Nuffield Council on Bioethics
Forward Look Seminar
29th – 30th April 2009

Note of meeting

Present:

Guests
Professor Priscilla Alderson
Robert Bailey
Professor Hazel Biggs
Dr Gary Burns
Mr Trevor Cook
Professor Simon Croft
Professor Paul Freemont
Mr Aulo Gelli
Matthew Harvey
Professor Göran Hermerén
Dr Niki Lang
Dr Markku Lehtonen
Dr Filippa Lentzos
Jacob Leveridge
Dr Kathy Liddell
Dr Julian Little
Dr Helen Munn
Dr Thomas H. Murray
Dr Maureen O'Malley
Professor Michael Parker
Professor Catherine Peckham
Dr Agnès Saint Raymond
Mike Rowson
Philippa Saunders
Dr Ian Shield
Ilina Singh
Laurie Smith
Professor Terence Stephenson
Dr Jeremy Tomkinson
Dr Heather Widdows
Professor Brian Wynne

Members of Council
Professor Albert Weale
Professor Hugh Perry
Professor Steve Brown
Professor Roger Brownsword
Professor Robin Gill
Professor Sian Harding
Professor Peter Harper
Professor Ray Hill
Professor Søren Holm
Dr Rhona Knight
Dr Tim Lewens
Professor Ottoline Leyser
Professor Anneke Lucassen
Professor Alison Murdoch
Dr Bronwyn Parry
Professor Jonathan Wolff

Secretariat
Hugh Whittall
Harald Schmidt
Katharine Wright
Dr Alena Buyx
Caroline Rogers
Catherine Joynson
Sarah Bougourd
Kate Harvey
Tom Finnegan
Varsha Jagadesham
Carol Perkins

TOPIC 1: DRUG TRIALS AND PRESCRIPTION IN CHILDREN

Clinical perspective

1 Unlicensed or off-licence drug use in children accounted for 11 to 33 per cent of drug use in primary care, 40 per cent in general paediatrics and 90 per cent in neonatal medicine. Whether or not a drug was licensed was at the discretion of the pharmaceutical company. For example, a drug might not be licensed if it was thought that the drug – even if effective – would require high expense to develop.

2 Legislation introduced in the USA, specifically the Food and Drug Administration Modernization Act (FDAMA; 1997), provided pharmaceutical companies with a commercial incentive to carry out paediatric drug trials. If a trial was conducted in children, a patent-extension of six months was granted even if the drug was found to have no use in children. Such legislation increased the numbers of trials held in the USA, and the number of children recruited. In the European Union (EU), the Regulation on Paediatric Medicines, which came into force in January 2007, placed a legal obligation on companies wanting to market a new medicine, or to change an existing marketing authorisation, to include data from paediatric studies in their application.

3 In the UK, the Medicines for Children for Research Network was established to improve the translation of paediatric research into practice, and the National Research Ethics Service (NRES) contained a list of websites and resources for ethical guidance for paediatric clinical trials.

4 Paediatric drug trials faced certain obstacles. For example, there was a great fear of litigation in pharmaceutical companies, which prohibited paediatric drug trials; although that this was reduced if the market for the drug was large. It was also costly to develop and bring a drug to market, and with some paediatric drugs, the market size was extremely small. However, it was demonstrated that by charging higher amounts for the drug, such paediatric drug development could be made more economically attractive to pharmaceutical companies. Ethical issues increased the difficulty of conducting paediatric drug trials also. For example, the question was raised as to how to obtain informed consent if there was no/ little time to get consent, e.g. trialling drugs for epilepsy, when the child is fitting.

5 Refusing to do paediatric clinical trials because of ethical concerns was not a strong enough reason to not do the research. More research of medicines in children was needed, as new treatments in childhood cancer

tested in randomised controlled trials were, on average, as likely to be inferior as they were to be superior to standard treatments. Therefore, if research was not carried out, new medicines, which were potentially inferior, were likely to be kept in medical practice by default. Survival rates in childhood leukaemia cases had drastically changed since the mid-1980s, with mortality rates previously of 70 per cent, to today survival rates of 70 per cent. This was possible due to paediatric drug trials. However, whilst it was imperative to carry out such research, it was critical that such research did not move in the other direction, where child safety was compromised.

6 There was evidence that children in drug trials actually did better than those who were not, irrespective of the treatment arm (intervention vs. control) to which they were assigned. This was attributed to more frequent medical checks.

