Nuffield Council on Bioethics
Forward Look Seminar
19 - 20 May 2011

Note of the meeting

Topic 1: Pandemics

1 The session began by thanking the authors of the background paper on the topic of pandemics. Reference was also made to the relevance of the Nuffield Council's earlier report on *Public health: ethical issues*, and the distinction it made between individual and community interests in the context of infectious diseases.

Presentation 1: Scientific challenges

2 The presentation highlighted the scientific challenges raised by pandemics, and argued that science is at the heart of pandemic policy. It also provided a summary of what has been achieved in the field of responding to pandemic influenza, and the possibilities for future research in the area.

3 Attention was drawn to the fact that influenza viruses are highly changeable due to the fact that they are RNA viruses. It was noted that, during the past 18 months, swine flu had dominated, effectively pushing out other Influenza A viruses, an example of 'the survival of the fittest'.

4 It was noted that at the heart of a pandemic virus are questions such as:

- How did the person get infected?
- Where does the virus go once it enters the body? What are the roles of the lower and upper airways?
- Is the virus replication driving the pathology? If it is, then we can conclude that we need to stop the virus replication, or during that replication, does the virus trigger an immune reaction? Are we dealing with an overactive immune system alongside virus replication?
- Are we also dealing with superinfections (i.e. an infection caused by an organism different from that which caused the original infection)?

Thus, understanding the precise pathology – and ascertaining how people are dying – remains at the heart of pandemic influenza research.

5 The challenge of the unknown is a key scientific challenge for pandemic influenza. The relationship between flu viruses and other illnesses was also felt to be important, and has arisen recently in the form of reports from Finland of the onset of narcolepsy in people who had received a flu vaccination. It was felt that such cases highlight the need for science to be able to respond to the unexpected.

6 It was argued that the response to these challenges has been made up of three elements: vaccination; the provision of antivirals; and hygiene.

However, it was noted that these three elements cannot operate in isolation; are all key.

7 It was noted that current antiviral drugs have been used for over 30 years, but there are other possibilities, and advances that could be made. For example, a specific form of antiviral drugs may potentially be used to induce a broader immune response and hence provide protection against a number of strains of influenza viruses. In addition, new drugs are already emerging. For example, in Japan, a drug has been developed which is more long-lasting than others available, and would only require one dose to be taken per week.

8 The third element which needs to be in place to respond to the challenges of pandemic influenza is hygiene; measures include both social distancing and cleanliness.

9 The importance of a 'home front' defence against pandemic influenza was also highlighted: the Department of Health cannot 'twist people's arms' and simply tell people what to do. This was felt to be especially so given the advent of social networking sites, where people access information and air their views directly rather than depending on health professionals.

Other issues arising out of the presentation

- It was noted that, in the context of influenza, we are all 'in it together'. The global nature of the virus, therefore, needs to be acknowledged. The role of the WHO was recognised, and the organisation was praised for its handling of the swine flu pandemic, especially in relation to more 'difficult' countries who, it was argued, may tend to focus on the welfare of their own citizens.
- The role of volunteers in clinical trials was raised. For example, work is currently being undertaken whereby volunteers are given £3,000 in order to be infected with influenza and for researchers to monitor the progression of the virus over a nine day period. Thus far, this research suggests that volunteers with a high level of immunity to certain proteins can be protected against influenza. This research has led researchers to hope that there is a possibility of developing a vaccine which induces a broad immunological response.
- On the specific issue of bird flu, it was noted that the campaign in Hong Kong to kill birds had been successful insofar as the virus was contained. It was suggested that the slaughter of birds was appropriate given the dangerous nature of bird flu.

Presentation 2: Policy challenges

10 This presentation addressed some of the policy dilemmas which have arisen in the context of pandemic influenza.

11 It was argued that pandemic influenza is essentially the same as seasonal influenza, but on a different scale and, in many ways, ethical and policy

questions arising from pandemic influenza are the same as those for seasonal influenza. Seasonal influenza was therefore used as a paradigm throughout the course of the presentation.

12 It was noted that for any influenza policy – be it seasonal or pandemic influenza – Government considers what will be safe, effective, and cost-effective. The last consideration raises an ethical dilemma about the use of resources: should policies be implemented that ignore cost-effectiveness and aim to provide for everybody, whatever the resource implication. Or, is policy to be built upon the principle that it is ethical to take cost-effectiveness into account? Policies also have to be appropriate to the circumstances.

13 However, although pandemic and seasonal influenza can be argued to be the same thing, they do have different policy dilemmas. Seasonal influenza, for example, focuses on protecting the individual. The Department of Health does not interfere with transmission of seasonal influenza, and nor does it focus on the potential burden on society. Conversely, pandemic influenza affects wider society, and may have a significant economic impact. Policy must therefore take into account the protection of the population, and consider how society will function outside the health policy arena in the event of a pandemic.

14 It was noted that, last winter, there were more deaths from seasonal influenza than there has been from pandemic influenza in the UK. A question was raised as to why this was the case, when the pandemic appeared to be so extensive. The rate of immunity was cited as a possible explanation; in 2009, close to two-thirds of young children in London, and around 45 per cent outside London, were immune after the pandemic either through vaccination or disease. This level of immunity might lead to the anticipation that the next wave of seasonal influenza would have a much milder impact. It was suggested that a good indication of the severity of an influenza season was usually to be found by examining influenza trends in the Southern hemisphere, as influenza outbreaks occur there first. Last year, the Southern hemisphere had very mild influenza – but the main cause was the seasonal strain (H3) rather than pandemic H1N1. This, it was suggested, could have led to an expectation that influenza in 2010/11 was going to be mild. This raises questions for the future: we had a pandemic, so if that virus from last year returns this year, will it be the same, or will it be different? Will it affect population groups differently? Will it still cause the same pattern of influenza? This both underpins and challenges how we must prepare for both seasonal and pandemic influenza.

15 It was noted that last winter, the peak for cases of seasonal influenza was almost the same as the peak for pandemic influenza from the winter before although the existence of the National Pandemic Flu Service in England during the pandemic raises some difficulties in direct comparison at the community level. Therefore, it was suggested that seasonal influenza can be as bad as pandemic influenza in terms of overall impact. So, what do we deal with? How do we prepare? How do we consider influenza on a year-by-year basis? It was argued that seasonal influenza and pandemic influenza are on-

par, so whatever is planned for one type of influenza, must also be planned for the other type.

16 The impact of the media on public perception was raised, including cases where reporting lacks accuracy or important information about influenza. The question was raised as to whether ethical dilemmas are actually *driven* by media coverage. An article published in 2009 with the headline 'Swine flu jab link to killer nerve disease' was cited as an example of such a case: yet the disease to which the article referred (Guillain-Barré syndrome) had actually occurred decades earlier, in 1976. Such reporting, it was argued, influences the public perception which in turn influences public expectations.

17 Similarly, the headline 'My darling daughter dies for the lack of a £6 jab' omitted to ask about the evidence upon which the policy was based. A question was therefore raised as to whether the Department of Health, and Government, is – or should be – trying to prevent every death in the context of a society where resources are constrained. Given resources are constrained, it was argued that Government has to use resources in the most cost-effective way.

18 An analysis of who actually died as a result of influenza last winter is also significant in policy terms. Those at the highest risk of dying were in the 45-64 age group, while the group at the lowest risk of dying were young children. In light of this information, how should 'at-risk' groups be defined? The analysis of data is clearly important here, and the Department of Health is able to collect and analyse data on the vaccination of every person in a particular risk factor group – according to, for example, which strategic health authority they live in – and also keep a record of who has been vaccinated.

19 The difference in the strength of protection, via vaccination, according to different age groups in the UK was noted. It was suggested, for example, that the UK has a good track record of caring for its over 65s, as 70 per cent of this group were vaccinated. Similarly, a high proportion of pregnant women are also vaccinated. Conversely, a much lower percentage of health care workers are vaccinated. A question was raised as to the acceptability of this state of affairs, and a comparison was drawn between the UK and the United States. In the latter, healthcare workers are not allowed to come to work if they have not been vaccinated. In other jurisdictions, hospital workers who have not been vaccinated are compelled to wear face masks during the flu season. In terms of UK policy, therefore, it was suggested that the overall aim should be to increase the rate of health care workers vaccinations, in light of concerns that not to do so would be ethically unacceptable. For example, it was suggested that there is a paradox in requiring health care workers to encourage their patients to accept a vaccination while not accepting one themselves.

