

5th July 2006

Professor Gordon W Duff
Chair of Expert Group on Clinical Trials
Department of Health
79 Whitehall
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Dear Professor Duff,

Expert Group on Clinical Trials

Thank you for giving us the opportunity to provide evidence to the Expert Group on Clinical Trials. We would like to draw your attention to a number of issues that the Council has considered in its Reports which we believe may be useful for the Group's discussions.

Consent

We discuss in several Reports the importance of 'genuine consent' in clinical trials. This was first described in *Human tissue: ethical and legal issues* (1995):¹

6.19 Expressions such as 'informed consent' and 'fully informed consent' are often used in discussions of medical ethics. They are somewhat misleading. Consent can be given to some course of action (for example, an operation, other therapy, donation, participation in medical or scientific research) only as described in a specific way. Since description can never be exhaustive, consent will always be to action that is incompletely described; moreover the descriptions offered are often incompletely understood. This incompleteness cannot be remedied by the devising of more elaborate consent forms and procedures for patients, donors and relatives. 'Fully informed consent' is therefore an unattainable ideal.

¹ Available at:

www.nuffieldbioethics.org/go/ourwork/humantissue/publication_298.html. See also: Nuffield Council on Bioethics (2002) *The ethics of research related to healthcare in developing countries* (London: Nuffield Council on Bioethics), paragraphs 6.4-6.8. Available at: www.nuffieldbioethics.org/go/screen/ourwork/developingcountries/publication_309.html

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6.20 The ethically significant requirement is not that consent be **complete**, but that it be **genuine**. Ensuring that consent is genuine is mainly a matter of care in detecting and eliminating lack of consent. Both in law and in ethics, consent requirements are not met wherever anything rebuts or defeats the presumption of consent. The ascription of consent is **defeasible**: the presumption of consent can be defeated by any of numerous circumstances, including violence, coercion, deception, manipulation, tendentious misdescription of action, lack of disclosure of material facts or of conflicts of interest and the like. A complete list of the circumstances that would defeat a presumption of consent is not feasible.

6.21 Evidently in medical and scientific practice involving human volunteers or the removal of tissue from cadavers, there are well developed (if necessarily incomplete) understandings of circumstances that defeat the presumption that proper consent has been granted. These will include failure to require patients, volunteers or relatives to read and sign the usual consent forms. However, such forms are only evidential, and signatures on forms, however carefully obtained, will not prove that consent is 'fully informed'. Obtaining genuine consent requires medical practitioners to do their best to communicate accurately as much as patients, volunteers or relatives can understand about procedures and risks, and to respect the limits of their understanding, and of their capacities to deal with difficult information. If all reasonable care is exercised, adequate and genuine consent may be established, although it will necessarily fall short of fully informed consent.

We recommend that the Expert Group ascertain whether the consent obtained from the participants to take part in the TGN1412 trial was genuine.

Inducements

It is common practice to compensate trial participants for their time and the risks they take when taking part in medical research. However, the level of compensation, whether financial or other, needs to be assessed carefully to avoid inducing people to subject themselves to risks that they would otherwise be reluctant to take. The Council discussed issues relating to undue inducements in its report *The ethics of research related to healthcare in developing countries (2002)*.² While the risk of providing undue inducements clearly is exacerbated in developing countries because of economic and other disparities, an outline of the general issues provided below may be of use in assessing whether the compensation of trial participants in the TGN1412 trial was appropriate.

6.25 Participants in research in developing and developed countries have a range of motivations for taking part in research (see paragraph 3.21). One motivation that may be offered to prospective participants is a benefit, such as a financial payment, or healthcare in the future, or for a

² Nuffield Council on Bioethics (2002) *The ethics of research related to healthcare in developing countries* (London: Nuffield Council on Bioethics), paragraphs 6.4-6.8. Available at: www.nuffieldbioethics.org/go/screen/ourwork/developingcountries/publication_309.html

period of time, for themselves or their families. Inducements which research ethics committees in developing countries have considered acceptable include money in the form of payments for travel, inconvenience or work lost, food, photographs or film, and healthcare for individuals and their families during research.³

6.26 The point at which inducements become inappropriate is not always clear. Principle 11 of the 1991 CIOMS guidelines draws attention to the fact that 'it can be hard to draw the line between exerting pressure, or offering inappropriate inducements, and creating legitimate motivation'. However, it is possible to offer some guidance to assist attempts to draw this line. It should be remembered that without some prospect of benefit, either for themselves or others, most individuals would be unlikely to consent to participate in any research. We consider that researchers should, at the very least, aim to ensure that participants are not placed in a worse position by participating in research. The payment of reasonable expenses incurred by the participant, or remuneration for loss of earnings suffered is generally considered to be acceptable and may be necessary in developing countries where high unemployment means that participants are only able to take part in research programmes with such support.⁴