Ethical issues

7 Therapeutic research might or might not involve the receipt of treatment. Equipoise, the state of uncertainty regarding the advantages or disadvantages of either therapeutic arm of a clinical trial, and uncertainty with regards to medical decision making, meant that there was a risk of undermining the standard of care. The honesty of the researchers was called into question as therapeutic benefit was not assured or might not be possible for the participants. There was also a potential for informed consent to be obtained under pressure, as the distinctions between the practitioner and researcher, and patient and research participant were blurred. The participant was conferring benefit to the researcher, but the patient also required the assistance of the practitioner.

8 With regards to informed consent, there was a large amount of literature but this centred on the need for individuals to be able to recall and recount the information they were given. It seldom focussed on the nature of the information given, and its adequacy to support informed consent. Obtaining informed consent involved "momentous trust and meaning", and the process was more than a one-off event.

9 The competence of a child to be able to give informed consent was assessed by an adult, and this raised the question as to what was the adult's competence to inform, listen to and support the child in the process. Therefore, it was necessary to assess the competence of the adult in the process. The competence of a child related more to their "embodied experience" rather than their age or intellectual ability. Assessing the competence of a child was important as it enabled the

possibility that their informed consent might be obtained. The benefits associated with this included the generation of a partnership, and the avoidance of any potential exploitation of the child. It was necessary to go beyond 'procedural ethics' towards 'macro ethics', where the main agents were the children and the parents. It was important to involve their knowledge to meet their priorities.

10 Who constituted a patient was ill-defined. Traditionally, a patient was held to be either an individual diagnosed and treated by a health care practitioner, or an individual who was 'sick', i.e. was exempt from their usual duties and cooperated with treatment to get better. However, the traditional definition of a patient was challenged by various circumstances. For example, due to pharmaceutical success, some illnesses might now last for far shorter periods of time compared to previously. Was the individual still a patient? Individuals with chronic illness such as cancer asserted that: "I'm normal". Individuals who historically were labelled as "sad, mad, bad, fat or ill" were now able to seek medical interventions for these conditions. Many children in the world were ill, impaired or injured but they were unable to access primary care or further medical care. Many individuals were also now being screened for illness, both physical and mental – the so-called "worried well". Were such individuals still patients? Whether or not an individual was a patient was important to consider so as to ensure that the right group of individuals were targeted for treatment and research.

Law and regulation

11 Legislation and regulation regarding paediatric clinical trials was complex. European law played a major role and in addition there was professional and ethical guidance from a number of bodies, such as the International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) and Council for International Organizations of Medical Sciences (CIOMS). EU/ UK law and regulations operated in conjunction with common law, and tensions existed between these.

12 For example, who was capable of giving informed consent? Common law, the case of Gillick vs. West Norfolk and Wisbeach Area Health Authority (1985), laid down the principle that a child under the age of 18 years was allowed to give consent for treatment, rather than their parents, if the child "achieves a significant understanding and intelligence to enable him or her to understand fully what is proposed". It was not possible to impose fixed limits on childhood, as this depended upon different social factors and experiences. However, the Family Law Reform Act (1969) set the age of consent at 18, but stated that a child

could consent to beneficial medical treatment at the ages 16–17 years. In Scotland, legal capacity was deemed at the age of 16, and European law stated that the age of consent was 18 years.

13 Parents were required to make the decision to enter their child into a trial in the child's best interests. However, given equipoise, it was not always possible to know whether entering the child in a trial would be in its best interests. Therefore, the consent obtained from them was not valid, and there was no case law to provide further guidance on this. The only potential case law came from Maryland, Grimes vs. Kennedy Krieger Institute Inc (2001) which appeared to impose restrictive rules on research with children when the subjects were put at risk but could not derive direct benefit from their involvement in the research project.

14 The UK Medicines for Human Use (Clinical Trials) Regulations (2004) implemented the EU Clinical Trials Directive (2001), and individuals who failed to comply would be prosecuted. However, there were areas of the Directive which warranted further attention.

15 Staff with experience of minors had to provide information and be knowledgeable of assessing how to assess a child's ability to consent. However, no guidance was given on how this should be done. Additionally, the Directive asserted that a clinical trial on minors could only be undertaken if "the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principle investigator". However, there was no provision for the minor to consent, or even assent. Also, their wish to refuse participation needed only to be 'considered' by the investigator. The Directive asserted that clinical trials must be designed to minimise pain and fear. However, whether this could be achieved; how 'fear' could be specifically dealt with, and whether this responsibility belonged to research ethics committees (RECs) was unclear.