20 Looking forward to Department of Health policy in 2011, it was noted that the Joint Committee on Vaccination and Immunisation (JCVI) will examine new mathematical and economic analysis of the policy options for expanding routine immunisation for those aged 50 to 64; asking whether the Department

should routinely vaccinate the under fives; and considering the vaccination of school-age children who, although they are not in the most at-risk group for influenza, are in an environment where the virus can easily spread. In addition, there will be an examination of how seasonal flu vaccine is bought and distributed, ensuring that the Department is well-prepared in terms of its contracts for pandemic influenza vaccine supply.

Presentation 3: Ethical challenges

21 It was suggested that the issues that arise in pandemic influenza should be considered in the wider context of rapidly emerging infections. It was noted that research is currently being undertaken together with a group in Vietnam and Médecins Sans Frontières addressing rapidly emerging infections.

22 It was argued that although pandemics capture the world's imagination, they are often rare and slow-moving. Much greater issues for people such as those who work with Médecins Sans Frontières are found with the emergence of small-scale, fast-moving epidemics such as Dengue fever, and it was suggested that there is an ethical vacuum around these outbreaks. If we consider these outbreaks to be 'virtual pandemics', then perhaps they should be included in any discussion of pandemics, especially given that once these epidemics become pandemics, it is often too late to respond effectively.

23 Research on rapidly emerging infections often needs to take place in the context of health services that are overwhelmed by the excessive caseload of victims and the significant disruption of essential services. Therefore, the very survival of these communities can be at risk. Moreover, the nature of the causal agents can be novel and unrecognised, and the magnitude of the contagion and the impact on individuals can be very difficult to predict; influenza is one example of this.

24 In terms of ethical issues which arise as a result of rapidly emerging infections, it was suggested that – as research clearly needs to be undertaken to address these infections – time constraints can mean that there is a very small window of opportunity in order to get approval for research. Moreover, consent may be difficult to obtain. Would it therefore be acceptable to obtain a waiver for consent? How might a consent waiver be justified? It was suggested that one answer to these questions might lie in the establishment of a community engagement project where the whole community 'consents' to the research. This would require a close relationship between researchers and communities to be formed. There are therefore a number of ethical issues which sit in the broad category of *research* ethics, but can be presented in a different way due to the rapidity of how the infection progresses.

25 For this type of research to work, it was argued that it is important for international collaborations to be founded. For example, it was noted that research on rapidly emerging infections may require samples to be collected from low income countries and exported to higher income countries where

most of the research takes place, and attention was drawn to a situation in 2008 where the Indonesian Government refused the export of samples. A question was therefore raised as to what the responsibilities of the international community, and also of researchers themselves, should be.

26 Moving beyond research to the field of prediction-monitoring, it was noted that data sharing between governments, and also non-governmental organisations, is very important. However, it was noted that it may be politically difficult for governments to share information that shows that they are less prepared than they ought to be. It was therefore suggested that it may be necessary to offer governments a promise of confidentiality in order for them to share the information that is needed by researchers in order to prepare and cope with rapidly emerging infections.

27 The question also arises as to how much resource should be expended now in preparing for the *possibility* of a pandemic, especially where there are a number of other conflicting health care demands in need of funding. Which principles should be chosen to apply, especially in relation to access to vaccines? For example, should principles be based on the aim of minimising the number of lives lost? Should we aim to protect the vulnerable? Should a principle be adopted that focuses on fairness and justice? Should some groups in society with a specific social value – for example, healthcare workers – be given priority? It is clearly not possible to answer in the affirmative to all of these questions, and therefore value judgments have to be made.

28 A further question was raised as to when it is legitimate to restrain people's liberty. To what extent and when should quarantine and restriction of movement be acceptable? To what extent and when, if ever, is it acceptable to enforce treatment and vaccination? Is it acceptable to breach confidentiality during a pandemic in order to gain access to confidential medical records and if so 7under what circumstances?

29 When a pandemic occurs, it was also argued that it is important for research to take place as it is happening, and also after it has happened. Carrying out research on current and previous pandemics will raise ethical issues which also arise in the research ethics arena, such as minimising risk, obtaining consent, and maintaining standards of care.

Issues arising during discussion

30 Several points were raised during the open discussion period which followed the three presentations, including:

- **A suggestion that further research needs to take place examining why there is a low uptake of vaccination among healthcare workers**
  It was suggested that the age of healthcare workers may be a contributing factor to the low uptake of the vaccination as influenza is seen to be an older person's illness. In addition, it was argued that myths about the flu vaccine, such as that flu is contracted through having a vaccination also need

to be dispelled. Despite these specific observations, however, it was felt that a low uptake occurred due to a series of factors rather than for one specific reason, including misunderstanding, and inertia among different groups. There may also be a practical issue regarding the ease with which healthcare workers can access vaccinations outside of working hours.

- **A question as to how to address the adverse effects of vaccination**
  It was argued that the flu vaccine is very safe, and that if you calculated how many people could be killed through having the vaccination, it would be close to zero. Furthermore, attention was drawn to the fact that while few deaths are thought to be actually caused by vaccination, some will be concurrent as vaccinations currently focus on at-risk groups. It was then suggested that the message that should be communicated to the public is that we have a safe vaccine. However, the research evidence on narcolepsy suggested the message of 'safety' is not quite so straightforward.

- **The role of commercially-available vaccinations**
  The impact of the distribution of vaccinations to commercial organisations was raised, and it was noted that the amount of vaccine that would be made available to the retail sector is very small by comparison with the total amount distributed. In relation to data collection, it was noted that the Department of Health has made it clear that data from the commercial sector should be submitted along with data collected from the NHS.

- **Vaccinations and time constraints**
  It was suggested that, should a pandemic occur again, it would be unlikely for a vaccine to be available during the first phase of the pandemic. Questions arising from this observation included whether it was ethical to produce a vaccine for a particular pandemic which might or might not occur.

- **The role of an ethics framework for pandemics**
  Given the Council's previous report *Public health: ethical issues*, which focused on infectious diseases, it was questioned what the function of a further ethics framework would be: who would it be aimed at? Would it be very general? Would it set out who does or does not get a vaccine? Should it inform all governments? It was noted that the UK Government had produced, with the help of an independent advisory committee, an ethical framework for the response to pandemic influenza in the UK. A number of other countries had also produced such frameworks (eg New Zealand) and WHO had produced global guidance on ethical considerations in preparing for and responding to pandemic influenza.

- **Uncertainties about terminology and groupings**
  It was suggested that there is an uncertainty both about the terminology of 'pandemic', and also about what is needed for a person to qualify as a member of a high-risk group. Moreover, if the focus is solely on pandemics, will the findings help with approaching other diseases? Or, will it be more of a hindrance, requiring us to fight a past battle which has already been addressed by a series of papers published by the World Health Organization?

- **The concern that effective treatments are undermined by scaremongering**
  It was highlighted that the best research should inform policy, rather than an attitude of 'I know I'm right, do what I say', which may have been the case during debates surrounding the MMR vaccine. Moreover, a well-founded policy should not react to people's anxieties and fears by giving cause for even more anxiety.

- **The awareness that policy must develop in line with advances in science**
  It was argued that vaccines are based on science as it now stands. Currently, this may mean that benefits outweigh any drawbacks. However, the assessment of risks and benefits to inform policy-making must be an ongoing process which responds to developments in science.

Topic 2: Germline therapies

Presentation 1: The science of mitochondrial donation

31 Mitochondria were described as present in all cells, with their primary function being to produce adenosine-5'-triphosphate, which is an energy source for various metabolic processes. Mitochondrial DNA (mtDNA) was noted to be maternally inherited and as having large numbers of mutations for its relatively small genome. Some of those mutations led to diseases, many of which clinically manifested; the level of the mtDNA mutations was usually reflected in the severity and nature of the disease. There were no cures for these diseases but some treatments did exist.

