and which make use of components that have been in the public domain for many years. Since the potential to exploit IP is often a priority for investors, some argue that the inability to protect IP makes it difficult for companies, especially smaller ones, to attract funding to develop their products and bring them to market, or to become attractive targets for acquisition by larger companies. It also means that research on product development is inadequately protected, and innovations can be made use of by other, particularly larger, competing companies.³⁶⁵
- 3.53 The fact that many components of a medical device may not be the novel inventions of the developer, but long-established technologies, or used under licence from other patent holders, sometimes leads companies to seek other ways to introduce elements that will secure them market share. For example, some companies may make minor modifications to their product which, while therapeutically unnecessary, can provide the basis for a patent application.³⁶⁶ Unlike pharmaceuticals, there are rarely consumables associated with devices, and indeed, unlike pharmaceuticals, a single device may be used to treat many patients over an extended period of time without generating additional revenue for the company. Developers may also seek to incorporate therapeutically superfluous consumable elements into a technology to enable the company to generate funds from repeated sales.³⁶⁷ While this might be regarded as cynical, it may actually provide some of the necessary conditions for the financial survival of the company in question. It therefore has an understandable economic rationale in a highly competitive field. Nevertheless, it is not always clear that it provides patient benefit.
- 3.54 In established medical technology markets, such as those for cardiac stents and valves, for spinal surgical implants, or for artificial joints, very small modifications are often made in the search for products that can claim greater efficacy.³⁶⁸ This characteristic of the medical device market is one reason for the high number of patent disputes. Companies are frequently involved in lawsuits claiming that others have infringed their patents on these minor improvements, with lawsuits used either to seek compensation or to delay the marketing of competitors' products.³⁶⁹ Such lawsuits often continue for many years with multiple appeals used to overturn rulings, and numerous countersuits; they rarely drive one of the parties out of the market, and often end with one of the parties paying large sums in compensation, and the parties subsequently collaborating as owners and licensees.³⁷⁰ These characteristics of the device market are hardly conducive to innovation by small companies, which are constantly open to predation by larger companies, which can afford to pay any compensation that is awarded.³⁷¹

³⁶⁴ Design Rights are the legal protection that permit those who hold them to prevent others from copying the three dimensional shape or configuration of an original design.

³⁶⁵ Brown N and Webster A (2004) *New medical technologies and society: reordering life* (Cambridge: Polity).

³⁶⁶ Factfinding meeting on industry and investment, 16 February 2012.

³⁶⁷ Factfinding meeting on industry and investment, 16 February 2012. An example was cited at this meeting, which noted that Neuronetics included a consumable plastic shield in its TMS device to enable it to claim patent protection: while this may appeal to patient or physician concerns about hygiene, it does not improve the performance of the device.

³⁶⁸ For example see: Frey M, Manchikanti L, Benyamin R *et al.* (2009) Spinal cord stimulation for patients with failed back surgery syndrome: A systematic review *Pain Physician* **12**: 379-97, at page 380; Mohandas A and Foley K (2010) Medical devices: adapting to the comparative effectiveness landscape *Biotechnology Healthcare* **7(2)**: 25-8.

³⁶⁹ JSDUPRA Law News (2012) *Medical device industry remains a hotbed for non-compete litigation*, available at: <http://www.jdsupra.com/legalnews/medical-device-industry-remains-a-hotbed-33002/>; Non-Compete and Trade Secrets (2013) *Mediating non-compete disputes in the medical device industry*, available at: <http://www.noncompetenews.com/post/2013/03/17/Mediating-Non-Compete-Disputes-in-the-Medical-Device-Industry.aspx>.

³⁷⁰ For example, see: Bloomberg (21 September 2011) *Medtronic wins \$101 million award from NuVasive over spinal device patents*, available at: <http://www.bloomberg.com/news/2011-09-20/medtronic-nuvasive-infringed-each-other-s-patents-jury-finds.html>.

³⁷¹ Perhaps the best know case is that of the LA surgeon, Dr. Michelson, whose patent disputes with Medtronic resulted, after four years, in a \$1.35 billion award paid by Medtronic to Dr. Michelson in 2005: £550 million to settle the lawsuit, plus \$800 million to acquire the patents. The New York Times (April 23, 2005) *Medtronic to pay \$1.35 billion to inventor*, available at: http://www.nytimes.com/2005/04/23/business/23medronic.html?_r=1&.