16 Within the Clinical Trials Regulations (2004), there was no provision for dissent. However, there would probably be a difference between the law in theory and what occurred in practice. It was hoped that there would be few researchers who would continue with research even when the minor had dissented.

17 The National Research Ethics Service (NRES) was applying the standards of the Clinical Trials Directive (2001) to medical research in children, even though in principle, these should be applied only to research

involving medicinal products. This could raise tensions from both sides. For example, RECs for research in children required assent, if not consent; however, this did not feature in the Clinical Trials Directive (2001). Indeed, if the Clinical Trials Directive (2001) standards were to be applied to the more general research in children, assent and consent would not be required here in contrast to previous experience.

Discussion

18 Often, the ability of an individual to give consent was correlated more with social status rather than competence and ability. This was concluded on the basis that many adults did not understand the procedure of giving consent, or the information relayed beforehand, and yet were still able to give consent.

19 The focus on acting in a child's 'best interests' was a 'red herring' since parents made decisions which could often not be conceived of doing so. Instead, the focus should be on making decisions which might not necessarily be in the best interests of the child, but also not against them.

20 Areas in which Council could be useful were detailed. Given that there was a lack of case law stating that the Gillick principle could also apply to research studies, guidance on this would be helpful. It was also suggested that the Council could review the capability of the child to act philanthropically, as well as consider the ethics of new designs of clinical trials. An example was given in which children with epilepsy, who were fitting and therefore where there is typically very little time to gain informed consent, were allocated a certain treatment depending on the month in which they were admitted to the hospital. Parents were informed of this after the child has been treated and were given the opportunity to withdraw their child from the "study". However, none did.

21 The topic of paediatric drug trials raised the 'new' ethical question of how to reconcile acting in the interests of the individual (in this case, the child) vs. acting in the interest of the common good. There was a moral imperative to conduct paediatric drug trials as there was a need for evidence-based medical practice. However, how could the interests of the research participants be protected and what role did these play? The introduction of the law here problematic, since it would, for example, set arbitrary age limits for the ability to give consent whereas a very young child might be able to make a decision to participate which was altruistic.

TOPIC 2: ETHICAL AND EFFECTIVE HEALTH INTERVENTIONS IN A GLOBAL CONTEXT

Factors affecting global health

1 There was variation in what was considered as 'global health'. The League of Nations, an international collaboration established in the 1920's, focussed predominantly on the control of infectious diseases and only some social determinants of health, such as housing. The World Health Organization (WHO) put forward the intention in the 1960's to focus on the control of infectious diseases and primary health care. The Alma-Alta Declaration in 1978 focussed on the control of infectious diseases and social determinants of health, and in more recent years, there was increased awareness of 'trans-border' factors, which included not only diseases, but also the 'causes of causes' such as climate change and tobacco control.

2 Disciplines used for the analysis of global health had changed. Whereas previously, global health was the remit of epidemiologists and health economists; this list had now expanded to include political scientists and macroeconomists.

3 The social sciences played a major role in addressing issues affecting global health. For example, a significant problem was low public uptake of efficacious interventions, such as vaccinations, and a lack of public trust for the public sector. A sociologist was able to assess what constituted a relationship of trust, and therefore make appropriate recommendations. With regards to differing child mortality rates between different population groups, an anthropological understanding was needed. However, other disciplines outside of the social sciences were also required, such as mathematics and engineering to understand why health systems failed.

4 Global health policy was instructed largely by medicine and epidemiology, with global health institutions dominated by medical doctors. This led to a medicalised approach to global health, a so-called 'policy-by-prescription' method. This approach assumed linearity and did not take into account how the wider, social context might impact on the effectiveness or implementation of the medical intervention. This led to repeated policy failure.

5 There was a lack of research into health care systems. Surveys revealed a widespread public distrust of health care systems, and it was possible that an individual's experience of poverty was reinforced if they sought

health care which ended up being uncaring and coercive in nature. However, tools to analyse health care systems were neither available nor developed. Other areas that required more research included: the translation of health care analysis into policy; how informally-commercialised markets work in poor countries, and how people respond to these; how non-market social determinants of health care affect health.

6 It was important to understand the effect of global forces on national health, and national forces on global health. For example, health care workers migrated from poorer countries with high child mortalities to richer countries with lower child mortalities. This reinforced global health inequalities through 'brain-drain', and therefore raised the question as to whether global health policy makers should intervene in global markets – for example, should such migratory patterns be prohibited? Controlling such factors was difficult and it might be necessary to accept it as something beyond control, and to address the situation in different ways.