32 mtDNA diseases were seen as a particular concern in the UK primarily as a result of a greater awareness of the needs of patients in comparison to many other countries. This was because of the national commissioning system for patients with mtDNA disease that exists in the UK, which provides for large cohorts of patients.

33 A patient and her sons were discussed. The patient in question was a woman with an mtDNA disorder. She had two sons. The mtDNA disorder manifested itself moderately in the patient, strongly in one son and not at all in the other. The patient and her sons were mentioned to highlight the difference between studying mitochondrial disorders and nuclear genetics. The difference was a consequence of the copy numbers of mtDNA. (If all copies are the same it is known as homoplasmy (either homoplasmic 'normal' or 'mutated'); where there is a mixture of normal and mutated mtDNA, it is known as heteroplasmy.) Where a patient is homoplasmic mutated, a disease manifests in a specific way. In the case of hetroplasmy, there is a relationship between the level of mutation and the severity of the disease. In the case of the patient mentioned above, the mother had 38% mutated mtDNA, the son without phenotypic expression had 0% and the son with strong expression had 78%.

34 Identifying how this level of variation occurs was important in order to identify the reproductive options for the women involved. There may be marked variation between the offspring of heteroplasmic mothers due to an extreme reduction in mtDNA copy number during germ cell development and/or selective genome replication of genomes leading to a “genetic bottleneck”.

35 From a clinical point of view, there were a number of options. Interventions for mtDNA diseases included counselling, egg donation, prenatal diagnosis (PND), pre-implantation genetic diagnosis (PGD), pronuclear transfer and spindle transfer.

36 PND and PGD were described as popular choices, with egg donation a relatively rare choice by patients. PND and PGD could be very satisfactory. However, PND could sometimes lead to difficult decisions about whether to terminate a pregnancy, if heteroplasmic mutated genotypes were detected. PGD for mtDNA disorders may also lead to difficult decisions when no mutant free embryos were available.

37 In cases where PND or PGD was not suitable, patients could either reproduce naturally in the hope of an unaffected pregnancy or have oocyte donation. However, new IVF based techniques are being developed to try to prevent transmission through pronuclear or spindle transfer, both of which involved transferring the nuclear genome to a recipient egg with unaffected mitochondria. In one experiment in abnormally fertilised human eggs using pronuclear transfer, four out of nine eggs had no carry-over of mtDNA, while in the other five there was less than 2 per cent carry-over. At that level, it would be very unlikely that mtDNA diseases would manifest.

Issues arising out of the presentation

- There were no cures for mtDNA diseases, but a number of reproductive interventions did exist. These included counselling, egg donation PND, PGD, pronuclear transfer and spindle transfer.
- The UK was among the countries that were more aware of the issues related to mtDNA diseases than other countries as a consequence of its national commissioning system.

Other issues arising out of the discussion

- **Emphasis on germline techniques**
  The relationship between mtDNA and nuclear DNA (nDNA) with regard to germline therapies was considered by some to be confusing. mtDNA donation was self-evidently germline modification while nDNA modification was almost always concerned with inserting one or a few genes. mtDNA donation did not actually involve DNA manipulation: rather than direct manipulation, entire functional mitochondrial systems were provided. As such, it was less controversial than the insertion of specific genes. However, there was a legal difference, specifically because mtDNA was treated differently in the 2008 Human Fertilisation and Embryology Act (HFE Act).

- **Paternal mitochondria**
  It was not technically possible to utilise paternal mitochondria in a reproductive context to overcome an mtDNA disease.

- **Abnormal segregation of mutated mtDNA**
  There was a small risk of abnormal segregation of mutated mtDNA. Some mtDNA mutations segregated to specific tissues, but those mutations tended not to go through the germline; there was little evidence inherited mtDNA mutations segregate into specific tissues.

- **mtDNA donation by female genetic relations**
  It was not possible to use the mtDNA of a female genetic relation of a patient in order to avoid some of the ethical issues relating to mtDNA donation: it is highly likely that all relatives will carry the mtDNA mutation and thus and female relatives' eggs will also carry the mtDNA mutation risk for the offspring.

Presentation 2: The ethical issues of mitochondrial donation

38 It was asserted that mtDNA donation constituted germline modification and was ethically permissible in certain circumstances. There were differences between mtDNA and nuclear DNA (nDNA) – size, function and transmission pattern, but these were not ethically relevant in terms of germline modification: as germline modification referred to the transmission of modification to future generations and therefore such differences were irrelevant to the core concept of germline modification.

39 Modification of nDNA was often considered a more ethically contentious proposition because of the belief that nDNA was relevant to individual identity in a way that mtDNA was not: in 2005 the Human Fertilisation and Embryology Authority (HFEA) accepted the argument that mtDNA was not associated with identity or any predetermined characteristics of the individual. An ethical objection to germline modification, based on altering genetic material relating to identity, was that of violating a person's 'right to an open future'. Both UK and Dutch law prohibited germline modification, but contained specific exemptions for mtDNA donation.

40 This dichotomy was untenable: the assumption that mtDNA was not associated with identity had been questioned by some studies and terms such as 'identity' and 'predetermined' had not been sufficiently defined to allow these conclusions to be drawn rationally – the HFEA and UNESCO had not attempted to define either term.

41 The relevant question was whether or not germline modification led to the birth of a different person. PGD did lead to such an eventuality, but it was less clear whether germline modification did – it was the same 'person', but modified.

42 Some understandings of identity separated the notion into two conceptions: 'qualitative' and 'numerical'. Qualitative identity described two units which were identical (such as two identical tennis balls); numerical identity

described two units which were one and the same (for example, the President of the United States and the *personage* of the President of the United States). It was argued that even if mtDNA had a basic cellular role only, donation would still entail a change in the qualitative identity of the individual – following the donation, the future person would no longer be exactly the same as prior to the modification.

43 From this perspective of identity, the dichotomy between mtDNA and nDNA was untenable: modification or donation of either nDNA or mtDNA would result in a change in the future person. The distinction may however be relevant from other perspectives, such as the physical risk associated with nDNA modification.

44 The position adopted by Habermas on genetic modification – that choosing the genetic make-up of a child may imperil its autonomy and therefore unacceptably violate its right to an open future – was discussed. The belief that the autonomy of the individual (future or otherwise) should be protected was endorsed. However, while germline modification through mtDNA donation would alter the identity of the future person, clinical usage of such methods was unlikely to violate the right to an open future through the inhibition of personal autonomy. Germline modification was to be permitted where it broadened 'general purpose means', i.e. allowed for capacities that are useful and valuable for carrying out *nearly all* plans of life. Health was, in most cases, an essential condition for most plans of life. Thus, germline modifications that allow for health was to be permitted. For example, it was reasonable to assume that germline modification to prevent a child developing a serious muscular disease would give the child more options, not fewer.

45 If germline modification through mtDNA donation were not substantively different from the modification of nDNA in terms of its effects on the identity of the future person, any conclusion regarding the moral acceptability of mtDNA donation applied mutatis mutandis to the modification of nDNA. Thus, modification of the nDNA is equally acceptable as long as, other things being equal, this did not violate the child's right to an open future. This line of argument suggested the acceptability of certain kinds of nDNA modification – however, it was not clear whether the ultimate impact of this was necessarily problematic. If the overall criterion of acceptability when considering germline modification were whether a child's right to an open future is protected, the actual process by which this was achieved was not necessarily relevant.

46 There were a number of conditions necessary to promote responsible use of germline modification: modification should only be for the purpose of allowing personal capacities useful and valuable for carrying out nearly all plans of life; the procedure was to be safe and effective; more and better evidence needed to be collected on the function of mtDNA and the physical implications of its modification etc.; appraisal of such evidence was best done by groups, not individuals; ethical guidance on mtDNA modification was needed; and, decisions were to be made on a case-by-case basis.

Issues arising out of the presentation

- mtDNA donation entailed germline modification;
- Germline modification through mtDNA donation has identity-altering potential.
- Alteration of identity was not necessary sufficient to prohibit germline modification.
- Germline modification could be acceptable under certain conditions.

