

AGENDA ITEM 5

Emerging Science and Bioethics Advisory Committee

Discussion paper

Topics for ESBAC's consideration

CORE ISSUES

➤ Ethical, Legal and Social Issues

There seems to be a tendency in recent European Commission funded projects, to spend time searching for 'new' ethical issues in new technologies. The conclusions of these searches seem very often to be that the ethical issues are not new, but are a restatement of more fundamental questions. However, before these core ethical issues are addressed, a different new technology or possible development is identified and the process of questioning whether new ethical issues accompany the new technology begins again, and the core values are never fully explored.

Central to these core values is the balance between autonomy and solidarity. Taking the public health debate as an example, there has been a distinct shift in public expectations about individuality. This can be seen in the shift to the acknowledgement of greater individual privacy in public health research, for example, seen in the revisions of the Helsinki Declaration or in the modern discussion about informed specific consent (compared with broad consent and other safeguards) in relation to the secondary processing of personal health data in biobanks.

This could be ESBAC's opportunity to find its distinctive bioethics voice. For example, how does the Committee construct an appeal to the public interest and how do we understand the function and place of privacy? When, would informed consent be necessary and when can broad consent be sufficient (and what alternative safeguards are appropriate to replace the protection afforded by informed consent)? Do we assume that citizenship is passive - i.e. that individuals do not have to participate or react to developments in science and technology - or can the starting point be a presumption of active citizenship (for example, a general acceptance that 'opting out' rather than 'opting in' is more appropriate in most situations of secondary inclusion in research)? Further, do we see consent, and other traditional safeguards used in bioethics (for example, anonymisation of personal data), as discredited in modern medical or biotechnological research? Are consensus models and participant involvement more appropriate governance models?

Related to these questions about citizenship involvement and the image of the participating stakeholder citizen, is the question of how the Committee approaches the range of sensitivities expressed by members of society in public opinion surveys.

The Eurobarometers on biotechnology, for example, display a range of opinions, often opposite positions, that are held by significant numbers of people. How should modern governance respond to these ranges, given that they are not extreme views in society, but are moderate, opposite views in society? As more biotechnology involves the individual as part of the raw material of the research rather than simply its beneficiary, can an approach that requires tolerance by one side be sufficient?

This discussion is informed by Dr Thomas Murray's recent work using the concepts of 'interest' and 'identity' (where some views are held as interests, which he sees as negotiable, whilst others are held much more deeply by individuals as part of their identity, which he sees as non-negotiable).¹

Regarding its role, should ESBAC be a form of early health technology assessment (HTA)? With expertise in economics, evidence based medicine, social science and ethics work with government, industry and consumers to enhance the user and system responsiveness of emerging technologies, and ensure that the evidence base for new technology will meet the needs of sponsors and regulators. Early HTA brings the process of technology assessment to bear earlier in the technology development process to provide decision support to innovators (e.g., industry, patent holders, early investors, researchers). Such initiatives can reduce uncertainty, wasted investment, and costly re-design efforts. Early HTA also serves health care systems by ensuring that only effective and cost effective innovations are introduced.

➤ **Overarching Issues for ESBAC to consider in its discussions**

▪ **Welfare/wellbeing**

ESBAC will need to consider welfare and wellbeing implications in its discussions from an individual and a societal perspective. [A definition is needed by what is intended by welfare and wellbeing in this context.]

▪ **Economy**

The interplay between ethics and the economy is even more pertinent in current economic climate. ESBAC will take into consideration in its discussions economic impact as well as the impact on research and development in the UK and international arena.

▪ **Scientific advance**

Ethical and legal issues must be considered holistically to promote scientific development. This is also intended to support the important role the UK plays in the international science and technology arena.

¹ <http://www.nuffieldbioethics.org/video/new-genetic-recipes-are-we-cooking-trouble-synthetic-biology>
(last visited 2nd July, 2012).

▪ **Responsibility in health**

In assessing ethical dimension of emerging science and technology, the implicit or explicit assumption about the attribution of health, ill-health and wellbeing must be routinely explored.

▪ **Communications**

ESBAC will need to establish and maintain robust communication lines with a broad audience. In formulating its opinion, ESBAC will need to consider how to best engage with the target audience and the wider public are engaged.