Role of science

7 Infectious diseases largely affected the developing world. The main challenges here included the development of drugs, vaccines, diagnostics, and the threat of emerging infectious diseases.

8 Developments in science and medicine improved global health to the extent that they provided tools to understand pathogens and the spread of disease. For example, many pathogen genomes were sequenced and further characterised to provide an understanding of the origin of disease, drug resistance, relationships with other diseases, and how they might spread. Epidemiology made it possible to estimate the magnitude of the problem.

9 Neglected diseases included sleeping sickness and trachoma. Whilst these were not associated with great mortality rates, they nevertheless significantly affected whole communities. An existing challenge was to make production of drugs for neglected diseases more economical for drug companies.

10 Coherence of international research and development was necessary to prevent unnecessary duplication of efforts and use of resources. International consortia provided means for addressing this issue. It was also important that international organisations, governments and funders set realistic targets and promoted training and awareness of quality and regulatory issues in developing countries.

11 To face emerging challenges, the infrastructure of scientific research and development must adapt, and a move towards multidisciplinary research was necessary. It was also important to remove barriers that prohibited translation of research into developments, and prevented communication between the private and public sectors. A clear understanding of intellectual property and risk analysis was necessary to this end. Public private partnerships (PPPs) were successful approaches for bridging the not-for-profit sector and industry.

Ethical issues

12 Ethical and effective global health interventions constituted an under-researched and neglected area of bioethics as such issues were less attractive to researchers compared to ethical concerns associated with high-tech scientific developments. Other contributing factors included the magnitude of the issues, as well as the need to analyse them within a wider context, which was often more complex to do. Recommendations were also more difficult to frame.

13 There was no reason why high-tech interventions should be favoured over low-tech interventions, and vice versa. All interventions should be assessed on their effectiveness. However, high-tech interventions were generally preferred as they were considered innovative. Low-tech interventions, in contrast, were associated with pastoral innocence. When interventions were ideologically driven, their effectiveness was reduced. The high-tech/ low-tech distinctions could be used to highlight existing assumptions and to recommend a new framework.

14 The patent system raised ethical issues within global health. A 10/90 disequilibrium existed in global health, in which only ten per cent of the global expenditure on research and development was directed at 90 per cent of the global disease burden. A key contributing factor was the high cost of developing a drug and bringing it to market. Drug companies focused consequently on drugs for the industrialised world, where costs could be recouped and profits made. Possible solutions included compulsory licensing, patent pools and incentive schemes. For example, the Health Impact Fund was a supranationally funded optional system, which paid drug companies an amount that reflected the reduction in global health burden that was attributable to their drug, if they agreed to sell their products at cost. The Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement was also problematic to global health and had caused almost one-third of the world's population to have no access to essential drugs.

15 When applying ethical frameworks in a developing country, it was important to focus on the potential danger of applying ethical norms without consideration of the context. For instance, seeking informed consent was often viewed as the 'gold standard' of Western bioethics. However, Western bioethics was individualised whereas the developing world's bioethics was generally communitarian. Therefore, it was sometimes more appropriate to take group consent, rather than informed consent, in developing countries.

16 The dominance of informed consent also illustrated how Western bioethics was still the 'core' of ethical frameworks in developing countries, rather than truly global models of ethical thought. In developing countries, other issues warranted greater consideration than informed consent, such as access to health care, and care received following participation in research. Contemplation of these areas could afford more protection for an individual than the model of informed consent.

17 Trust and benefit-sharing were two emerging ethical frameworks. The trust relationship was used by biobanks, and held that a person receiving a donation would act as the trustee or steward of that donation. Broad consent was sought for the donation, as it was impossible to give informed consent given the lack of knowledge of how a future research protocol might use one's donation. Different mechanisms existed to protect trust, including election of a donor onto a REC, and suggesting that the REC consider what would be the public good or benefit of a project using the donations.

18 Benefit-sharing aimed to share the benefit gained from research with the community from which resources necessary for the research were derived. Whilst benefit-sharing was useful in helping overcome global health inequalities and respecting and protecting the resources of developing countries, it was also associated with problems. That its scope was not global meant that benefit-sharing was often restricted to only the community or locality where the research occurred. Benefit-sharing also depended on the bargaining power of the developing country, and what it was able to offer the researchers. Also, given the flexibility of the concept, it was open to abuse.

Discussion

19 Global health policy involved targets to remediate issues on a global scale. However, within this, individualised responses to global health

strategies influenced the effectiveness of the approach, and often accounted for a large part of the strategic failure. Therefore, Council could take illustrative case studies and investigate this disjunction between the global and individual, with the aim of proposing a bridging framework.