Other issues arising out of the discussion

- **Open futures and option sets**
  There were significant ethical implications in choosing particular option sets, the predicted value of that option set and making certain paths of that option set unavailable to someone. Making a decision where one is fairly certain that a particular intervention will provide the ability to acquire a better future was easy, but complications arose where two futures were compared or where one does not radically change an individual's potential future. The worth of each future was dependent on particular social values within which the individual lived.

- **Identity**
  There was debate regarding the importance of identity in determining the acceptability of germline therapies. The issue of identity was not sufficient in itself to rule out or confirm the acceptability of germline therapies. Rather, it was argued that the main issues were a lack of, and impossibility of obtaining, consent to perform the procedure (from the person resulting) and safety problems – it was not possible to test safety, as any such test would *be* the execution of the procedure.

  The public understanding of identity did not include philosophical notions of qualitative and numerical identity; public understanding of identity was concerned only with 'who you are', in its most basic sense. Regardless of the dissonance between public and academic understanding of identity, considering germline therapies through the lens of identity did not stand up to scrutiny: any disease would result in a qualitative identity change and even if, for example, mtDNA donation did result in a numerical identity change, this was exactly what PGD did and PGD was generally accepted.

- **Safety**
  There was disagreement regarding the issue of safety in terms of medical interventions. Medical interventions were often not entirely understood. Those who performed them were not necessarily aware of all the relevant evidence and if they were aware, they did not always understand it. Many medical interventions would never have been developed if the 'safety bar' was set too high. For example, if the same degree of scrutiny as was applied to current research had been applied to the development of intracytoplasmic sperm injection during the early 1990s it would never have been permitted.

  There was concern that overly strict safety requirements would prevent breakthroughs being made in countries like the UK and research would be

driven into in countries with lower safety standards. Researchers felt that their hands were being forced; centres in the UK had been approached to perform research in other countries, although these overtures had to date been rebuffed.

- **General purpose means**
  It was claimed that arguing that modification should only be allowed for broadening 'general purpose means' was evasive and avoided ethical debate. For example, 'health' was not monolithically constructed and as such could not be relied upon as a universal justification.

- **Correcting heteroplasmy and avoidance of ethical concerns**
  If it were possible to convert a heteroplasmic egg into a perfectly functioning homoplasmic egg, the major ethical concerns regarding mtDNA donation (genetic identity and safety, for example) would be avoided. However, current technology did not allow for the direct modification of mtDNA necessary to achieve such an outcome.

Presentation 3: The legal and policy challenges of mitochondrial donation

47 Germline therapies posed a number of legal, political and policy challenges. The main question was whether those challenges concerned the principle of modification itself or of the degree of change entailed.

48 Whether mtDNA donation was a good test case for other ethical debates around future germline therapies was treated as axiomatic by some and very much contested by others.

49 It was unclear whether there was unity of meaning surrounding the concept of parenthood in terms of the possibility of a child having three genetic parents. The separation of gestational and genetic motherhood was a familiar concept. The separation of major and minor genetic contributors was less familiar and it was unclear whether it raised new questions regarding law or the social construction of motherhood.

50 Legally, it was unlikely to pose a practical problem in terms of the understanding or interpretation of 'motherhood'. In Anglo-Welsh law, primacy was given to the gestational mother, especially given s.47 of the HFE Act 2008, which made clear that an egg donor will not be considered a parent simply by donating an egg. The HFE Act 2008 also gave clarity of meaning to the legal concept of motherhood by providing for two women parenting together: there is one 'mother' and the other partner is a 'parent'.

51 The Joint Committee on the Draft Human Tissue and Embryos Bill made a comment on the draft Bill regarding the assumptions made by the Government, i.e. that there would only be two registered parents in mtDNA donation cases, but the child should be able to find out who the donor is. This was not made clear in the 2008 HFE Act or the explanatory notes and it therefore appeared that only nDNA had relevance to parenthood.

52 Other jurisdictions approached this issue differently. In 2005, the New Zealand Law Commission tabled the possibility of recognising three legal parents in the context of donor insemination. In 2007, a Canadian court made a declaration of parentage in favour of a co-mother as a child's third legal parent. However, given the primacy already granted to the gestational mother in Anglo-Welsh law, it seems unlikely that any other approach would be adopted here.

53 The social construction of motherhood in this context was the subject of significant debate, especially in the media, although there was little academic work on the area. There were some anthropological studies regarding how parents construct kinship, but much less work on how children do so. It was therefore difficult to assert with evidence whether children would suffer psychological harm as a consequence of three people providing genetic material at conception.

54 It was contested whether mtDNA contributed to one's sense of identity. There was a need to balance scientific and social constructions of identity. The debate needed to be framed clearly and carefully – the HFEA's construction in 2005 was very narrow.

55 The 1990 HFE Act generally did not attach much priority to genetic matrilineal connections except in relation to some instances of surrogacy – although there were no legal case examples, one parent was required to be genetically related to the child to get a parental order. It was unlikely that mtDNA would be sufficient connection.

56 The intergenerational aspect of mtDNA modification was important. Work had been done regarding the social construction of motherhood comparing mtDNA modification to tissue donation. However, tissue donation had no intergenerational element. Whether mtDNA donation, specifically, caused significant questions for kinship construction depended to some extent on whether mtDNA donation was seen as a test case for future germline therapies. If it was not so seen, the topic would attain less significance and would probably be considered a discrete area – safety and efficacy would be the primary concerns, rather than morality and the law.

57 It was questionable whether mtDNA donation was safer than nDNA modification. There was a need for further research. There was a possibility that widespread mtDNA donation would put pressure on an already limited supply of donor eggs. However, it may lead to a reduction of terminations. There were applications outside serious disease: for example, the possibility of a same sex couple both being genetically related to their child, or a woman who has a major DNA disease (who would traditionally opt for egg donation but who wishes to maintain some genetic relationship with her child) could use her egg with the nDNA of a donor.

58 It was noted that two main questions remained unanswered in relation to mtDNA and kinship: which of the scientific or social constructions were most

important and were the disruptions to these understandings sufficient to call into question the current paradigms in this field?

Issues arising out of the presentation

- The relevance of mtDNA donation as a test case for other germline therapies was subject to debate within the relevant literature.
- The social construction of parenthood was not well understood, especially from the perspective of the child.
- The legal construction of motherhood, at least in Anglo-Welsh law, was clear: primacy was given to the gestational mother and the HFE Act 1990.
- Other jurisdictions had contemplated the possibility of recognising three parents.
- It was unclear whether issues relating to mtDNA donation and the social and legal construction of kinship were sufficient to require re-assessment of the paradigms in the field.

Other issues arising out of the discussion

- **Framing**
  It was argued that, regardless of its coherence, the moral debate was framed by international declarations which prohibited germline modification and established rights to 'genetic integrity'. However, there was a perception that the concerns posed might be artificial. For example, there were hints of genetic exceptionalism underlying the stated concerns; the policy documents that framed the debate were established prior to the development and elucidation of some of the techniques and issues involved. The importance of genetic identity and the possibility of three genetic parents had not been demonstrated as inherently important.

Topic 3: Hyper-expensive new therapies and the prioritisation of research and development

Introduction

59 This discussion about hyper-expensive therapies was particularly timely. Expensive new drugs were being developed by pharmaceutical companies at an increasing frequency. In addition, the issues evoked by hyper-expensive therapies were potentially compounded by the current context of funding cuts across the public sector and limited finance for healthcare. The presentations in this session centred on: i) the clinical perspective; ii) how drugs were priced and evidence evaluated; iii) the direction of biomedical research; and iv) the ethical issues associated with hyper-expensive therapies. The session concluded with a panel discussion of all the speakers, with questions taken from the floor.

Presentation 1: Hyper-expensive new therapies in clinical practice

Cancer therapies: their cost and how to obtain them

60 The cost of cancer therapies had risen. Whereas previously clinicians had taken a relatively crude approach to cancer therapy,[1] clinicians today were able to adopt more nuanced methods due to the advent of the 'biologics' (i.e. medicines developed from living organisms with the help of disciplines like proteomics and molecular biology). This, however, was associated with greater cost. Cancer therapy was also increasingly more individualised, in reflection that cancer was a spectrum of diseases along which patients could be stratified for treatment. This increase in individualisation was mirrored also by an increase in cost.