Exploiting regulatory measures – medical devices

- 3.55 Delays in gaining market approval may have significant impact on profits as well as reducing ‘first mover’ advantage in a highly competitive market, given the time limit on patents and the rapid rate at which incremental innovation in the device sector can progress. This may be a particular issue for start-up companies funded by VC, where the timeframe for recovery of investment is usually a few years. This creates incentives for companies to use the fastest available routes to market which make the least amount of demands on companies to provide evidence or, indeed, to conduct their own, costly, clinical investigations.
- 3.56 As we discuss in more detail in Chapter 7, the regulatory system for medical devices in Europe entails relatively (in comparison to that in the US, for example) light touch pre-market requirements for evidence. It does not oblige manufacturers to produce data demonstrating a device’s efficacy before it may be placed on the market.³⁷² There is some anecdotal evidence that this may attract device manufacturers to enter the market in Europe first, rather than undertake the more onerous pre-market approval process in the US,³⁷³ which uses a procedure analogous to new pharmaceuticals, requiring valid scientific evidence (usually based on clinical trials) that demonstrates both safety and efficacy.³⁷⁴
- 3.57 Moreover, devices classed as medium risk under the European Medical Devices Directive (such as those delivering TMS) can be approved without additional clinical investigations if a similar ‘predicate’ device is already on the market.³⁷⁵ Approval can be granted if the manufacturer can provide literature showing that their device’s safety and performance are substantially equivalent to the existing device that already has market approval.³⁷⁶ A similar ‘predicate’-based route is also available under the US FDA premarket notification system for devices considered to be lower risk: a process often referred to as 510(k).³⁷⁷ In the context of the US system, which generally requires efficacy data, 510(k) is seen to be particularly lenient. One criticism levelled at the 510(k) route in the US is that termed “predicate creep”, by which devices can be approved through claiming they have the ‘same intended use’ as other devices that were themselves approved via substantial equivalence, leading to the expansion of reasonable equivalence.³⁷⁸
- 3.58 While these routes may be in manufacturers’ immediate economic interests, and potentially enable devices to be made available to patients more swiftly, they could also be criticised for placing the interests of the market above patients’ safety and their need for effective interventions.³⁷⁹ These routes might also encourage an approach to product development that fails to foster innovations that bring additional benefits to patients. It has been suggested that investors might be particularly attracted to the development of devices that, by reason of their similarity to products already on the market, could demonstrate compliance with regulatory

³⁷² Cohen D and Billingsley M (2011) Europeans are left to their own devices *British Medical Journal* **342:d2748**: 1-7, at page 2.

³⁷³ Medtronic (2012) *Grand designs – how to take your medical device innovation from patent to production*, available at: http://www.medtronic-eureka.com/innovation-articles/making-it-happen/patent_to_production.

³⁷⁴ FDA (2013) *Overview of device regulation*, available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/overview/default.htm#pma>.

³⁷⁵ Annex 5 of the Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (MDD).

³⁷⁶ Cohen D and Billingsley M (2011) Europeans are left to their own devices *BMJ* **342:d2748**, at page 2; European Commission (2009) *Clinical evaluation: a guide for manufacturers and notified bodies*, available at: http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_1rev_3_en.pdf, at page 8.

³⁷⁷ US Food and Drug Administration (2009) *510(k) clearances*, available at: <http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/510kclearances/default.htm>.

³⁷⁸ Hines JZ, Lurie P, Yu E and Wolfe S (2010) Left to their own devices: breakdowns in United States medical device premarket review *PLoS Medicine* **7(7)**: e1000280, at page 4.

³⁷⁹ Cohen D and Billingsley M (2011) Europeans are left to their own devices *BMJ* **342:d2748**.

requirements and so reach market without the need for additional pre-market testing.³⁸⁰ This raises the possible risk that the availability of predicate routes, and the willingness of manufacturers to exploit them, could have a chilling effect on the kinds of innovation that might fill the most important gaps in the market for genuinely novel devices that address unmet patient needs.

- 3.59 In the US, the Humanitarian Device Exemption (HDE) is a regulatory route intended to incentivise innovation to address unmet need through the development of devices for the treatment or diagnosis of diseases that affect fewer than 4,000 people in the US per year. An HDE application made to the FDA does not require any evidence that the device is effective for its intended purpose, but must convince the FDA that the device does not pose an “unreasonable or significant” risk and that the potential benefit outweighs the risk.³⁸¹ However, concerns have been raised in the US about misuse of the HDE; particularly where it was invoked for a DBS device intended to treat OCD. It is questionable whether OCD can be considered an ‘orphan’ condition when the population of people affected by the disorder in the US far exceeds 4,000.³⁸² Moreover, it has been observed that the HDE effectively removes the requirement for a device to undergo clinical trials and may be seen to be enabling the manufacturer to access patients, rather than providing patients with access to therapies grounded in sound scientific evidence.³⁸³
- 3.60 The regulatory routes described above are intended to support innovation by reducing requirements for pre-market evidence and thus seeking to make development trajectories swifter and less costly. This might serve to make a therapeutic product more attractive to investors and help it to reach market – and patients – more swiftly (or at all). However, this is not a desirable outcome unless it also provides sufficient protection to patients’ interests in accessing treatments that have been demonstrated to be safe (and, ideally, effective) by robust clinical evidence. This serves to illustrate the point that difficulties faced by developers in securing sufficient funds to bring a product to market are not the only kind of challenge to patients accessing the kinds of treatment they need. This produces a dilemma: how can the need to stimulate innovation to provide much needed therapeutic products be reconciled with ensuring that patients’ wider interests in the safety and efficacy of these products are protected? We discuss the efficacy and proportionality of the regulation of medical devices in Europe and the US in more detail in Chapter 7.