TOPIC 3: NEW APPROACHES TO BIOFUELS

Science and technology – industry perspective

1 The agricultural industry invested wholeheartedly in food development and production because demand was constant and government subsidies were not required. This was not the case for biofuel crops. Agricultural companies were aware of the potential for poor public relations as a result of investing in biofuels. As such, investment in biofuels was often cautious and/or limited. Outside Brazil and some South-east Asian countries, biofuels were effectively a political decision, although reasoning differed (i.e. greenhouse gas reduction in Europe and energy security in the USA).

2 Government subsidies had had a significant influence on biofuel crop growth, and the UK had taken the lead on the certification of biofuels. For example, the UK required adherence to sustainability criteria when sourcing biofuels. There was difficulty in exporting this standard globally.

3 Biofuel-specific genetic modifications for maize included the insertion of a gene or genes capable of expressing amylase *in situ* in order to make 'self-processing' crops. Current processing methods involved the addition of amylases to grain in order to digest starches. Pre-digestion of these starches would cut down the cost of processing.

4 It was concluded that GM food was problematic but broadly a 'success'; industry was cautious of getting involved in 'politically motivated' initiatives, but was capable of having an impact (e.g. development of crops with a lower carbon footprint). GM crop use for biofuels was in its infancy.

Science and technology – academia/ plant breeding focus

5 The potential of lignocellulosic crops as biofuels was high, especially in the UK. There was not enough available land in the UK to use temperate crops as fuel. The use of lignocellulosic crops allowed for more of the country to be used (such as woodland), prevented concentrated farming and allowed for distributed energy systems.

6 Lignocellulosic crops had a high 'energy balance' as a fuel. Short rotation coppice willow produced more energy than was required to manufacture and process it as a fuel. In contrast, petrol required more energy to extract and process than it provided.

7 Modern conventional plant breeding research was often sophisticated and supported by molecular biology programmes. 'Conventional' plant breeding was a form of genetic modification, and the differences between genetic modification and conventional breeding were overemphasised in public debate, given that both strategies produced effectively the same traits via different means. However, genetic modification did provide the possibility of introducing traits for which no useful variation existed within the crossing pool, while the conventional breeder was restricted to existing variations.

8 Current regulations for indigenous energy crops subjected to conventional breeding were adequate. Scrutiny of the introduction of new plants into the UK was more important than the scrutiny of the methods used to create them.

Social and ethical concerns

9 Land and labour rights were an important concern in the global production of fuel crops. Large areas of land in Africa were used as commercial crop growing zones without full permission from the inhabitants. The UN estimated that 60 million indigenous people were at risk from the expansion of biofuel crops. Examples of good labour rights included a wage floor, labour unions, safe and appropriate living conditions, sanitation, safety equipment and collective bargaining rights. These were not necessarily common. Three quarters of all biofuels in the UK originated in Brazil, and there was no way of assuring that the fuel was produced in accordance with these criteria.

10 The social impact of biofuel production on a local level was significant. The production of palm oil, for example, took place primarily on smallholdings. This meant that there was a high risk of farmers being caught in a 'cycle of debt' whereby companies would loan equipment at high interest rates, resulting in debt-bonded labourers.

11 Biofuel demand was estimated to be responsible for 20 to 30 per cent of the spike in food prices that began in January 2008. 100 million people had been pushed into poverty as a result of this spike. Prices were set by changes in supply and demand at the margin of the market, and during the period in question biofuels accounted for over half of the increase in demand. In the medium term there was less of an impact on food prices, as production was beginning to respond to demand, stabilising prices. However, this may have caused further damage, as it was unclear if the land used in production was 'new' or if food crops were being displaced.

12 The price of foodstuffs was beginning to track the (often volatile) global oil price. Frequent peaks and troughs were more problematic for those in poverty because gradual increases in price could be adapted to, while sharp rises could not. The impact of biofuels on 'farm gate' food costs was one of the reasons for US and European interest in encouraging biofuel use, as it could help domestic agricultural industries.

13 Most of the current debate regarding the use and growth of GM crops was centred on the acceptability of the process of genetic modification itself. However, the influence biofuel crop growth had on changes in land-use, leading to negative effects on the environment and the climate, was not to be underestimated.

14 Biofuel production was an historically unique energy problem because of the tension between food and fuel crop production and government subsidisation of biofuels for reasons of sustainability. Resources dedicated to biofuel development and production were often misallocated. Other changes could have had an equal or greater impact: an improvement in US vehicle fuel efficiencies by 1 mpg could have reduced emissions by as much as the total global maize bioethanol production.