61 If a patient required a therapy for which there was no NICE approval, the clinician either looked for ongoing trials involving the therapy or started proceedings to determine whether there might be exceptional circumstances under which the therapy could be approved. This latter option was very time consuming, although sometimes, if there was a history of similar cases, the drug could be approved more quickly because there had already been deliberations. The interim cancer drug fund – introduced in July 2010 to help cancer patients who need access to drugs – comprised groups of oncologists which examined potential future scenarios and pre-approved cancer treatments. This initiative had also helped in some areas to reduce the time period for approval. In some cases where funding was not obtained, clinicians used inferior alternatives – therapies which had since been superseded by newer ones.

Clinical perspective

62 Clinicians wanted to provide the best available therapy for their patients; however, they were also aware of their financial responsibilities as part of the NHS. Thus, among those practising in the cancer field, a collective approach had arisen to determine what were un/acceptable practices, and this had been distilled into guidelines.

63 Clinicians were under intense pressure, however, to use expensive therapies. Patients – well-acquainted with internet sources regarding cancer therapies – had high expectations over what could be achieved for their prognosis. Stories represented in the media – sometimes factually inaccurate, sometimes highly relevant – also contributed to raised patient expectations. Charities also drove up expectations.

64 Prejudices also existed. For example, in the UK there was the prevailing notion that one should not spend too much on the elderly. As a consequence, many of the hyper-expensive medicines were seen as being too expensive

[1] E.g. if a certain dosage was found to be effective in one hour, it was assumed that ten times the dosage would act ten times faster.

for this population group. The effect of this would increase in scale as the population continued to age. Among pharmaceutical companies, there appeared to be a reluctance to undertake groundbreaking research that would produce hyper-expensive medications, as companies feared that there would be no return. Faced with this situation, clinicians sometimes felt as if they were “drowning”.

NICE issues

65 The NICE approval process had several issues, the first of which being that it was a lengthy procedure. While it removed clinical decision making and therefore helped to prevent abuse of finances, it simultaneously engendered rigidity in what could and could not be done by clinicians. Also, NICE prevented clinicians from prescribing therapy without evidence but this created a situation where the necessary evidence could not be obtained as there could be no clinical practice to obtain the evidence. In addition, NICE typically determined cost-effectiveness based on trials that involved younger patients: this limited the application of the process for the elderly population.

Inconsistencies in healthcare spending

66 Clinical practice highlighted several inconsistencies regarding how money was spent in the NHS. For example, there was comparatively little scrutiny of investigative procedures, such as a CT scan. Also, poor choices were often made. For example, in the treatment of some cases of chromic myeloid leukaemia where the approved drug was deemed not effective, there had been a move back toward transplantation. Transplantation cost around £150,000. This prompted the question as to whether this step backwards therapeutically was really the best use of resources. In the case of chronic lymphocytic leukaemia, there had also been a move toward an older drug which was ineffective and potentially caused secondary leukaemias, even when better alternatives existed, such as rituximab.

Concluding comments

67 There was a role for hyper-expensive medicines; it was also important to be able to approve these more quickly. The decision making for approval should be local so that the needs in that area could be addressed. Decision making should also lie with those who dealt with the patients: this would help make the relationship between the doctor and the patient easier.

Presentation 2: The method of measuring evidence and pricing drugs

68 This presentation described the Government’s plans for value-based pricing and how NICE had amended its approval procedure to date both to achieve better access and to reflect better societal opinion. It was difficult to know how much of the content would be relevant to the future as the regulatory context was changing continually.

Value-based pricing

69 The Government had taken the view to move toward value-based pricing (VBP), ultimately to improve patient access to effective medicines. There were four objectives:

- To achieve better outcomes through better access to effective treatments;
- To stimulate the innovation and the development of high-value medicines (this was directed toward industry and concerned the choices it made regarding its direction for research. An issue to be challenged was industry tending to do research where it was cheapest and quickest);
- To widen the scope of benefits to be assessed (currently, NICE examined only quality-adjusted life years (QALYs) because they were required to do so by statute); and
- To ensure value for money and best use of NHS resources.

70 VBP would apply to new medicines on the market from 1 January 2014. In this system, the Government would set out a range of maximum threshold prices reflecting the different values that medicines offer. QALYs *and* a cost-effectiveness threshold would be used. Higher price thresholds would be attributed for medicines that: tackle disease of high unmet need or severity; demonstrate greater therapeutic improvement and innovation; and demonstrate wider societal benefits. Categories and weights would be determined by the Secretary of State on the basis of expert advice, and within a framework determined in advance.

71 There were issues with the VBP system. For example, VBP involved documentation that was even more complex than the already complicated current NICE assessments. Methodological issues also existed, including the risk of double counting in moving away from the use of QALYs. There was also concern as to whether VBP would have due regard for the Equality Act 2010.

NICE initiatives

72 NICE only said ‘no’ to funding for approximately eight to ten percent of cases; however, as these cases mostly related to cancer and end-of-life therapies, they were highly emotive in nature. To improve access to medicines, NICE had introduced various initiatives. The initiatives worked to weight a QALY for the end of life. NICE had taken this approach following research it had commissioned separately from Cam Donaldson and Paul Dolan. Both had come to the conclusion that society *did* want QALYs weighted, but there was no consensus as to how they should be weighted. There had, however, been sufficient evidence to at least weight QALYs on the end of life.

73 Thus, NICE had brought in supplementary advice for advice committees on appraising life-extending end-of-life treatments. A result of this was that if it was known that a patient only had a few months to live, those few months

were deemed more valuable than a comparable time in another individual in a different stage of life. A patient access schemes were also established. This examined ways of *equivalently* dropping the price of a therapy without actually dropping the price. The NICE Citizens Council published a report, the Kennedy Study, on ultra orphan drugs (drugs for very rare conditions) and end-of-life drugs and following this, changes were made to the way drugs were assessed. For example, if a drug was very innovative, this was taken into account. NICE also commissioned a number of research projects, through NIHR and NIHR/MRC programme, to consider these issues.

74 These initiatives had been engaged in NICE's procedure for assessing interventions; however, there were still limits. For example, following the Kennedy Study, industry was asked about what was innovative about the drug and why indeed it should cost more. It was also asked how often a NICE assessment missed something important to the patient. Even with this additional evaluation, several medicines were not captured.

75 More recently, NICE had commissioned research led by Mark Sculpher: this would be completed next year. This research examined the threshold that the NHS could afford to pay for an intervention – an assumption that was integral to NICE's analysis. Early results indicated that a QALY equated to £15,000, in contrast to current figures which placed a QALY around £20,000–£30,000. If this was the case, NICE should not have approved even more medicines. This research would be particularly interesting for the future as VBP was depended on the position of the thresholds.

Value-based pricing: NICE's perspective

76 NICE took the view that, within the VBP system, the economic appraisal of the evidence should still be carried out by a multidisciplinary panel comprising doctors, nurses, academics etc. However, the information gathered by the panel should be more formalised (currently, only a report either from industry or an academic group was submitted), and NICE believed that this process should involve public consultation. The findings of the panel could then be used by the Government to negotiate with industry on a value-based price for the drug.

Presentation 3: The direction of biomedical research

Industry research: its direction and representation in the literature

77 Research in the public sector used finite public resources and as such, there was consideration of public opinion by those determining its direction. In the private sector, there was a less of a sense of research being a public good. There was a feeling that there should be a return on investment, and this influenced what research was conducted. Many pharmaceutical companies engaged in so-called 'me-too' drug development where, following the expiration of patent protection for a drug, companies produced drugs that were structurally very similar with only minor differences to the original.

78 There was well-documented evidence regarding how pharmaceutical companies represented their results favourably in the literature. Strategies included: publishing only desirable results in high-impact journals; omitting research that showed undesirable results; and trialling a drug against another drug that was administered at a lower dose than was clinically effective. Neither the peer review process nor the business model (discussed below) adopted by biomedical journals was able to contend with these issues.