Selling devices to the NHS

- 3.61 Regulatory approval is prerequisite for monetising devices and medicines, but it is not sufficient. One of the most important ways of capitalising on a novel technology is by ensuring successful sales within a healthcare market. This can be particularly difficult for technologies that are expensive, such as ATMPs, or that lack comprehensive efficacy data, as is the case for most novel devices.
- 3.62 NICE’s technology appraisals make recommendations relating to the use within the NHS of new and existing medicines and treatments.³⁸⁴ The NHS is unlikely to provide medicines that are not recommended by NICE. One of the major barriers to neural stem cell therapies (once any are

³⁸⁰ Royal Academy of Engineering and The Academy of Medical Sciences (2013) *Establishing high-level evidence for the safety and efficacy of medical devices and systems* available at: http://www.raeng.org.uk/Medical_devices_and_systems.pdf, at page 17.

³⁸¹ US Food and Drug Administration (2012) *Humanitarian Device Exemption*, available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/default.htm>.

³⁸² Fins estimates that there are 440,000-660,000 people with chronic, severe and treatment-resistant OCD. See: Fins JJ, Mayberg HS, Nuttin B *et al.* (2011) Misuse of the FDA Humanitarian Device Exemption in deep brain stimulation for obsessive-compulsive disorder *Health Affairs* **30(2)**: 302-11, at page 304.

³⁸³ *Ibid*, at page 306.

³⁸⁴ NICE technology appraisals are only relevant for the NHS in England and Wales. See: NICE (2012) *About technology appraisals*, available at: http://www.nice.org.uk/aboutnice/whatwedo/abouttechnologyappraisals/about_technology_appraisals.jsp.

licensed) being made available through the NHS is that such treatments are likely to be expensive due to manufacturing complexity, resource requirement, high labour costs and timescales. To justify such an expense, NICE will require returns such as life-changing treatment or cure.³⁸⁵ Attempts are being made to provide some recourse for both developers and potential users of novel medicines, which could potentially include stem cell therapies. For example, in 2012 the MHRA launched a public consultation on an Early Access Scheme for Medicines in the UK. The intention of the scheme is to create a more “progressive regulatory environment” while also providing earlier access to treatments for people with serious life threatening or debilitating illnesses.³⁸⁶ However, the MHRA estimate that based on eligibility criteria, it is unlikely that more than one or two medicines each year will become available via an early access route.³⁸⁷

- 3.63 Unlike medicines, which require significant data from clinical trials before being granted a licence, medical devices are available for purchase and use in the NHS with comparatively little research data, which can make them less amenable to early assessment by NICE’s evidence-based technology appraisals. Alternative assessment options include NICE’s Medical Technologies Evaluation Programme (MTEP) for new or innovative technologies; if the technology receives a positive assessment, NICE encourages its use through guidance (although unlike technology appraisals, it does not *oblige* provision). However, MTEP still requires significant amounts of data and, to date, has only published 13 pieces of guidance.³⁸⁸
- 3.64 In the absence of NICE guidance, interventional procedures³⁸⁹ are often adopted in a haphazard way. A recent study found that, in most cases, the introduction of such technologies was initiated by clinicians,³⁹⁰ a further study notes that hospitals often buy novel devices *directly* from the manufacturer without the knowledge of NHS commissioners.³⁹¹ The consequence for patients is that access to expensive novel neurotechnologies has been variable between NHS Trusts. For example, people with the same indications for Parkinson’s disease will not necessarily have been afforded the same DBS treatment throughout the NHS.

Box 3.3: Specialised Services Commissioning Innovation Fund

In December 2011, *Innovation Health and Wealth*³⁹² announced the introduction of the Specialised Services Commissioning Innovation Fund (SSCIF). The fund is intended to provide a clear pathway for novel technologies to enter the NHS where there is not yet sufficient evidence available to justify full commissioning of the technology. The fund will be launched in the summer of 2013 with funding of £50-5m until April 2014. Applications will be online, with Clinical Reference Groups³⁹³ assessing their viability.

³⁸⁵ Very expensive drugs that lead to only a few months of extra life are unlikely to be recommended by NICE: this has led to high profile controversies, especially in relation to drugs for late stage cancer. See: BBC (2 February 2012) *NICE: Prostate cancer drug too costly for NHS*, available at: <http://www.bbc.co.uk/news/health-16838825>; NICE (2013) *Breast cancer treatment not value for money says draft NICE guidance*, available at: <http://www.nice.org.uk/newsroom/pressreleases/BreastCancerTreatmentNotValueMoney.jsp>.