6.27 An inducement may persuade an individual to change his or her mind about entering a research project, but this in itself is not enough to make it inappropriate. For example, it may well be a rational choice not to take part in a research project, which may or may not provide any personal benefit, unless some extra benefit is provided. However, inducements can also change a prospective participant's mind in a less benign manner, so that their calculation of the costs and benefits of the research results in their decision that the benefit offered by the inducement outweighs all risks, however substantial. This could cause individuals to expose themselves to risks or potential harms that they would ordinarily view as unacceptable, and it is in such circumstances that the inducement would be inappropriate.⁵

6.28 The greater the inducement, the more likely it is to be inappropriate, because it may cause an individual to ignore or devalue his or her concerns about the risks involved in a research project. Special care must be taken, therefore, when research is accompanied by significant risks. The more serious the risks faced by a participant in research, the more closely the level of inducement should be scrutinised, to ensure that it is not inappropriate.

³ Nuffield Council on Bioethics (1999) *The Ethics of Clinical Research in Developing Countries* (London: Nuffield Council on Bioethics), paragraph 44. Available at: www.nuffieldbioethics.org/go/ourwork/developingcountries/publication_305.html

⁴ Principle 12 of the 1991 CIOMS guidelines states that it is acceptable to repay expenses incurred, and that promises of compensation and care in case of damage, injury or loss of income are not to be considered as inducements.

⁵ The CIOMS 1993 guidance states that payments should not be so large or provision of medical services so extensive 'as to induce prospective subjects to consent to participate ... against their better judgement'.

6.29 It is an inescapable fact that people who are ill may place great weight on a possible health benefit, even if the probability that it will occur is relatively low. This means that involvement in research which, of necessity, involves medical treatment, may amount to an inducement since the participant will receive medical treatment for his or her condition and may thus be less likely to refuse. This does not necessarily mean that the individual has been exploited. However, when participants are ill and do not have alternative ways of receiving treatment, the possibility for exploitation is greater. The CIOMS guidelines note that 'someone without access to medical care may be unduly influenced to participate in research simply to receive such care'.⁶

6.30 Guaranteed healthcare or a payment offered to individuals on condition that they take part in a research project could be considered to be exploitative if otherwise there is a very low probability of receiving such a benefit. This contrast in benefits, depending on whether an individual enrolls in research is particularly important in developing countries (see Box 6.5). Research ethics committees should bear this in mind when assessing whether it is acceptable to conduct a research projects which may involve more than minimal risk. In such circumstances special care should be taken when determining the nature of additional healthcare to be offered to participants as an inducement.

6.31 We suggest when assessing the acceptability of inducements to participate in research in developing countries, those designing the research and research ethics committees should pay particular attention to:

- *harmfulness*: whether there are potential risks to the participants' health from taking part in the research
- *proportionality*: whether the inducement being offered is in proportion to the risks and costs to the participant involved in the research
- *vulnerability*: whether guaranteeing substantial benefits for taking part in research is more likely to constitute an undue inducement because prospective participants are especially vulnerable, for example because they have a terminal or chronic illness.

6.32 The CIOMS guidelines note that the propriety of inducements must be 'assessed in the light of the traditions of the culture'.⁷ For example, some cultures may have a tradition of gifts or exchanges which will make some forms of inducement more appropriate than others. The majority of respondents to our public consultation noted that many decisions about which inducements are appropriate will depend on local circumstances.

⁶ CIOMS in collaboration with WHO (1993) *International Ethical Guidelines for Biomedical Research Involving Human Subjects*: Commentary on Guideline 4.

⁷ CIOMS (1991) *International Guidelines for Ethical Review of Epidemiological Studies*, CIOMS, Geneva: Principle 11.

In such cases, local knowledge will be essential in making appropriate distinctions. One respondent commented:

The level [of compensation] would have to be determined locally e.g. what is considered an appropriate sum to cover time and inconvenience in the US (say \$50) would be equivalent to several years earning in rural Uganda.⁸

We recommend that dialogue is needed with sponsors, external and local researchers and communities to ensure that any inducements to take part in research are appropriate to the local context, especially in circumstances where the research exposes participants to a risk of harm. Decisions about appropriate levels of inducement will need to be justified to local research ethics committees.

The validity of research involving animals

Although complete information is not available, the MHRA report⁹ on clinical trials states that TGN1412 was tested on both rabbits and Cynomolgus monkeys prior to being tested on humans. These tests did not predict the severe adverse reactions that were later seen in the six human participants.