The effect of industry on the direction of biomedical research

79 The business model of biomedical journals typically relied on a significant proportion of income being derived from reprints bought by pharmaceutical companies. This introduced a positive publishing bias for industry articles. In addition, industry studies tended to be cited more often than public sector research anyway, due to the high use of randomised control trials (which industry could afford) and publishing in the high-impact journals which had more marketing power. These factors affected what fields biomedical researchers chose to enter, as it was ultimately a choice influenced by where the publication opportunities were, and the level of industry sponsorship (since this drove revenue for journals). Indeed, there had even been cases of researchers in other non-English speaking countries receiving assistance from drug companies to publish their research in a particular journal, from which the drug company then purchased reprints.

80 In the context of industry research for hyper-expensive drugs, some risks were potentially greater. For example, there would be greater pressure on industry to make its drugs look good given the expense required for development.

Other comments

81 There were concerns about industry research, and hyper-expensive drugs, in general. For example, given that industry research still required public participants and sometimes used public researchers, what should be the benefit for the public? If pharmaceutical countries carried out hyper-expensive drug research in countries where it was cheaper to develop these, how affordable would the hyper-expensive drugs then be in the same country? Cost-effectiveness was typically based on randomised control trials involving young healthy people; it would be more accurate if the participants were those from the actual clinical context. If research participants included those living with the disease, the question thus followed as to whether hyper-expensive drugs should be used initially in the research setting only and, if so, what safeguards were necessary?

Presentation 4: Ethical issues

The focus on hyper-expensive drugs

82 Previous talks in this session had discussed hyper-expensive “drugs”, “therapies”, “treatments” and “medicine”. It was important to identify which of

these was being discussed as they were conceptually distinct and generated different ethical questions. Discussions about hyper-expensive medicine often focussed on drugs; however, this might not be the best place to start given only a small proportion of the NHS budget was spent on patented drugs (under £10 billion out of £100 billion). Also, if other medical interventions were evaluated using similar procedures to those used for drugs, many of these would not be funded on the NHS, e.g. kidney dialysis, various scans and surgical procedures. This differential approach toward healthcare spending was perhaps explained by popular distrust of pharmaceutical companies which rendered these targets for scrutiny. However, if there was to be a discussion about hyper-expensive treatments, it was crucial to broaden the debate beyond hyper-expensive drugs. Currently there was very little of this.

A QALY is not a QALY is not a QALY

83 NICE took the stance that "a QALY is a QALY is a QALY", i.e. a life year gained in any way, for example drug intervention, is equivalent to a quality-adjusted life year gained through another method, such as surgery. But it was evident from ongoing political discussions that the public did not believe this. For example, there would tend to be a public preference for maintaining the life of one person for one year, rather than affording a large number of people with a smaller health benefit which would effectively add up to one QALY also. The cancer drug fund was a further example. So far there had been no public objection, and this perhaps implied that the public deemed a QALY gained from treating cancer to be more important than other QUALYs. Thus, the NICE view appeared not to be true when it related to cancer, end-of-life care and severe diseases. Rarity also seemed to precipitate a greater willingness to pay more for drugs; this related to orphan drugs. The question thus arose: why should there be this differential view of QUALYs? Why should an expensive drug be funded when the drug is expensive because the condition is rare (and therefore has a small market), as opposed to a drug that is expensive because it is derived from materials/procedures that are currently expensive? From the health economist's perspective, the differential view of QALYs demonstrated "pandering" to the public prejudices. It also raised issues of fairness.

How should the NHS budget be spent?

84 Ultimately, such discussions reduced to the question of on what the NHS budget should be spent. Some took the narrow view that there was only one purpose of the NHS budget – to maximise health gain. Often, decisions were criticised because they were perceived to not maximise health gain. However, it was not written that the only purpose of the NHS should be to maximise health gain. There were potentially other prioritises: e.g. to prioritise the vulnerable, the worst off for treatment etc. The use of the NHS budget was a decision for politicians, and ultimately the public since it was the public that would pay. There was, however, no good evidence regarding public opinion on NHS spending.

Issues arising out of the discussion

The role of NICE

85 It was considered whether NICE could play a role in assessing measures intended to improve public health – effectively, preventive medicine and health promotion. NICE did evaluate such public health measures, using the same methodology it used for medicines evaluation. NICE had developed several guidance notes regarding such measures but these were currently on hold as they had been deemed not to fit with the model of 'nudge' that was emphasised in the recent White Paper on Public Health. On the broader issue of the effectiveness of public health measures, there was no evidence that if the public was fully engaged with disease prevention and health promotion that money would be saved. Public health measures did not change peoples' lives quickly and as such there would be no immediate savings.

86 It was asserted that there should be assessment of the whole patient pathway cost – including scans, drugs, accommodation costs etc. – and there should be appropriate guidance on how to contain costs. Patient pathway assessment would enable auditing, which would assist in achieving compliance with the guidance.

The use of QALYs

87 It was important that in assessing treatments, the 'real' benefits were captured. Accordingly better measures than QALYs were needed; these would then help ensure better outcomes for money spent. Thus, while the amount spent on drugs did only constitute a small proportion of the NHS budget, it was still possible to obtain greater benefits for that amount spent.

The ethical issue of expense

88 It was considered what was ethically problematic about expense in medicine. There were potentially two reasons why expense might be troubling. Firstly, if the expense involved a 'bad buy', for example because the treatment was ineffective. Secondly, if there was cost sharing for the expense, and it was felt that the cost was being borne unfairly, for example disproportionately by patients. This latter issue related to how the cost was *distributed*, rather than the absolute cost.

89 From a physician's perspective, it was ethically troubling to spend money on treatment which was not going to achieve significant health gains. Indeed, expensive care did not necessarily equate to the best clinical care or outcomes. Physicians, however, were subject to a great amount of pressure from patients to prescribe expensive medicines. This generated opportunity costs for others, given that the NHS was effectively based on a cost-sharing scheme.

90 It was observed that affordability was a political concept, in contrast to absolute cost which was objective. What was deemed ‘affordable’ had implications in what was provided in medicine. Indeed, it was felt that due to preconceptions as to what was affordable, a culture had arisen where it was sufficient in medicine to do what was ‘just good enough’ as opposed to what was the best for the patient.

Patient expectations and science communication

91 Scientists also contributed to raised patient expectations by giving the impression that there was a ‘quick fix’ around the corner. High-impact journals, seduced by such messages, then published these articles. A greater critique of papers and openness in the scientific community would go some way to addressing this. There was a great need for such a movement.

The focus on cancer

92 People tended to react irrationally in the face of dread and risk; for example, one might pay more for insurance against acts of terrorism, rather than the causes of terrorism. The question arose: was this also demonstrated with the seemingly prioritised funding of expensive cancer treatment, or did it reflect a genuine – rational – public concern?

93 Patient expectations contributed to the focus on cancer, as there were greater expectations with regards to what could be potentially achieved. In recognition of this, it was important for clinicians to manage patients’ expectations. This could, in the end, benefit the patient directly. For example, there were cases of patients with cancer – driven by their expectations – selling their belongings so as to be able to afford expensive yet futile treatment. Doctors too could become party to this: there was a fear on the doctor’s behalf that they might be ‘failing’ their patient in not being able to cure them, when perhaps only maintenance of life or palliative treatment was possible.

Prize fund vs patent protection

94 Patent protection resulted in high costs that worsened the economics of innovation. It was considered whether an alternative approach to patents was plausible, such as a prize for innovation. This could be afforded to encourage research towards the most socially desirable ends but without state control. Additionally, the knowledge developed could become a public good, thus giving rise to competition.

95 If the aim of the prize was broad enough (e.g. cure cancer rather than discover a drug for a specific aspect of cancer), it might be possible to establish a prize system. There could be benefits in the prize coming at the end of R&D, in contrast with the current system which effectively involved ‘bets’ being placed on research beforehand. In the current academic system, it was noted that once an academic received tenure, they were not as

accountable in terms of the direction of research and its usefulness. On the other hand, such a 'blue sky' environment could enable valuable discoveries.

96 There was a question as to who would fund the prize. Other problems existed in that, presumably, the prize would only be given to those who made the discovery first. This could be healthy in terms of eliminating research, such as that which led to the me-too drugs. However, the risk of not achieving the reward was potentially prohibitive to pharmaceutical companies; it would be difficult for these to adhere to such a system. Also, me-too drugs were sometimes linked to healthy competition which was desirable from a consumer's point of view. It was also important to note that pharmaceutical research was often not an exact science; 'useful' discoveries were often made serendipitously and therefore a prize fund was not guaranteed to yield significant results.