³⁸⁶ MHRA (2012) *Consultation on a proposal to introduce an early access to medicines scheme in the UK*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/websiteresources/con173756.pdf>.

³⁸⁷ MHRA (2012) *Earlier market access for medicines in the UK: impact assessment*, available at: <http://www.mhra.gov.uk/home/groups/es-policy/documents/websiteresources/con173758.pdf>, at page 22.

³⁸⁸ NICE (2013) *Medical Technologies Evaluation programme*, available at: <http://www.nice.org.uk/aboutnice/whatwedo/aboutmedicaltechnologies/medicaltechnologiesprogramme.jsp>.

³⁸⁹ Interventional procedures are technologies used for diagnosis or treatment involving an incision, puncture, entry into the body cavity or the use of electromagnetic radiation.

³⁹⁰ Lourenco T, Grant AM, Burr JM and Vale L (2011) The introduction of new interventional procedures in the British National Health Service—A qualitative study *Health Policy* **100**(1): 35-42, at page 38.

³⁹¹ Health Service Journal (22 February 2012) *Embracing new technologies can drive innovation in healthcare services*, available at: <http://www.hsj.co.uk/resource-centre/best-practice/qipp-resources/embracing-new-technologies-can-drive-innovation-in-healthcare-services/5041593.article?sm=5041593>.

³⁹² NHS (2011) *Innovation, health and wealth: accelerating adoption and diffusion in the NHS*, available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_134597.pdf.

³⁹³ NHS Commissioning Board (2013) *Clinical reference groups for specialised services: a guide for clinicians*, available at: <http://www.england.nhs.uk/wp-content/uploads/2013/01/crg-guide.pdf>.

- 3.65 Apart from concerns about equity of access, the lack of a clear pathway for the introduction of novel devices militates against best practice (such as systematic and comprehensive data collection) and ensuring that clinicians build their experience of the device by treating lots of patients. Such pitfalls may be intensified in the case of novel treatments for neurological diseases, where patients' desperation makes them exceptionally vulnerable to the promise of a novel or experimental treatment. However, in April 2013, NHS England took responsibility for specialised services³⁹⁴ (previously commissioned by 10 Specialised Commissioning Groups). One outcome of this more centralised approach will be the intention to reduce variation in the availability of services, including those novel technologies used to treat neurological and mental health conditions.

“[D]rugs/devices will only be funded if they are endorsed within a national clinical commissioning policy and the patient meets the agreed criteria. Those excluded drugs/devices that are either not NICE approved and/or endorsed within a national clinical commissioning policy can be considered via an individual funding request. However, where the intervention relates to a cohort, a business case will be required. Excluded drugs/devices recommended within a NICE IPG and/or guideline will not be routinely funded unless endorsed within a national clinical commissioning policy.”³⁹⁵

Conflicts of interest

- 3.66 The role of clinicians in the development of devices raises particular concerns that do not arise to the same extent in the context of pharmaceuticals, largely because the development of medical devices is far more reliant on clinicians' experience. In this context, particular attention has focused on the close financial links between the companies and clinicians and surgeons, especially those carrying out clinical trials.³⁹⁶ Clinicians are often involved in the conceptualisation, invention, and development of devices, and frequently advise companies on the further development of a device into a commercial product. They often act as enthusiastic promoters for these devices.³⁹⁷ Links between clinicians and companies may be strengthened by the provision of educational grants from those companies to enable further device development, which the company in turn hopes to develop into an improved marketable product. Moreover, far more than with pharmaceuticals, the success of a device relies on training and surgical skill to ensure intended clinical outcomes and hence market authorisation. Indeed, clinicians are often dependent on industry to produce the devices that they wish to use in their research.³⁹⁸
- 3.67 However, conflicts of interest in relation to non-neurotechnological medical devices have been highlighted by a number of researchers and doctors. Thus, for example, consultant cardiologist Peter Wilmschurst has argued that:

“...technical skills allow some clinicians to appreciate a gap in the market and conceive a design. They may have built and tested prototypes... They may have done initial *in vivo* animal or human trials. They or their employing hospital often owns the patent for the device and gets royalties for its sale. They may have

³⁹⁴ There are four factors that will determine whether NHS England commissions a service as a prescribed specialised service: 1) The number of individuals who require the service; 2) The cost of providing the service or facility; 3) The number of people able to provide the service or facility; and 4) The financial implications for Clinical Commissioning Groups (CCGs) if they are required to arrange for provision of the service or facility.

³⁹⁵ NHS Commissioning Board (2012) *Prescribed specialised services: commissioning intentions for 2013/14*, available at: <http://www.commissioningboard.nhs.uk/files/2012/11/comm-int.pdf>, pp.28-9.

³⁹⁶ La Violette PA (2007) Medical devices and conflict of interest: unique issues and an industry code to address them *Cleveland Clinical Journal of Medicine* **74(Sup2)**: S26-8.