SPECIFIC TOPICS

➤ **Genetic Testing**

As genotyping technology becomes cheaper and more broadly available, there is likely to be increased uptake of these tests by the public and increased pressure on the system including from patients with access to their genome. Such tests may also give rise to certain “incidental findings” of certain or uncertain clinical relevance to the patient or the patient’s family, (e.g. BRCA²) and patients may initially get information about genetic susceptibility to disease from private firms (e.g. 23andme).

Issues raised:

- Shift focus to prevention even where it might not be cost-effective.
- Implications for children of those sequenced as the sequence will carry information about them.
- Questions about masking / unmasking results and information.
- Challenges for GPs (including training to keep abreast).
- Ownership of the genetic data being collated by companies such as 23andme.
- Security of information being stored.
- Prevention of data being used for commercial gain by companies supplying the tests.
- Provision of medically-informed gene counselling where health risks are identified.
- Implications for employment, insurance, health-related behaviour, and reproductive decisions.

² A **BRCA mutation** is a mutation in either of the genes *BRCA1* and *BRCA2*. Harmful mutations in these genes produce a hereditary breast-ovarian cancer syndrome in affected families.

- Results are often described deterministically and over-interpreted, even when the actual data linking specific polymorphisms to common complex disease phenotypes is weak.
- Ability to sequence is likely to far exceed understanding about the functional biology of genomic variation. How will this new genomics data be stored, analyzed, and interpreted? Will consumer genomics companies be providing information to the public that we are currently unable to interpret?
- What are the consequences of these new advances in genomic profiling for gene patenting and the commercial exploitation of genetic data?
- As our ability to interrogate and interpret the human genome increases, what are the implications for personalised medicine, prenatal screening, employment, and health insurance?
- In addition to learning more about the genetic basis of many human disease phenotypes, we are also identifying alleles associated with 'normal' (non-pathogenic) variation in behaviour, personality, intelligence, and physical characteristics. What are the implications of this information being easily accessible?
- We may be moving from a paradigm which assumed that less was more (i.e. that diagnostic tests should not be ordered unless they can meaningfully inform clinical decision making and that an excess of data might confuse rather than clarify), to a paradigm which assumes that knowledge is power and that the more data one has then the greater the potential for improved clinical outcomes.
- Other high throughput technologies (in proteomics and metabolomics) are also research tools and require further investment to achieve a greater level of technical standardisation. There may be questions here about whether the potential value of these technologies merits greater public investment in their development.
- Implications of genomics (being able, rapidly and cheaply to sequence whole human genomes) for risk stratification - are the public ready to handle this kind of information?

➤ **Stem Cell Research**

The CJEU decision in *Brustle v Greenpeace* in 2011, ruled that anything involving the prior destruction of a human embryo is not patentable, regardless of whether it is specified in the patent claim. This view has recently been upheld in the updated European Patent Office guidance.

The consequences of this decision have already been seen in the exclusion of embryonic research from European public funding mechanisms³ and are expected to have further repercussions on private funding and companies operating in this field. A more thorough review of other indirect impacts of this case and of the related WARF case, including the current rules of the UK Stem Cell Bank (SCB), which makes it very difficult to develop any commercial products in the UK based on publicly funded HESC research⁴, may be warranted.

➤ **Pluripotent Stem Cell Research**

Stem cell research provides significant potential benefits for many different areas of health and medical research, but there are obvious ethical issues surrounding the use of human embryonic stem cells.

The development of induced pluripotent stem cell (iPSC) technology should help to overcome some of these issues, providing invaluable models of disease and the potential for future drug screening and even 'therapeutic cloning'. This technology is not free of legal and ethical concerns.

IPSCs can be expected to raise ethical issues around the increasing commercialisation of human tissues more generally, for example if they prove capable of giving rise to immortalised, highly proliferative cell lines, raising issues around the rights and responsibilities of human donors, academics, health providers and commercial companies⁵. In addition, there are issues relating to consent, safety, efficacy, capacity for scale-up, experimental regulation, and the future potential for human cloning that could be explored.

➤ **Medical tourism**

Growing numbers of clinics abroad are marketing unproven, costly stem cell therapies to medical tourists "exploiting patients' hopes," and there is an increasing number of stem cell treatments being provided abroad to UK nationals.