Research by pharmaceutical companies

97 It was felt that there was a great misunderstanding over research conducted by the pharmaceutical industry. Industry evaluated three qualities of its research: cost, speed and quality. R&D had to develop medicines that would last for several decades. It was felt that commercial research was some of the most highly regulated and highest quality research.

Other comments

- 'Hyper' was a marketing term; it was more accurate to describe the drug as being expensive with limited opportunities for access.
- It was important to note that generics today, such as statins and ACE inhibitors, had once been high-cost drugs. Hyper-expensive drug development could be an important step in the development of future generics.

Topic 4: Genomics, health records, database linkage and privacy

Presentation 1: An overview of data protection and privacy issues

98 It was important that data protection was understood as being intended to protect fundamental rights and freedoms, in particular, privacy. Prior to 2009, when the Treaty of Lisbon came into force, the legal basis for this protection in the European Union was to enable and encourage the free flow of data for the purpose of assisting the European single market. Since the Treaty of Lisbon, the protection of fundamental rights and freedoms had been incorporated, in effect, into the European constitution through the European Union Charter of Fundamental Rights and Freedoms (the EU Charter), Article 7 of which provided a legal right to the protection of personal data. The consequence of this shift in legal basis was to provide for enforcement; the shift would be reflected in the up-coming revision of the EU Data Protection Directive, which in turn would be reflected within the implementing legislation of EU Member States.

99 The right to privacy was provided for by Articles 7 and 8 of the EU Charter and the European Convention on Human Rights, respectively. This right was very broad and included, for example, the right to bodily integrity, the right to make decisions about how to lead one's life, and a right to control the use of one's personal information. As such, it was not to be read as only concerning the concealment of identity.

100 The right to privacy, as provided by Article 8.1 of the European Convention on Human Rights, was not an absolute right: Article 8.2 provides a variety of exceptions to entitlement guaranteed by the right. These include national security, public safety and the prevention of disorder. These exceptions only provide a justification for a breach of the right, not a nullification of the right itself; fulfilling the exceptions did not mean the right had not been breached. They could also be appealed to only to the extent that it was necessary to do so, i.e. a number of criteria had to be fulfilled, including that the breach was in accordance with the law, necessary within a democratic society and proportionate.

101 There were a number of questions that concerned data protection and the right to privacy, and how they relate to genomics, health records and database linkage: what defines personal data? Is genomic data personal? Should there be generic exemptions to privacy and data protection requirements with regards to medical research? Is anonymisation of data an appropriate safeguard for the right to privacy?

102 Under the EU Data Protection Directive, personal data was considered data relating to a (living) identified or identifiable individual who can be identified directly from the data or from the data and other information which is in the possession of, or is likely to come into the possession of, the data controller or any other person. The UK Data Protection Act 1998 implemented this requirement more restrictively, by applying it only to the data controller, and not also to 'any other person'. As such, there was a potentially serious discrepancy between EU and UK law. If there was a discrepancy, UK law would have to be modified in line with EU law.

103 EU data protection law did not apply to data that was anonymised. Therefore, it was necessary to be able to define 'anonymised data'. The inability of a data controller to identify the individual to whom the data related did not in itself mean that the data being processed was anonymised; if someone else could reasonably identify the person, the data could not be considered anonymised. It was argued that if it were possible to provide the protection required by law then the data was, by definition, not anonymised.

104 Genomic data was not considered personal data per se: if it could be linked to a means of identifying the person to whom the data related, then it was considered 'personal data'. There were plenty of indications that the revised EU Data Protection Directive would directly confirm genomic data as personal data, at least under certain conditions. It was suggested that the

European Court of Human Rights case *S and Marper v The United Kingdom (2008)* supported this view.

105 It was argued that only if *all* medical research was considered so important that its performance was justified in the face of a research subject's explicit objection should a generic exception to data protection requirements be granted. If this was accepted then it had to be considered that it would be acceptable to conduct medical research in the face of a patient *explicitly* denying consent. While ignoring such explicit objections might be justified in some research, it was unlikely to be justified in all research.

106 Anonymisation of personal data was not a panacea for data protection and privacy concerns. Protection of data was not just concerned with privacy, but with any fundamental rights and freedoms that might apply. Anonymisation did not always protect privacy, as it was possible to argue that individuals had a right for medical research to be conducted under the right to privacy, i.e. a right to know the personal implications for oneself of research. Furthermore, it was noted that anonymised data was less useful for medical research. Therefore, anonymisation of data may actually cause harm, given that anonymisation generally inhibits the effectiveness of medical research and the poorer the results of any research, the weaker the justification for the research.

Issues arising out of the presentation

- The basis for data protection has changed from assisting the European single market to a fundamental right incorporated into the European constitution.
- The right to privacy is not absolute.
- There may be significant discrepancies between UK and EU data protection law.
- Where data is entirely anonymised, data protection regulation cannot be applied by definition.
- Genomic data is not personal data per se, but may be considered such if certain conditions are met.
- Granting a generic exception to data protection regulation for medical research is only coherent if all medical research is considered so important that performing such research is justified in the face of a research subject's explicit objection.
- Anonymisation is not a panacea as there are other goods to consider beyond privacy. For example, potential health gains from medical research may be retarded by anonymisation for the purposes of preserving privacy.

Other issues arising out of the discussion

- **Legal applicability of the data protection Directive and implementing legalisation**
  It was argued to be impossible to apply the protections offered by the EU data protection Directive to truly anonymised data, given Recital 26 of the Directive.[2]

- **Anonymisation**
  Anonymisation was not a simple solution to questions surrounding personal data, confidentiality, data protection and privacy. There was no such thing as anonymised data per se, only anonymised context. Furthermore, it was argued that the interests of the research participant did not end with anonymisation of their data. For example, an individual with a strong personal aversion to the development and usage of chemical contraceptives could still be judged to have an interest in preventing their personal data, even if anonymised, being used in research intended to develop such products.

Presentation 2: We have your medical records on file: the human side of 'big IT'

107 It was argued that the ethical concerns relating to 'big IT' should not be addressed only from an academic perspective; academics were also husbands, wives, fathers or mothers, and patients. The positions taken by an individual often reflected the manner in which they experienced the relevant event – professionally, as a patient or as a relative of a patient.

108 Such a 'human level' approach led to two main messages. Firstly, that the human side of 'big IT' was not only ethical, it was personal, practical and technical. Also, that the ethics of 'big IT' could not be solved in the abstract. To emphasise these claims, a number of case-studies were presented, highlighting various perspectives.

109 It was noted that medical professionals working in the fields of psychiatry and psychology were concerned by the proliferation of medical databases. The case of a patient suffering from paranoid delusions was outlined: a trainee GP had been 'consenting' the patient for inclusion into a research study where his NHS electronic health record (EHR) would be accessed as part of a larger research database. When the patient discovered this he ascribed his delusions, manifesting as external agents 'putting thoughts in [my] head', to researchers' access to his EHR. Although this case was unusual, it aimed to

[2] "Whereas the principles of protection must apply to any information concerning an identified or identifiable person; whereas, to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the controller or by any other person to identify the said person; whereas the principles of protection shall not apply to data rendered anonymous in such a way that the data subject is no longer identifiable; whereas codes of conduct within the meaning of Article 27 may be a useful instrument for providing guidance as to the ways in which data may be rendered anonymous and retained in a form in which identification of the data subject is no longer possible"

emphasise how the perception of reality may also alter behaviour in non-delusional people.

110 The behaviour of relatives was extremely important when considering data protection and databases. ‘D’, who died age 76 of vascular dementia and complications of type 2 diabetes, had a strong aversion to being included in databases. When he was recalled for diabetes screening after being symptom-free for 11 years following diagnosis, he questioned how ‘they’ knew to contact him. His presence on the relevant databases was hidden from him by his relatives, who believed he would demand to be removed if he knew the truth. Consequently, it was important to bear in mind that the (apparent) behaviour of patients was often dictated by the experience and behaviour of their relatives.