³⁹⁷ Cohen D (2011) Out of joint: the story of the ASR *British Medical Journal* **342**:d2905.

³⁹⁸ Fins JJ, Schlaepfer TE, Nuttin B *et al.* (2011) Ethical guidance for the management of conflicts of interest for researchers, engineers and clinicians engaged in the development of therapeutic deep brain stimulation *Journal of Neural Engineering* **8(3)**: 1-6, at page 2.

founded a company to develop the device or sold or leased the rights to a commercial company.”³⁹⁹

Further, Wilmshurst argues that, following the granting of a licence, doctors act as part of the “company’s marketing arm”, cascading skills to other doctors to increase the take up of the device in question, acting as “paid investigators in clinical trials” of the devices and, in return, receiving shares in the company that they are investigating.⁴⁰⁰ It has been suggested that the sums that clinicians can generate by these means, in some cases, amount to millions of dollars.⁴⁰¹ Related research has claimed that, in some cases, direct payments have been made by manufacturers to clinicians for the use of their devices;⁴⁰² in some cases clinicians may be reluctant to report complications that arise from the use of the devices for reasons that include a fear of damaging their relations with the manufacturers.⁴⁰³

- 3.68 In the context of neurodevices, the relatively small market intensifies the monopolistic environment and hence the potential for pressures to be exerted on clinicians by industry.⁴⁰⁴ Similar risks of conflicts of interest have been examined in relation to DBS; in particular, it has been argued that, where DBS is concerned the situation is exacerbated by the semi-monopolistic relations that obtain between the small number of investigators and small number of companies involved.⁴⁰⁵
- 3.69 Other authors, however, have cast doubt on the extent of these conflicts as applied to neurotechnologies. One article explores the relations between the industry and neurosurgeons, in the light of the criticisms that “surgeon-held patents and royalties incentivise surgeon loyalty, influencing decision making as to which devices are used intraoperatively.”⁴⁰⁶ On the basis of a search of US patent records and the physician payment registries of the largest device makers, the authors of this article found that 147 neurosurgeons (three per cent of the total of 4,868 recognised by the appropriate professional body) held a total of 582 patents and that the royalties expected to be paid to neurosurgeons in 2010 amounted to a little over \$13 million (the lowest payment was a mere \$7,000 while the largest was \$8.261 million). They concluded that, despite public and legislative concerns, in this area at least, the conflicts of interest were limited.⁴⁰⁷ Nonetheless, clearly for some neurosurgeons, they may be significant.
- 3.70 Whether or not neurosurgeons are making profits from inappropriate relations with industry, the potential for mismanagement of conflicts of interest is clearly a significant issue in the medical devices industry. In relation to neurotechnologies that intervene in the brain, the situation is more worrying because, in addition to shaping the developmental pathways in perverse ways, such conflicts of interest may result in devices being brought into clinical use without objective and impartial assessments of safety and efficacy. The difficulties may be exacerbated by the vulnerability brought about by some neurological and mental health conditions, and the potential for overselling the therapeutic benefits of the devices in question to patients who have few, if any, other options.

³⁹⁹ Wilmshurst P (2011) The regulation of medical devices *British Medical Journal* **342**:d2822, at page 1.

⁴⁰⁰ *Ibid.*, at page 1.

⁴⁰¹ *Ibid.*, at page 1.

⁴⁰² Cohen D (2011) Out of joint: the story of the ASR *British Medical Journal* **342**:d2905, at page 1,118.

⁴⁰³ *Ibid.*, at page 1,119.

⁴⁰⁴ Fins JJ, Schlaepfer TE, Nuttin B *et al.* (2011) Ethical guidance for the management of conflicts of interest for researchers, engineers and clinicians engaged in the development of therapeutic deep brain stimulation *Journal of Neural Engineering* **8**(3): 1-6, at page 2.

⁴⁰⁵ Fins JJ and Schiff ND (2010) Conflicts of interest in deep brain stimulation research and the ethics of transparency *The Journal of Clinical Ethics*, **21**(2): 125.

⁴⁰⁶ Babu MA, Heary RF and Nahed BV (2012) Device innovation in neurosurgery: controversy, learning, and future directions *Neurosurgery* **70**(4): 789-5.

⁴⁰⁷ *Ibid.*

Obstacles to accessing treatment

3.71 At the start of this chapter, we illustrated the high and global incidence of disorders that novel neurotechnologies seek to treat. The challenges to securing investment to bring a product to market described earlier in this chapter account for some of the reasons that many who might benefit from novel neurotechnologies do not currently have access to them. However, we cannot assume that investment alone would deliver the neurotechnologies to meet the needs of all of those living with neurological and mental health disorders in a global context. The cost of delivering treatment using many of these technologies presents a further obstacle to access. It is likely, at least for the time being, that even if products *do* secure funding to reach the market, they will be expensive. Approximate indications of the cost of treatments using the neurotechnologies considered in this report are given in Box 3.4.