15 Endurance of the problems associated with first generation biofuels was not necessarily required in order to enjoy the benefits of the second. Lessons were to be learnt from experiences with the first generation. A balance between competing factors was required in developing biofuel capacity. For example, sustainability for Western energy production should not result in damaging social conditions in developing countries.

Case study – the Brazilian experience

16 Brazil was a special case in the development, production and use of biofuels. It was important to learn from Brazil's history of biofuel production and consider the role Brazil may play in future biofuel markets.

17 There was a global supply of over 40 billion litres of bioethanol in 2007, which was projected to grow by a further 20 per cent in 2008. Global biodiesel production was 10 billion litres in the same time-frame. Bioethanol was the dominant fuel in Brazil, while the majority of biodiesel use was based in Europe. Significant growth in the use of biofuels was expected in the USA, Brazil, the EU, China and India.

18 The Proálcool biofuel programme was adopted in Brazil in the early 1970s, during a period in Brazil's history in which it was governed by a military dictatorship. This may have been a factor in the programme's

successful implementation. The ability to develop and implement new fuel systems was a difficult and complex process, one that was unlikely to be achieved without subsidies (hidden or explicit) provided by a government.

19 Bioethanol production was the most environmentally sustainable of current biofuels, as it produced 86 per cent less greenhouses gases than petrol. In addition, water, fertiliser and pesticide use in bioethanol production was lower than for most biofuels.

20 The economics of bioethanol production were a complex set of trade-offs. The benefits to Brazil included the fact that bioethanol produced in Brazil was the cheapest biofuel (at US$35/ barrel) and £61 billion in the last 8 years had been saved in oil imports. However, there were opportunity costs involved including: a potential technological and institutional 'lock-in' due to the development of production capacity; the initial outlay costs of time and money in developing the technology and the risk that the benefits gained flowed mainly towards the rich, rather than the poor.

Discussion

21 The further point was raised that three main ethical constraints in relation to biofuels had to be met. These were provisionally identified as food security, environmental sustainability and 'equity' (such as labour rights or social welfare), or another similar concept. Behavioural change within advanced societies was difficult. It was unlikely that these constraints could be satisfied by behavioural change alone. The Council was encouraged to identify whether there were other relevant constraints and also if there was something inherent about the science and technology of biofuels that meant these constraints could be satisfied.

TOPIC 4: SYNTHETIC BIOLOGY

Science

1 Synthetic biology was an interdisciplinary science, and it brought together engineers, scientists, life scientists and social scientists.

2 Since 2000 there had the 'genome era' i.e. large amounts of information had been known about the genetic make up of most living organisms on the planet. In the 1960s to1970s, scientists learnt the 'central dogma' of modern molecular biology: DNA replicates and is transcribed into RNA, RNA is then translated into protein. Synthetic biology would take this to a new level, working on a larger continuum scale of increasing biological complexity, from genes and proteins up to cells and organs. The 'dogma' had changed and focus was shifting towards interactions and networks that affect biological properties in living cells and organisational structures. The integration of biological information was one of a number of challenges for synthetic biology.

3 Systems biology (the application of genome-scale measurement technologies to construct computational and mathematical models of cells), was an emerging field of synthetic biology. Systems biology has three components: Theory, Computation and Experimentation.

4 Synthetic biology could be defined as:

- The design and fabrication of biological components and systems that do not already exist in the natural world; or
- The re-design and fabrication of existing biological systems.

5 The three driving concepts were:

- To enable the systematic engineering of biology;
- To promote the open and transparent development of tools for engineering biology; and
- To help construct a community that can productively apply biological technology.

6 In one view, synthetic biology could be thought of as a similar conceptual framework to traditional engineering where feedback loops, circuits and communications seen in biology were likened to engineering circuits. Standard devices and systems were used to approach problems and standard parts were used for each function. Reliability, robustness and quality control were needed, such as a registry of standard biological

parts from different organisms. Using this analogy, an 'Abstraction hierarchy' for synthetic biology had four component levels – systems, devices, parts and DNA, where engineers working on different components did not need to understand or work on the other levels. This was known as decoupling.

7 The International Genetically Engineered Machine Competition (i-GEM 2008) was a competition for undergraduates with 1,200 participants from 21 countries.