111 Experience of a disease often had a significant influence on how an individual approached particular ethical dilemmas. Prior to his diagnosis with, and subsequent survival of, cancer, ‘J’ (a research professor on life threatening diseases) believed that a lack of informed consent was sufficient to exclude a potential participant from being involved medical research. Following his experience with cancer, he believed that only people who had not experienced a life threatening disease would allow a lack of informed consent to inhibit systematic and rigorous research into treatments for life threatening illnesses – he professed to finding it very difficult to accept that a lack of consent on the part of some individuals should influence *his* survival.

112 The experience of individuals with the administration of medical research, especially concerning the provision of consent, was influential in terms of their continued participation in that or future research. ‘S’, who had a rare blood disease and small children (one of whom had ADHD), believed that her seven-year-old child with ADHD may have inherited her disease. ‘S’ had been sent a six page document relating to a study inclusion that may have benefited her son. She was considering not entering him into the study due to the length and complexity of the document in light of her other obligations and external stress in her stress life. Her case highlighted the practical and personal nature of medical research ethics; consent processes could shape and change people’s access to healthcare dramatically.

Issues arising out of the presentation

- The personal perspectives of those involved with or affected by medical research challenged professional views and approaches.
- Experience and perspective can radically shape behaviour and approaches to the issues at hand, such as privacy and medical research.
- The consent process for medical research is often inadequate, especially on a practical level.
- What is ‘ethical’ for one person might be unachievable, impractical or inapplicable to another.
- Contemplation in the abstract was not particularly useful – matters should be considered on a personal, human level.

Other issues arising out of the discussion

- **Patient and participant involvement**
  It was noted that one of the most interesting developments of the last few years was the involvement of patient groups in public debate. For example, it was difficult to consider HIV research without thinking of the HIV community. That community had given novel and articulate views on HIV research. However, networks of individuals talking as one about these issues can be problematic, as the individual's ability to speak, or be recognised, on their own behalf might be compromised. It was, however, argued that it was appropriate that such networks be part of the overall dialogue.

  Attitudes to consent were changing; rather than require the researcher or ethics committee to consider the position of participant, it could be more appropriate to communicate with participants directly. It was argued that the '2.0 technologies' might allow this even in large research projects, if implemented carefully. (In this context, 2.0 technologies were seen as those information and communications technologies that allowed rapid identification of, and communication with, specific individuals.) For example, if the aim of a study was to promote global public health, then participants should help frame the approach. However, not all members of society, especially those from lower socio-economic groups, would be interested or capable of meaningful participation.

Presentation 3: The benefits and ethical/legal challenges of developing genetic databases

113 The field of genomics was moving towards next generation sequencing such as exome sequencing (which is concerned with identifying the coding regions of the genome responsible for disease), and away from genome-wide association studies (which is concerned with identifying single-nucleotide polymorphism associations); also, using nanotechnological techniques to directly determine base pairs (and thus move away from the use of reagents and polymerase chain reaction). In parallel to the development of new genomic technologies, the ability to process, store and transmit information was undergoing a similar transformation: the technology was becoming easier to use, cheaper, quicker and more distributed. Jurisdictional boundaries were less relevant to data processing than hitherto. The open access movement was increasingly influencing approaches to sequencing data and possibly also phenotypic data; new information and communication technologies (ICT) were leading to new ways of performing science.

114 Scientific research was increasingly interconnected and research networks existed on all levels: regional, national and global. This was influencing the nature of research, especially where large datasets were concerned. Given the nature of these networks, and the increasing sophistication of ICT systems, researchers could access large, seamless datasets where

previously they would have had access to more fragmentary data. These trends tested medical research ethics in a number of ways.

115 The applicability and acquisition of consent, as currently conceptualised and practised, was probably no longer relevant or practical. This was broken down into concerns relating to ‘informed’ and ‘broad’ consent

a. Informed consent in medical research was generally seen in relation to physical harm and in association with single project-research – the globalised nature of scientific research and the ICT systems involved (enabling data sharing at an unprecedented level) meant that it was increasingly difficult to inform research participants at the time of consent collection of all potential uses of data derived from their participation. As such, acquiring informed consent was in danger of becoming a ‘tick-box’ exercise. Furthermore, informed consent was generally conceived in relation to the effects of research on the individual giving consent: contemporary genomic research strained this understanding and revealed the inadequacy of traditional informed consent processes in taking into account the interests of family, groups and populations.
b. ‘Broad consent’ was intended to provide consent for a range of purposes by requesting one-off consent for the use of medical information, which would be used for many years building up profiles of individuals. It was considered a contentious issue as it was effectively a request for consent for *governance*: difficult decisions were delegated to research ethics committees and advisory boards.

116 The right (and ability) to withdraw from research at any time was tested by data sharing processes: the ability to withdraw could not be guaranteed when data was spread over multiple projects across the globe.

117 The procedures surrounding research participation, especially concerning consent, developed on the basis of the altruistic and solidaristic intent of the research participants, who were guaranteed anonymisation and confidentiality of their personal data. Given that the ability to anonymise and treat confidentially the personal data of research participants had been called into question by the developments in ICT and global research networks, the social contract underpinning research involvement had been challenged. These issues went beyond the medical research context: the advent of commercial genomic sequencing companies, such as 23andMe, meant that collection and analysis of genomic data was no longer restricted to the medical research community.

118 It was argued that patient and research participant centred ICT systems should be developed with the specific aim of granting patients greater control of their data and the attitude of researchers changed to reflect the new reality.

119 The developments discussed posed new challenges, some of which had not yet been answered: should researchers expect altruistic research

participation if confidentiality cannot be guaranteed? Given the likelihood of incidental findings in genomic research, should there be an obligation on researchers to feed back to participants?

Issues arising out of the presentation

- Global research networks, large scale data sharing and new ICT capabilities had led to new challenges to research ethics, specifically in relation to consent and the right to withdraw from research.
- The 'social contract' underpinning much research was under threat from these developments. Confidentiality was increasingly difficult to guarantee. New approaches were needed.
- ICT systems needed to be designed to provide greater control of data to patients and participants. Researchers should alter their approach and governance strategies should shift from local to global.

Other issues arising out of the discussion

- **Approaches to consent**
  Consent was not an absolute solution: it was not the ultimate justification for a particular action as other 'goods' were relevant. For example, under the Human Tissue Act 2004, taking tissue without consent would be illegal without consent and lawful with: obtaining consent was both necessary and sufficient for lawful behaviour in that context. However, where a person could not give consent, it was possible to *deem* them to have done so. Therefore, the actual reason for the legitimacy of a particular action was not that consent was or was not obtained, but that one sought to prevent something worse happening to another person. Quarantine enforced without individual consent, for the good of the wider populace, was given as an example of a situation where consent was not usually considered necessary for lawful or ethical behaviour.

  The example of enforced quarantine highlighted the tensions between the public good and the consent of the individual. It was noted that many lives were saved by looking at the public good created by certain types of activities where no consent was deemed necessary for enforcement, such as use of seatbelts and crash helmets.

- **Approaches to data protection**
  Data protection legislation in Europe was a blunt instrument, the underpinnings of which were formulated in the mid-1980s. Global data sharing and changes in research methods had rendered the Data Protection Directive's focus on privacy inappropriate – current research was moving towards protecting confidentiality, not privacy. Additionally, social change influenced a participant's approach to research and protection of their personal data, at least on a global scale. The focus was now on governance frameworks and accountability procedures, not on the trust invested in the professional conducting the research, as such trust was difficult to develop in most circumstances, but almost impossible to achieve at a global level.

Although new technologies made it difficult to offer total protection of certain values, this did not mean that the attempt should not be made. When such technologies rendered this protection impossible, then amelioration became the goal – it was important that values be balanced.

- **Challenges and responses to new technologies**
  It was unclear whether it would ever be feasible to offer a right to withdraw from all forms of research. For example, in the case of published meta-analysis it would be practically impossible for a participant to withdraw, as the data had already been published. However, medical research policies were always challenged by new technologies and it was important that attempts should always be made to meet the challenges – in this case, evidence suggested that the majority of participants would be satisfied with simply being informed how their data is used.