The establishment of the Catapult Cell Therapy Centre and the high economic value of derived cell lines could be incentives for the NHS to establish an international cell therapy centre alongside a commercial partner. If successful, this would subsidise advanced therapies under the NHS by means of (benign) stem cell tourism.

In addition, private clinics in the UK are reportedly offering the extraction of stem cells during liposuction. There is a desire among researchers to see stem cells from liposuction in stem cell banks.

There is a clear call for better transparency, oversight, informed consent, patient follow-up.

³ http://www.europarl.europa.eu/meetdocs/2009_2014/documents/juri/pa/902/902069/902069en.pdf

⁴ Courtney, A., de Sousa, P., George, C., Laurie, G., and Tait, J. (2011) Balancing Open Source Stem Cell Science with Commercialisation, *Nature Biotechnology*, 29(2), Feb. 2011, 115-116.

⁵ Mastroeni, M., Mittra, J. and Tait, J. (2012) *Methodology for the Analysis of Life Science Innovation Systems (ALSIS) and its Application to Three Case Studies*. TSB Regenerative Medicine Programme: Value Systems and Business Models. REALISE Project. Innogen Centre Report to Technology Strategy Board. 29th May, 2012.
<http://www.genomicsnetwork.ac.uk/media/REALISE%20Case%20Study%20Report%20-%20Innogen.pdf>

➤ **Stratified Medicine**

Stratified (or personalised) medicine is receiving a large amount of policy support from government through funding programmes (from the MRC and TSB for example). Personalised medicine could radically overhaul patient care, reducing costs whilst ensuring the correct treatments get to those who need them.

However, there are a number of outstanding issues:

- Whether the current medical research model could actually sustain a personalised medicine approach, which will inevitably bring fewer block buster drugs and therefore reduced profits for companies involved in the research.
- Is there a need to provide a continued incentive for companies to invest and is this financially sustainable?
- Access to diagnostic tests will be an important component of a personalised medicine approach and what ethical issues surround patient access to those?
- The increasing use of diagnostics to stratify people out of treatment, which will soon start to indicate who shouldn't be receiving existing standard of care and may indicate that no further therapeutic options are likely to benefit, which on past experience will lead to patient/public outcry.

➤ **ICT including assisted living**

Keeping patients and the elderly in their homes for longer provides potential social benefits and cost savings in terms of care. The technologies that include remote monitoring (which raises a number of ethical issues) could also help develop new companies in the UK.

➤ **Germline therapies**

The recent Nuffield report on techniques that aim to prevent the transmission of maternally-inherited mitochondrial DNA (mtDNA) disorders highlights the need to consider potential germline therapies involving the nucleus.⁶ Aside from the safety issues, debate includes whether these techniques should be limited to the elimination of genetic disease or be used to 'genetically engineer' people (e.g. confer disease resistance or address other minor traits). In addition it would be helpful to consider the outcomes (expected in 2013) of the public consultation and dialogue on techniques to prevent mtDNA disorders being undertaken for HFEA.⁷

⁶ <http://www.nuffieldbioethics.org/mitochondrial-dna-disorders>

⁷ <http://www.hfea.gov.uk/6896.html>

➤ **Gender differences**

Research is revealing a greater understanding of gender differences in susceptibility to disease and response to treatment. There are implications for healthcare generally and for clinical trials.

➤ **Epigenetics**

Increasing evidence suggests that epigenetic processes can be influenced by exposure to numerous factors in the environment (e.g. nutrition, stress, toxins, drugs, medications). The near exponential increase in research into epigenetic processes will have considerable repercussions to develop understanding about the causes of human health and disease and is likely to inform novel diagnostic, prognostic, and therapeutic interventions in medicine. It would be timely to start considering ethical, legal and commercial implications of -omics research with focus on more than issues related to DNA sequence variation.

➤ **Patient data/research data**

The advantages of and public concerns about the use of patient data a very important (but well rehearsed) issue. The outcome of the Caldicott review⁸ will be important. Patient data combined with Information and Communication Technology (ICT, e.g. smart phones and mobile devices) could allow major improvements in the way in which medical professionals communicate amongst themselves and with patients. Patients having access to their own data, combined with the increasing amount of medical information (and misinformation) on the web will lead to a more informed patient with implications for the doctor-patient relationship.