The Council is not able to comment on specific cases such as the TGN1412 trial. However, a recent Report by the Council on *The ethics of research involving animals* (2005)¹⁰ discusses in detail the general issues surrounding extrapolating the results of animal studies to humans. The Expert Group may wish to consider these when addressing the issues surrounding the transition from pre-clinical to first-in-man Phase 1 studies.

Some of those who oppose animal research on scientific grounds argue that anatomical, physiological, cellular, biochemical and other differences between humans and animals seriously compromise most extrapolations of results from animal studies to humans. In the Report, we describe a wide spectrum of different kinds of biomedical research activity, between them employing a variety of different kinds of animal model to address a range of different objectives (Chapters 5-9). The cases presented show that there are numerous instances in which extrapolations from animal studies can be made in a meaningful way, provided that the animals involved are sufficiently similar to humans in relevant aspects of the biological phenomenon or disease being studied. We also describe a number of examples that illustrate some of the difficulties involved in extrapolating from animals to humans. For example, although there has been extensive use of animals in HIV/AIDS research, modelling of this complex disease is difficult, and all of the currently available animal models have limitations (paragraphs 6.36-6.37).

⁸ Response by Dr Dilys Morgan to the Working Party's consultation.

⁹ Medicines and Healthcare Products Regulatory Agency (2006) *Clinical trial final report*.

Available at:

www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2023822&ssTargetNodeId=389 Accessed on: 26 June 2006

¹⁰ Available at: www.nuffieldbioethics.org/go/ourwork/animalresearch/publication_178.html

Given the vast complexity and variability of biological systems, it is not surprising that there are sometimes problems in developing effective experimental approaches in biomedical research and in extrapolating from model systems to humans. These problems are not confined to animal studies, but are also encountered in developing and applying other experimental approaches, such as *in vitro* and clinical studies. None of these methods can reproduce exhaustively all the features that characterise the wide diversity and variation of genetic and biological processes that occur in a population of humans (see paragraphs 10.33-10.34).

Taking into account the discussion and evidence presented in the Report, we note that there have been a great number of cases where animals have been used successfully to provide models for humans (or other animals of different species). We therefore agree with the findings of a Report by the Animal Procedures Committee (APC), which observed that:

‘the scientific validity of animal experiments is a condition capable of being fulfilled, but has to be judged case by case and subjected to detailed critical evaluation’.¹¹

There is a need for continuing review of the scientific case for using animals in research and testing. We observed that there is a relatively limited number of useful reviews currently available (paragraph 10.46) and we make a number of recommendations on this matter:

15.77 The question about the scientific validity of animal experimentation for medical purposes is often confused with questions about complex ethical issues. We emphasised in Chapter 3 that the separation of scientific and ethical questions is essential if greater clarity is to be achieved in the debate about research involving animals. **In principle, it would therefore be desirable to undertake further systematic reviews and meta-analyses to evaluate more fully the predictability and transferability of animal models.** We are aware that carrying out such reviews may be complicated by a number of problems.

15.78 First, it may be difficult to assess if an animal experiment failed to yield specific data because the wrong animal model was used or because the study design was flawed. Any proposed review should identify clearly whether there are areas of research in which scientific methodology (for example, statistical analysis) needs to be improved, or whether there is reason to question the scientific validity of using specific animals as models in particular areas of research.

15.79 Secondly, care should be taken when selecting the studies to be analysed in any review, and the reasons for selection must be made explicit to avoid misunderstandings. Problems could arise if, for example, a

¹¹ Animal Procedures Committee (2003) Review of the cost-benefit assessment in the use of animals in research (London: HO), p26

review focuses exclusively on an area where progress has been difficult, as the results might be interpreted by some as suggesting that animal research *in general* yields insufficiently transferable results. Similarly, reviews that focus exclusively on areas where progress has been relatively straightforward might be interpreted as proof that *all* animal research yields useful and directly applicable results. Clearly, such interpretations are not useful and contrary to the evidence presented in Chapters 5–9.

15.80 On balance, we consider that there is merit in undertaking appropriately designed and presented reviews on the scientific validity of animal research in specific areas. Since the scientific evaluation of animal research is fundamental to the cost-benefit assessment of any research, **we recommend that the Home Office, in collaboration with major funders of research such as the Wellcome Trust, the MRC, the BBSRC, animal protection groups and industry associations such as the ABPI, should consider ways of funding and carrying out these reviews. In devising a strategy, priorities should be identified which, in order to respond to concerns of the public, consider, among other things, the validity of research that falls in the substantial category, and research that involves primates.**

Recent literature

Finally, although not considered in the Council's Report, we would like to draw to the attention of the Expert Group some recent literature which may have some relevance to your discussions.