8 Alternatives to the engineering analogy included a more challenging bottom-up approach, for example making a protocell with integrated systems – this was usually done by biochemists. A top-down approach was to minimise a genome and re-program to make the circuits simpler.

9 The underpinning technologies of rapid DNA synthesis and synthetic chromosome assembly were non-limiting, cheap and available. Many challenges were ahead but it was predicted that in 10 to fifteen years time there may be the potential for synthetic genomes and lab-made mammals.

10 There were many conceptual possibilities of synthetic biology. Future applications included bio-fuels (these could go into production by 2013), bio-medicine (for example using engineered bacterial cells to target cancer), biosensors (such as a bio film detector device for urinary catheters) and new drugs (such as the anti-malarial drug artemisinin). Synthetic biology experiments did not always use living cells, in some cases the contents of cells were used to run re-engineered genetic programmes.

Social and ethical issues

11 When trying to identify what the social and ethical issues were with a complex and dynamic technical scientific field such as synthetic biology, many were transversal social issues that were recognised in other modern scientific innovations, for example in the production of biofuels. The social issues did not lie outside of the science; rather the questions were in the science or technology.

12 One focus of synthetic biology was to identify what would count as a minimal functional genome. The concept of minimal was open to interpretation when deciding what functions of the genome, cell or organism were assumed or defined. Assumptions about 'what counts as

minimal' and 'what is correct function' were often an important part of risk assessment.

13 With the engineering approach to synthetic biology there was likely to be a process of externalisation, for example unposed and unanswered questions regarding new conditions and situations that cannot be predicted. The key question was: who is taking responsibility?

14 'What does life mean?' was a central question when considering the ethical and social issues. It was impossible to define in a stable and universally recognised way, yet could it matter even more if synthetic biology was leading the 'new' technical- material definition of life.

15 The ethical and social contexts that were salient but not intrinsic to synthetic biology included:

- Pressures to commercialise what may be immature science(s) – as with genetically modified organisms.
- Policy, industrial and scientific anxieties over anticipated public reactions - as with nanotechnology
- The hype problem: promising (or being required to promise) impacts, and the *political economy* of promise
- 'Facts' based on imagination

16 Risk assessment was a central institutional means of deciding on the licensing of new scientific innovations in society. In the case of synthetic biology, which brings together several different fields of science, the question was whether risk assessment was, on its own, enough. Risk assessment did not deal with unknown or unpredictable effects, and it was thought that public concerns about unpredicted consequences (as in previous innovations such as genetically modified crops) had never been fully addressed.

17 Whilst synthetic biology was not a public issue at present, similar public concerns would be expected and reasonable, given such historical examples as thalidomide and CFCs. In these cases, risk assessments had been carried out based on the best science available at the time, but had failed to ask, or even identify, certain key questions that came to light only afterwards. The reliance on risk assessment alone in the role of full 'social appraisal' of technologies was thought to be a problem, because it could not deal with unknown possibilities. It was important to think about additional questions for the regulatory agenda such as:

- How fast is immature laboratory knowledge trying to be translated into commercial products?
- How important is this development for society?
- Will it invest in diversity?

18 Looking back at public concerns over genetically modified foods, much of the confusion arose because it was not clear what people were referring to as 'science'. Risk assessment and regulation had been framed as 'science' and therefore as a public authority, used to reassure people. But who was doing the framing? This 'science' only included a given set of questions and was different to research science that promotes openness, experimental thinking and debate. A similar context would apply to synthetic biology, and there was thought to be much confusion amongst the public, and amongst scientists themselves, over what 'science' actually means. This could undermine public confidence in synthetic biology. Some people felt that the grand age of science as a universal truth was now gone.

19 In future if synthetic biology becomes a public issue, the shift from hypothesis-driven science to a 'build it and see' engineering approach would change the ethical questions being asked. If it was only possible to understand something by building it, then by the time the ethical questions have been defined, the scientists are already a long way down the road. Would the only valid ethical questions therefore be about the historical shift away from hypothesis-driven science itself?

20 Science was driven by imagination, but a political economy of promise was driving science policy, with scientists under pressure to make promises in order to get research funding. This was a key dilemma with a public issue such as synthetic biology. It was important that scientists did not to take the name of science in vain for political purposes. The 'political economy of promise' was thought to apply not just for synthetic biology but for other technologies such as nanotechnology. The study of bioknowledge economies was one of three key themes of research in human genomic technologies from 2007-2012.

21 Further social and ethical issues included:

- Biosecurity and bioterror - which had been well debated
- DIY genomics or 'garage biology' – this was an entirely new form of public engagement with science
- Dilemmas about open source and IPRs – what was meant by social control of a genome?