➤ **‘Human enhancement’**

The joint Academies workshop on human enhancement in the workplace (to be published in Autumn) identified two issues worth further attention now in the context of cognition enhancers.

- Cognition enhancing drugs are already available without prescription over the internet, are relatively cheap, and are increasingly being used by healthy individuals. Little is known about their long term impacts especially on the developing brain. These might therefore be a high priority for continued attention (this has an impact on other Government departments including the Home Office).
- Digital cognition enhancing technologies (e.g. augmented reality) don't require the same regulatory oversight as pharmacological interventions,

⁸http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4068403

and yet the effects could be very significant. Since they are not regulated, the impact analysis is often not undertaken.

➤ **Use and availability of publicly funded research**

The public are responsible for supporting a large amount of basic medical research in the UK with the MRC, BBSRC and Department of Health (through NIHR primarily) investing millions per year.

Emerging healthcare is likely to become even more expensive and the system should be open to ideas (and the implications of such ideas) focused on saving NHS resources and, to the extent that it does not impede healthcare, making money from the system. In this context, there may be a call for a proper debate regarding the benefit that the UK should get from this research.

Issues raised:

- Ownership of scientific data that is paid for by public money.
- How to maximise the benefits (health and economic) of scientific research.
For example:
 - ❖ Could the NHS gain commercial value from data it generates?
 - ❖ The UK taxpayer receiving greater financial returns through enhanced IP rights around future profits, or conversely would it be of greater benefit to UK growth for this research to be given away more freely to allow private commercialisation and translation?
- Explore whether a precondition to obtaining genomic-mediated treatment under the NHS should be the use of genomic data for purposes of research and commercial exploitation.
- Safeguards for patients to be put in place to ensure UK patients are able to benefit from a medicine or technology, that they have helped fund, when it has reached market.
- Ethical issues surrounding products being placed on the market at a price that may be unaffordable to the NHS.

➤ **Regulatory challenges of emerging areas of science**

It is important to stress at the outset that most UK life science law is European. This goes as much for patent law as for the regulation of medical devices and medicinal products. This is not to underestimate the importance of national legislation, for example under the Human Tissue Act 2004 and under the amended Human Fertilisation and Embryology Act 1990. However, it is significant because European law provides the principle framework for life science activities. As such,

recommendations on changes to an existing UK legal framework are likely to involve changes at an EU level. It is important to note that successful laws, especially in this area, depend upon public understanding.

Regulation of technologies and devices is a well-known challenge. An example is ensuring that ICT-based non-invasive devices can be licensed quickly enough to avoid the technology 'moving on'.

A flexible yet robust legal framework and governance is needed to ensure the law keeps up with the fast pace of scientific and technological developments, and delivers safe and effective treatments and therapies. These must comply with fundamental ethical principles while also enabling innovation to take place on shorter timescales, and to be delivered by a broader range of companies than is currently the case. Addressing this issue would enable more competition in the development of therapies, and more public and commercial benefits to be gained from the considerable public investment in basic and translational research, while also delivering treatments and therapies for currently intractable diseases^{9,10}.

There are a number of discussions in the UK, Europe and US regarding changes to the regulatory pathway. The US is attempting to expand its Accelerated Approval pathway, in the UK we have the proposed Early Access Scheme and there are wider discussions regarding an 'Adaptive Licensing' approach.

Exploratory discussions regarding this are focusing upon the regulatory aspects. However, there are ethical issues to consider as well, particularly regarding the risk appetite that a new regulatory pathway would adhere to.

Issues include:

- Fitness for purpose of the existing framework of European legislation (and the devolved national legislation, which rests thereon), to adapt to the changes in technology.
- Efficiency of a system under which medicines are centrally authorised while their companion diagnostics are authorised locally.
- Defining a tolerable risk (if it allowed patients earlier access to potentially life saving treatments).
- If observational trials are used more in future in place of formalised randomised controlled trials (RCTs), are such trials still ethical if they retain a control arm not receiving medication (which, by virtue of it receiving a form of license is considered to have a degree of efficacy)? Conversely, without such a control group is the data less reliable on which to base a final approval decision?