Box 3.4: Approximate cost of treatments using novel neurotechnologies

DBS: In 2011, the East of England Specialised Commissioning Group (SCG) estimated the average cost of DBS was £33,000 per patient (including surgery, hospital stay and follow-up) and that their eligible disease population was approximately 27, taking the annual cost up to about £891,000 *per annum*. East of England was one of ten specialised groups commissioning DBS (now commissioned by NHS England), and the cost of DBS for Parkinson's disease across England can therefore be estimated as approximately £9 million *per annum*.⁴⁰⁸

Neural stem cell therapies: There are currently no neural stem cell therapies available in the UK and costs are likely to reflect long lead-times for manufacturing and licensing arrangements. NeuroInsights report that companies developing neural stem cell products cite the cost of neurodevices (\$30,000-\$100,000) as a reasonable price point for future stem cell treatments.⁴⁰⁹

TMS: In the US, Neuronetics' TMS device costs approximately \$70,000.⁴¹⁰ A typical course of outpatient TMS therapy involves 20 to 30 sessions, occurring five days a week over a four-to-six-week period. The cost varies from approximately \$300 to \$600 per session.⁴¹¹

BCI: Non-invasive BCIs for therapeutic or assistive purposes are likely to be closer to commercial application than those which are invasive. Multiple factors dictate the price of non-invasive BCIs, including types of electrodes (whether these are active, passive, wet or dry), signal quality, impedance checks, and software. Expensive laboratory systems with higher numbers of electrodes and good signal quality are estimated to cost between \$6,000-14,000.⁴¹² This, however, does not include the personnel costs associated with training of and support for users. Invasive BCIs will inevitably be considerably more expensive, not least because of the costs of neurosurgery.

3.72 Development of neurotechnologies is not, of course, limited to high-income countries. For example there is both research and development of DBS in China and India,⁴¹³ with clinical use of the technology in an increasing number of cases, largely for Parkinson's disease and some other movement disorders.⁴¹⁴ The development of neurotechnology industries in emerging economies and the routinisation of production of neurodevices are likely to contribute to incremental cost reductions. However, the expense of treatment using many of these neurotechnologies is not due only to costs associated with the development and marketing of products themselves.

⁴⁰⁸ NHS East of England Specialised Commissioning Group (2010) *Commissioning policy on the use of deep brain stimulation for Parkinson's disease, tremor and dystonia*, available at: <http://www.derbycitypct.nhs.uk/UserFiles/Documents/DocumentsDownloads/policies/P037V1%20EMSCG%20Policy%20for%20DBS%20V1.pdf>.

⁴⁰⁹ NeuroInsights (2012) *The neurotechnology industry 2012 report* (San Francisco: NeuroInsights), at page 236.

⁴¹⁰ NeuroInsights (2010) *Neurotechnology industry reports revenues of \$143.1 billion in 2009*, available at: <http://www.neuroinsights.com/neurotech2010release.html>, at page 283.

⁴¹¹ *Ibid*, at page 283.

⁴¹² Future BNCI (2011) *A Roadmap for Future Directions in Brain / Neuronal Computer Interaction Research*, at page 217.

⁴¹³ Functional Neurosurgery: Jaslok Hospital (2012) *About Dr. Paresh*, available at: <http://www.neurologicalsurgery.in/about-dr-paresh/>; The Times of India (9 February 2011) *City docs try alternate cure for Parkinson's disease*, available at: http://articles.timesofindia.indiatimes.com/2011-02-09/mumbai/28541185_1_subthalamic-nucleus-deep-brain-stimulation-parkinson.

⁴¹⁴ Hu WH, Zhang K, Meng FG, Ma Y and Zhang JG (2012) Deep brain stimulation in China: present and future *Neuromodulation: Technology at the Neural Interface* **15(3)**: 251-9.