A recent study found that differences exist between human and chimpanzee immune cells.¹² Human T cells were seen to give much stronger proliferative responses to specific activation via the T cell receptor than those from chimpanzees. There has been speculation that this may explain why tests on monkeys did not uncover any adverse reaction to TGN1412.¹³

It has also been suggested that the reaction seen in the participants could have been predicted if the drug had been tested on different animals, for example, genetically modified mice.¹⁴ 'Humanised' mice can be used as a preclinical model to evaluate *in vivo* human adaptive immune system development as well as immune responses, for example, to vaccines or live infectious pathogens. The literature describes this technique and its potential applications in more detail.¹⁵ As you will be aware, a Working Party established jointly by the Academy of Medical Sciences, the Medical Research

¹² Nguyen DH, Hurtado-Ziola N, Gagneux P and Varki A (2006) Loss of Siglec expression on T lymphocytes during human evolution *PNAS* **103**: 7765-7770.

¹³ The Times (2 May 2006) *What the ape can tell us about that horrific human drug trial*. Available at: www.timesonline.co.uk/article/0,,2-2160469,00.html Accessed on: 27 June 2006

¹⁴ BBC News Online (17 March 2006) Animal tests 'false reassurance'. Available at: <http://news.bbc.co.uk/1/hi/health/4817178.stm> Accessed on: 26 June 2006

¹⁵ See: Macchiaroni F, Manz MG, Karolina Palucka A *et al.* (2005) Humanized mice: are we there yet? *JEM* **202**: 1307–1311; Chicha L, Tussiwand R, Traggiai E, *et al.* (2005) Human Adaptive Immune System Rag2-/-_c -/- Mice *Ann NY Acad Sci* **1044**: 236–243

Council, the Royal Society and the Wellcome Trust¹⁶ also considers the scientific basis for recent, current and future use of non-human primates within biological and medical research, and is expected to report in autumn 2006.

Replacements for the use of animals in research

A key element of the debate on research involving animals concerns the use of replacements. The Expert Group may wish to consider the following questions: which non-animal tests were used in the TGN1412 trial, which other non-animal tests are or could be available for this type of drug, whether these would have better predicted the adverse reaction seen in the human participants, and whether the animal studies carried out were necessary and valuable. If so, the information below may of some use.

Before a licence is granted by the Home Office, researchers are required to demonstrate that the 'Three Rs' (Refinement, Reduction and Replacement) have been implemented to reduce animal suffering as far as possible. In particular, replacing the use of animals is a highly desirable goal and progress in this area has been made in the UK. Nevertheless over 2.78 million animals were still used in experiments in 2004.¹⁷ The use of alternatives is discussed in the Council's Report on *The ethics of research involving animals* (2005).¹⁸ The Report gives examples of the Three Rs, and considers barriers to their implementation and ways in which these could be overcome (see Chapters 11–12).

Some, often those involved in animal research, point out that the use of alternatives to animals is a legal requirement in the UK; that alternatives are always used if they are available; and that it is simply not possible to avoid the use of animals in most of the experiments that are currently carried out. They argue that large sums of money are spent on the search for alternatives; and that most research on Replacement methods is in fact undertaken by the scientific community.

Others, often those who work for animal protection organisations, and some scientists, argue that efforts to develop new, alternative methods and use of those already available could be increased substantially; that funding to develop (and validate) alternatives ought to be augmented; and that the search for alternatives requires greater commitment and focus. They argue that much more could be done with political will, greater resources and greater motivation within the scientific community. Some commentators also assert that animal experiments are poorly validated and sometimes misleading, and that alternative methods are therefore 'better science'.

We concluded that there is a moral imperative to use currently available alternatives and to develop new alternative methods where gaps exist. The

¹⁶ <http://www.acmedsci.ac.uk/index.php?pid=47&prid=6>

¹⁷ Home Office (2005) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO).

¹⁸ Available at: www.nuffieldbioethics.org/go/ourwork/animalresearch/publication_178.html

Report includes a number of recommendations that aim to improve the implementation of the Three Rs (see paragraphs 15.57-15.62).

I am pleased to enclose a copy of the Council's Reports on *The ethics of research related to healthcare in developing countries (2002)*, and *The ethics of research involving animals (2005)* for your reference. Please do not hesitate to contact us if you require clarification on any of the information contained in this letter, or further copies of the Council's Reports.

Thank you again for the opportunity to provide evidence to the Expert Group.

Yours sincerely,

A handwritten signature in blue ink that reads "Sandy Thomas". The signature is written in a cursive, slightly slanted style.

Professor Sandy Thomas
Director