⁹ Tait, J. with Wield, D., Chataway, J. and Bruce, A. (2008) *Health Biotechnology to 2030*. Report to OECD International Futures Project, "The Bio-Economy to 2030: Designing a Policy Agenda", OECD, Paris, pp 51; <http://www.oecd.org/dataoecd/12/10/40922867.pdf>.

¹⁰ Tait, J. (2007) Systemic Interactions in Life Science Innovation. *Technology Analysis and Strategic Management*, 19(3), 257-277, May 2007.

- The extent of the perceived threat from the regulation of autologous cell products to impede the practice of medicine.
- Recommendations as regards recent Commission proposals on medical devices.
- Attribution of liability when bioinformatic assays are undertaken by algorithms in California or Indonesia, interpreted in China and acted upon in the UK by a patient encouraged to take control of her healthcare, using her iPhone. Do existing data protection laws impede translation?
- How well does competition law address the tying of medicinal products and to medical devices. Is there a need for an *in silico* devices directive?
- Genomics has the potential to create new pathological taxonomies, with advantages to patentees faced with a patent slump. How significant is this to the cost and effectiveness of healthcare?
- Increasingly the commercial and clinical implementation of stratified medicines will rely upon diagnosis conducted in vitro or in silico (namely in computer or via computer simulation). Is the existing framework of European legislation (and the devolved national legislation which rests thereon) fit for this purpose? What recommendations can the Committee make for the reform of this framework?
- Reform of the Biotechnology Directive (Directive 98/44 EC) - Mitochondrial transfer technology, has highlighted the need to review the Biotechnology Directive with a view to possible amendment. How fit for purpose is this Directive? Are there opportunities to provide better protection for cell lines, for example, against *bona fide* purchasers? Would it be more problematic to amend it later than to act now?
- The draft EU Data Protection Regulation and its impact on emerging technologies.

➤ **Governance of innovation within the NHS**

Also termed by Michael Hopkins as “hidden innovation by NHS staff”. There are a number of areas of emerging science where this hidden innovation system is likely to play a crucial role e.g. next generation sequencing and cell therapies. At a time when the NHS itself is undergoing major reform then this seems all the more salient.

➤ **Evidence and clinical trials**

It is clear that emergent technologies generate disputes about the level and types of evidence which are required both for market approval and decisions about coverage and reimbursement. For instance, in the area of personalised/stratified medicine there is discussion about the relative merits of retrospective and prospective trials,

about randomised control trials versus observational data, and about whether trials involving only biomarker positive subjects are acceptable. In 2004 both the Food and Drug Administration's (FDA) Critical Path Report and the European Medicines Agency (EMA) Road Map suggested that new forms of clinical trial design such as adaptive trials might be of value but thus far there has been little progress with both industry and regulators exhibiting caution.

In addition, there may be some immediate questions for ESBAC about reporting incidental findings in a clinical setting. The Wellcome Trust and the MRC are following up on their research and work in this field and ESBAC could visit this issue once their work is complete.

➤ **Intellectual Property Rights (IPR)**

The issue of intellectual property rights was the subject of the final report from the Human Genetics Commission, which looked at the impact of DNA patents on diagnostic innovation. The report, which summarised a stakeholder discussion at a half-day workshop, called for further work on the topic. A broader investigation of the impact of IPR on biomedical innovation might be of merit, one that allowed consideration of the general issues as well as looking at how they play out in different technologies/applications.

There may also be considerations for ESBAC on the proposed legislation on intellectual property reform (Enterprise and Regulatory Reform Bill).

➤ **Animals containing human material**

The Academy of Medical Sciences' report on the use of animals containing human material in research¹¹. The recommendations of the Academy's report are primarily for the Home Office (as it implements the Animals in research directive and HFEA (in ensuring no gaps between it and the Home Office). However the research facilitated by these animals (e.g. in neurodegenerative disease) is important for DH so developments in the science and the development of regulation along with public attitudes are worth monitoring.

➤ **Synthetic Biology**

- ❖ Use of genetically-modified organisms in food chain and pest control.
- ❖ Informatics: the use of population medical records.