- 3.73 Unlike pharmaceuticals, treatment costs associated with many novel neurotechnologies will not drop dramatically with the expiry of IPR. Treatment using most novel neurotechnologies discussed in this report requires the continuing presence of medical personnel and is almost always administered in a hospital or clinical setting. For example, in the case of DBS, medical intervention does not stop at the initial highly-skilled surgery needed to situate electrodes and battery packs, but continues with regular medical follow-up care which is required to check that the technology is functioning as it should, to vary stimulation parameters.⁴¹⁵ Discrepancies in the cost of delivering treatments such as DBS may lead to people from higher income countries travelling abroad to access cheaper treatment options; there is some evidence of hospitals already positioning themselves for such a market.⁴¹⁶
- 3.74 Where neural stem cell therapies are concerned, while production methods used to develop and manufacture these products may eventually become more routine and reduce costs, this currently remains a distant prospect. High costs of treatment could mean that even if some therapies *do* reach the market, they may not be available in the UK through the NHS. The barriers in terms of affordability are clearly even more profound in low- and middle-income countries.
- 3.75 The lure of novel treatments, with their promise of cutting-edge medical innovation to address conditions that are currently untreatable, means that the possible incentives for patients to access cross-border treatment may not be limited to cost considerations alone. At the time of writing, no neural stem cell therapies have been approved for commercial use in the UK, Europe or the US, although some therapies are in the clinical trial phase.⁴¹⁷ This gives some people living with currently untreatable conditions a strong impetus to travel abroad to access treatments in other jurisdictions.⁴¹⁸ There is already a market for unregulated and unproven stem cells therapies. There is significant evidence that unproven treatments, in particular those claiming to use stem cells to treat stroke and Parkinson's disease, are being offered in unlicensed and unregulated clinics in countries such as China and India, exploiting the desperation of patients both within and from outside those regions.⁴¹⁹ While the outcomes of such interventions are rarely reported in scientific journals, those offering the treatments often make bold claims of efficacy.⁴²⁰ Undoubtedly, these developments raise concerns in those regions themselves; for example, in China, there have been several attempts to develop regulations to curb unlicensed stem cell treatments.⁴²¹ However these characteristics of the developing transnational market for neural stem cell therapies do not only raise challenges for regulation; they also have the possibility of driving the development of novel neurotechnologies in a direction that does *not* meet wider public need.

⁴¹⁵ 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.

⁴¹⁶ Dr. Dheeraj Bojwani (2012) *Deep brain stimulation in India*, available at: <http://www.dheerajbojwani.com/deep-brain-stimulation-therapy-low-cost-advantages-India.html>.

⁴¹⁷ ReNeuron (2013) *Clinical trials in disabled stroke patients*, available at: <http://www.reneuron.com/the-pisces-clinical-trial-in-disabled-stroke-patients>; Neurogeneration (2009) *Groundbreaking paper publishes long term results of a successful phase I clinical trial using autologous neural stem cells to treat Parkinson's disease*, available at: <http://neurogeneration.com/pdf/NGNPress021609.pdf>.

⁴¹⁸ For example, see: China Medical Tourism (2012) *China medical tourism brain injury stem cell therapy 3 clip*, available at: <http://www.youtube.com/watch?v=Lpre3UoObKs>.

⁴¹⁹ Barclay E (2009) Stem-cell experts raise concerns about medical tourism *The Lancet* **373(9667)**: 883-4; Murdoch CE and Scott CT (2010) Stem cell tourism and the power of hope *The American Journal of Bioethics* **10(5)**: 16-23; Cohen CB and Cohen PJ (2010) International stem cell tourism and the need for effective regulation: part I: stem cell tourism in Russia and India: clinical research, innovative treatment, or unproven hype? *Kennedy Institute of Ethics Journal* **20(1)**: 27-49.

⁴²⁰ See, for example, the claims made in ChinaStemCellNews *8 SCI survivors talk improvements* available at: <http://stemcellschina.com/>.

⁴²¹ New Scientist (11 January 2012) *China attempts to halt unproven stem cell therapies*, available at: <http://www.newscientist.com/blogs/shortsharpscience/2012/01/china-halts-new-stem-cell-tria.html>; McMahon D and Thorsteinsdóttir H (2010) Lost in translation: China's struggle to develop appropriate stem cell regulations *Scripted* **7(2)**: 283-94.

Box 3.5: Stem cell tourism

The size of the unregulated neural stem cell market is difficult to estimate and is based largely on self-reporting by clinics providing treatments. For example, Beike Biotech, a Chinese clinic specialising in neurological disorders, claims to have treated over 3,000 patients at its 24 hospital clinics in China: its website appeals directly to potential medical tourists, and contains videos of patients claiming remarkable therapeutic effects for their therapies which have not been validated by clinical trials.⁴²² ACT, from Turks and Caicos, and Emcell, from Ukraine, claim to have treated over 700 and over 2,000 patients, respectively.⁴²³

Research conducted on the websites of 19 clinics advertising stem cell therapies, including those based in China, India, Ukraine, Philippines, and Dominican Republic, concluded that the portrayal of stem cell medicine on provider websites was optimistic and unsubstantiated by peer-reviewed literature.⁴²⁴

An observational study of the stem cell treatment of spinal cord injury in Beijing concluded that the “procedures observed did not attempt to meet international standards for either a safety or efficacy trial. In the absence of a valid clinical trials protocol, physicians should not recommend this procedure to patients.”⁴²⁵

- 3.76 It seems unlikely that neurotechnologies will provide a comprehensive and affordable answer to the increasing global incidence of neurological and mental health disorders in the near future. The economic drivers and constraints upon the development of novel neurotechnologies present considerable challenges to ensuring that products are available in ways that are consonant with the values of equitable access in response to urgency of need. This may, in turn, raise the risk that desperate patients will be attracted by the promises made for cheap treatments in inadequately regulated jurisdictions.