- More needed to be known about the specific technologies and organisms before the ethical issues can be fully defined
- Who would define 'social benefits' in science, how would that occur, and how might conditions of effective public participation be established for synthetic biology?

Governance

22 Synthetic biology had generally been categorised into three different areas of research: creation of minimal genomes; production of artificial cells; and the production of standardizing parts, pathway engineering and expanding the gene pool. There were however other ways to characterise it, including 'in vivo versus in vitro' and 'natural versus unnatural'.

23 The reason for categorising synthetic biology in this way was that different research activities had obtained different levels of media coverage and policy discourse. For example, the de novo synthesis of viral genomes has received wider coverage than artificial cell creation. The variance in coverage was thought to be reflected in the changing levels of concern and public engagement with each type of research, which in turn would drive discussion about its regulation.

24 Governance was an umbrella term covering a number of regulatory measures from acts of parliament and statutory measures through to private regulation by standard operating procedures, to informal overview systems such as research practises and peer review. All of these applied to synthetic biology but different voices were being raised in the media as to who should be responsible for regulation. A number of gene synthesis companies had proposed guidelines for screening DNA orders.

25 A primary safety concern was the unknown risk of exposure to synthetic microorganisms of laboratory staff, the public and the environment; since genes could transfer into existing microorganisms, alter ecosystems and thus cause unexpected side effects. There were technological solutions available such as building self-destruction mechanisms into synthetic organisms.

26 A new safety issue for synthetic biology was that many researchers were young and were therefore not sensitive to the type of laboratory safety procedures practised when using recombinant DNA. In addition, the people working on it were often chemists, physicists or engineers who did not have the same culture of lab safety as biologists. In order to address these potential deficiencies, a generational and cultural transfer of biosafety knowledge was required.

27 Biosafety, and particularly the threat of terrorism, was another key concern. People were worried that synthetic biology may be misused for hostile purposes such as making a pathogen more virulent, more infectious or altering its host range. It could be argued that this focus on terrorism was misplaced, for a number of reasons. Primarily, it was very difficult technically to turn a pathogen into a weapon. Acquiring a host pathogen would be hard in the first place, and furthermore, it would need very specific characteristics such as infectivity, stability and virulence – only a small subset of pathogens would actually be useful. Then there would be difficulties with scaling up and storing the pathogens, and there were also many technical hurdles to dissemination. The effect of any attack would also depend on the general health of the population and the speed and manner in which the public health authorities respond.

28 Historically there had only been three confirmed attempts to use weapon against humans - in 1984, the early 1990's and in 2001. The first two attempts had failed and the third had caused five deaths. Given these limited incidents with naturally occurring pathogens, it would be hard to imagine anyone being able to synthesise a successful pathogenic weapon, as this would involve a completely new layer of further complications. Instead of focussing on the threat of bioterrorism, the security debate over synthetic biology should focus on state sponsored programmes of biological weapons and military use. Another area where there was increasing concern over regulation was biohacking, or 'garage biology', - this raised a further set of new issues that must be considered.

29 In summary, the development of regulation for new technologies was a result of social negotiation between key participatory groups. A critical stage in the development of a regulatory framework for synthetic biology had been reached where the risks of the technology had not yet been agreed on. There was felt to be an increasingly narrow focus on biosecurity concerns, and whilst it was sensible to take these concerns seriously, it was also important that other concerns such as long term social and environmental issues were not marginalised.

30 This was an opportune time to hone down the regulatory framework for synthetic biology. The Nuffield Council could have an important role in encouraging the range of concerns to be presented in the policy discourse.

Discussion

31 A further point was raised that the existing framework in European law for genetic modification and associated intellectual property issues could potentially be applied to synthetic biology. It was possible that intellectual property cases with synthetic biology would be simpler to resolve because it involved creating new microorganisms using a 'bottom-up' approach. Past legal problems that had arisen due to attempting to patent something that is naturally occurring were therefore immaterial. In light of the discussion about using electronic and engineering frameworks, it was also noted that the majority of patenting applicants were not from the pharmaceutical or biotechnology industry but from the electronics companies. It was hoped that a legal framework for synthetic biology would define open source requirements and address the issues of security.

32 It was apparent that synthetic biology was continuing the ethical, legal and social dilemmas associated with other areas of bioethics such as genetic modification. For example, questions about playing God, the 'natural vs. unnatural' debate, and concerns about cross-contamination. It would be interesting to investigate what causes people to focus on these concerns.