➤ **Increasing use of “generic consent” for analysis of tissue samples and patient data records.**

¹¹ <http://www.acmedsci.ac.uk/index.php?pid=99&puid=222>

➤ **Nicotine vaccination**

Other issues raised:

i) Covered elsewhere

- Pandemics: mass-vaccination programmes, treatment with anti-virals, fast-tracking research in pandemic situation – This is already covered by the work of CEAPI, although currently dormant.

ii) Lower priority - unless significant scientific or clinical developments re-open the debate

- Dementia
- End-of-life issues, euthanasia, palliative care
- Beginning-of-life, premature babies
- Antibiotic resistance: key science issue, not sure if there is ethical angle. There has been some progress in prescribing of antibiotics, but may need more
- Bias in clinical trials: under-representation of children, pregnant women (and women in general), elderly

Nuffield Council on Bioethics

Summary of current and recent work

CURRENT WORK

Emerging biotechnologies

Emerging biotechnologies such as synthetic biology and nanotechnology have the potential to provide benefits for health, the environment and the economy, but they also raise concerns.

This Working Party is considering cross-cutting ethical issues raised by emerging biotechnologies, such as benefit, harm, risk, precaution, uncertainty, public perception and intellectual property and implications for policy, governance and public engagement.

This Working Party was set up in January 2011. A public consultation was held in 2011 and the final report will be published in autumn 2012.

www.nuffieldbioethics.org/emerging-biotechnologies

Donor conception: ethical aspects of information disclosure

Parents of people conceived using donor eggs or sperm may or may not choose to tell them about their genetic origins. Is this a private family matter, or are there wider public interests at stake? What kind of information might donor-conceived people and their parents need about their genetic origin? What interests do donors have in receiving information?

This project is examining the ethical issues that arise in connection with the disclosure of information about genetic origin in the context of families created through assisted reproduction using donor gametes, embryos or surrogacy. The Working Party started in February 2012, the public consultation was completed in May 2012 and a report will be published in spring 2013.

www.nuffieldbioethics.org/donor-conception

Novel neurotechnologies: intervening in the brain

Technologies and devices that intervene in the brain are being developed to help treat diseases such as stroke, dementia, obesity and depression. This, and the possible use of such technologies for non-medical purposes, is becoming a subject of debate.

This Working Party was set up in November 2011 to explore the ethical, social and legal issues arising from novel neurotechnologies such as deep brain stimulation, brain-computer interfaces (BCI), and neuron replacement therapy. A public consultation was held during March and April and a report will be published in summer 2013.

www.nuffieldbioethics.org/neurotechnology

RECENTLY PUBLISHED WORK

Novel techniques for the prevention of mitochondrial DNA disorders: an ethical review (June 2012)

Mitochondrial DNA disorders are incurable genetic disorders that can cause severely debilitating symptoms and can be fatal in early childhood. New techniques that could prevent the transmission of these disorders are being researched, but the techniques are currently unlawful for use in treatment. The report is intended to promote and support further debate on the possible use of such treatments in future. The Council concluded the techniques would be an ethical for affected families if proved to be sufficiently safe and effective through further research.

www.nuffieldbioethics.org/mitochondrial-dna-disorders

Human bodies: donation for medicine and research (October 2011)

Donated bodily material for medicine and research, such as organs, eggs and sperm, are in high demand, and current levels of donation fall short of need. This report sets out guidance to help people consider the ethical acceptability of various ways of encouraging people to donate, both for treatment of others and for scientific research.

www.nuffieldbioethics.org/donation

FUTURE WORK

Genomics, Health Records, Database Linkage and Privacy

A workshop with Council Members and invited guests was held in February 2012 to explore the ethical issues raised by collection and sharing of biodata. Work will begin on this project in early 2013. The Council has identified key themes including:

- Consent and control of personal biodata by individuals
- Authorisation to access, share and link personal biodata without the consent of a person to whom the data relate
- Anonymisation, data security and privacy protection
- Feedback of information and the ongoing relationship between controllers and subjects of biodata

Children and Clinical Trials

A workshop exploring the ethical issues raised by children taking part in clinical trials was held in December 2011 and a project on this area is due to begin in 2013. Key issues that are likely to be discussed as part of the project are:

- What is different about children's trials?
- Consent and decision-making
- Questions of risk and benefit