Concluding remarks

- 3.77 In this chapter, we have described the national and global extent of the neurological and mental health conditions for which there are, currently, few good, effective, and economically viable forms of treatment, and which novel neurotechnologies might hope to address. We have then examined the extent to which the current ‘economy’ of novel neurotechnologies – that is to say the financial and economic factors that shape their development – facilitates or hampers their development in ways that can meet these needs. We have identified a number of characteristics of the current innovation landscape which are obstacles to such developments: features which do not always stimulate innovation, do not always direct research and development to the areas of greatest global need, and which sometimes appears to militate against research and innovation that meet the interests of patients in accessing safe and effective therapies.
- 3.78 We have argued that, despite much discussion of the problems of funding the development of biotechnologies, there remain major difficulties in innovators bringing their potentially valuable products through from early stage development to marketable products, in particular across the difficult terrain that has been colloquially termed ‘the valley of death’. While this funding gap has been widely recognised, the costs in bridging the gap between early, small scale and short term technological development and the subsequent scaling up of effective innovations to meet market requirements, are often very great, as some of our examples have shown. Private investors are often reluctant to commit funds over the long periods that may be required, and it is difficult to imagine public funders committing to decade-long financing of inherently risky developments.

⁴²² Beike Biotech *Mom hopes stem-cell treatment will give her child the gift of sight*, available at: http://beikebiotech.com/index.php?option=com_content&view=article&id=388:mom-hopes-stem-cell-treatment-will-give-her-child-the-gift-of-sight&catid=5:beike-in-the-news&Itemid=5.

⁴²³ Lau D, Ogbogu U, Taylor B *et al.* (2008) Stem cell clinics online: the direct-to-consumer portrayal of stem cell medicine *Cell Stem Cell* **3(6)**: 591-4, at page 591.

⁴²⁴ *Ibid.*

⁴²⁵ Dobkin BH, Curt A and Guest J (2006) Cellular transplants in china: observational study from the largest human experiment in chronic spinal cord injury *Neurorehabilitation and Neural Repair* **20(1)**: 5-13, at page 5.

- 3.79 This then presents the challenge of how to create an economic landscape that favours inventiveness and innovation in products that meet the needs that we have identified. This will require identifying means for commercial enterprises to access secure medium term funding for product development. It remains an open question as to what the source of this kind of funding might be. For example, is the withdrawal of large pharmaceutical companies from CNS drug development indicative a more general problem of market failure that only long-term and sustained public investment can resolve?
- 3.80 While it may not be possible to specify the precise sources of sufficiently secure funding, it is clear that whatever form it takes, this needs to support, rather than disincentivise, innovation pathways that have patients' interests in securing access to safe, effective therapies as a central priority. As we have suggested, patients' interests may be undermined by innovations, the primary aim of which is to secure first mover advantage and market share by the exploitation of regulatory routes that do not necessitate the highest standards of pre-market clinical evidence, and by financial incentives to test particular technologies that may compete with clinicians' duties towards their patients. Nor should securing investment in innovation rely upon, or encourage, hype and premature and exaggerated promises as the current situation does. While many of these problems are not unique to neurotechnologies, the fact that we still know so little about how neural processes are affected by interventions such as DBS, gives us special cause for reflection. There is an important role here for large public health providers, like the NHS, regulators, such as the MHRA, and non-departmental public bodies such as NICE, in managing and stimulating the innovation landscape according to public norms of efficacy and value.
- 3.81 Given the global nature of some of the conditions we have discussed (including stroke, dementia, and chronic pain) and given the cost and complexity of some of the neurotechnological interventions discussed in this report, the immediate reality is that even where novel neurotechnologies have been proven to be safe and effective, they are likely to be available only to the wealthy few. The challenge remains as to whether novel neurotechnologies can be developed in such a way that maximises equity of access globally as well as locally.
- 3.82 In Chapter 7, we return to many of the topics we have introduced here as part of our assessment of the regulatory systems operating in the UK and Europe. We ask how these systems may operate in effective and proportionate ways to support innovation and the entry into the market of much needed therapies, while protecting patients' safety and well-being in ways that are appropriate to novel technologies that intervene in the brain. As part of this discussion we also consider how the market may not be the only means to access treatment using novel neurotechnologies and review the means by which treatments for single, or small groups, of patients are regulated (see paragraphs 7.73 to 7.82).
- 3.83 Before examining the regulatory landscape, we turn first to the task of identifying which ethical considerations are key to guiding the practices of all actors involved in funding, developing, regulating, using and promoting neurotechnologies and to providing safe and effective therapies to address unmet health needs. As such, the ethical framework we provide in Chapter 4 supplies not only a means of assessing the values and interests that are crucial to the clinical care of patients and research participants, it also provides a guide to understanding what constitutes responsible research and innovation in the field of novel neurotechnologies, and thus what obligations fall on those who fund and pursue innovation under the pressures and constraints we have identified in this chapter.