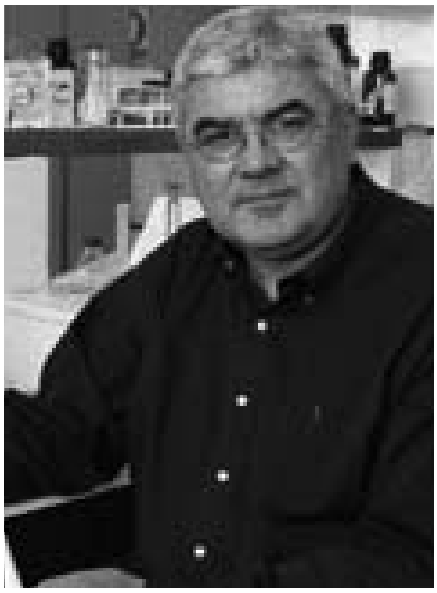
Recommendations to increase the safety of first-in-human clinical trials following the TGN1412 clinical trial in 2006



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Background

In March 2006, a first-in-human clinical trial of a monoclonal antibody, TGN1412, took place in a private facility at Northwick Park Hospital in London. The clinical trial was suspended immediately when very serious adverse reactions occurred in all six of the healthy volunteer subjects. TGN1412 was being developed as a medicine to treat leukaemia and autoimmune diseases such as rheumatoid arthritis. Its target was a molecule that can activate T lymphocytes, key cells of the immune system. The rationale was that this stimulation by TGN1412 would improve the regulation of immunity.

In the clinical trial, all six healthy volunteers experienced life-threatening reactions soon after receiving TGN1412 by intravenous infusion. All six trial subjects required intensive treatment and supportive measures that were provided by the Intensive Therapy Unit at Northwick Park Hospital. Subsequent clinical investigation showed that the recipients of TGN1412 had experienced a large release of cytokines, small proteins that signal between cells of the immune system. The phrase 'cytokine storm' has been used to describe this life-threatening reaction.

Previously, first-in-man clinical trials had had a very good safety record, and the outcome of the TGN1412 trial, where all recipients experienced such severe and similar adverse reactions, was unprecedented.

The Expert Scientific Group

Following this, the Secretary of State for Health set up an Expert Scientific Group (ESG) to learn from these events and to make recommendations to increase the safety of future trials involving the first human exposures to new medicines that warrant special consideration because of their scientific innovation or the novelty of their pharmacological targets.

The ESG terms of reference and ways of working:
1. To consider what may be necessary in the transition from pre-clinical to first-in-human Phase 1 studies, and in the design of these trials, with specific reference to:

- biological molecules with novel mechanisms of action;
- new agents with a highly species-specific action;
- new drugs directed towards immune system targets.

2. To provide advice, in the form of a report, for the future authorisation of such trials with an interim report to be provided within three months

The ESG comprised 19 individuals including two lay members and specialists in clinical medicine, clinical pharmacology, toxicology, immunology, clinical trial design and ethics. The opinions and advice of stakeholders was sought and considered in detail before formulating interim recommendations that were published on July 26th 2006. Further written and verbal submissions from stakeholders, including four of the trial subjects and their representatives, the Northwick Park physicians, patient groups, individuals, national and international public sector institutions, the biotechnology and pharmaceutical industries and contract research organisations were received after the interim report was published in the form of an open consultation document. These submissions were taken into account in formulating the final report with 22 recommendations published in December 2006.

Approach to the Problem

The need for better and safer medicines is clear, as is the fact that the first human exposure to a new medicine will always carry some risk, even if extremely small. The aim of the ESG was to optimise the safety of future first-in-human trials of the types of medicines within its remit without stifling innovation or raising unnecessary barriers to the development of useful new medicines.

The ESG reviewed the pre-clinical development of TGN1412, the results from MHRA investigations and the likely causes of the unpredicted severe toxicity at the dose given in the trial. Toxicity had not occurred in the cynomolgus monkey, the animal model chosen for studies to calculate the dose for the first human exposure to TGN1412. At a dose that was numerically 500 times larger than that given to human volunteers, cynomolgus monkeys did not experience any apparent adverse effects.

Results of independent scientific tests carried out by the National Institute

for Biological Standards and Control (NIBSC) to clarify the toxicity seen in the TGN1412 trial may provide some answers to scientific questions surrounding the adverse reactions in human recipients, and why similar reactions were not detected in pre-clinical testing in animals or in tests using human blood cells. The results of these NIBSC studies were summarised in the final report and will shortly be published in detail.

Risk reduction and risk management are the cornerstones of safe clinical trials. Understanding the potential risks in clinical trials of new agents or agents with new pharmacological targets cannot entirely be guided by previous experience, and such agents should receive special scientific consideration. The ESG focused on risk reduction and risk management.

Scope of the Recommendations

What kind of clinical trial?
The recommendations apply to first-in-human clinical trials, and not to Phase 1 Trials in general (which might include trials of agents with an established record of safety in humans). Special caution is needed during first human exposures to new medicines at doses likely to cause a pharmacological effect.

However, added caution is also needed when administering a medicine with the potential for risk to a distinct new population, be they healthy volunteers or patients, or of different age, gender, ethnicity or medical condition.

What kind of agent?
The remit covered three categories of medicines that may require special consideration before being given to humans for the first time: biologicals with novel mechanisms of action; new agents with a high degree of species-specificity; and new agents with immune system targets.

The recommendations were intended to apply to medicines or potential medicines in any one of these three categories, unless a careful assessment of the physiological role of the target molecules supports a low risk of harm in first human exposures. It was not suggested that any agent that falls into one of these categories necessarily poses a high risk on first human exposures, but that a clear and strong scientific case should be provided in support of an assessment that the risk of harm is extremely low.

For example a conventional vaccine, although aimed at stimulating an immune response, may not pose a high risk, or a new agent similar to one with an established safety record in humans and aimed at a known target where the pharmacology can be predicted with confidence, may not require special consideration beyond the conventional careful approach to risk assessment and risk management that must be taken in all clinical trials.

When might special consideration be needed?

In the report factors were discussed that should raise the level of caution for first human exposures to new agents. No comprehensive list can be made but such factors might include:

- potential to cause severe physiological disturbance to vital body systems;
- agonistic or stimulatory actions;
- novel agents and novel mechanisms of action where there is no prior experience;
- species-specific action making pre-clinical risk-assessment difficult or impossible;
- pharmacological potency, eg compared with normal physiological processes;
- multifunctional agents, eg bivalent antibodies with FcR binding domains;
- cell-associated targets;
- targets that by-pass normal control mechanisms;
- immune system targets;
- targets in systems with the potential for large biological amplification in vivo.

A thorough assessment of risk should always be carried out before first-in-human trials. The risk assessment should be clearly described in the trial documents and be fully examined by the regulator.

Increasing the safety of future first-in-human clinical trials

The ESG made 22 recommendations that covered:

- pre-clinical and early clinical development;
- preparation and review of clinical trial applications, and early access to advice for both regulators and sponsors;
- determining and administering the initial doses in humans;
- the clinical environment and conduct of first-in-human studies;
- developing the skills and training to meet future needs.

There was a focus on sharing of information relevant to safety, the calculation and administration of first doses, the conduct of the clinical trial and regulatory access to independent specialist opinion in the appraisal of trial applications.

Stakeholders raised several areas of concern that were not within the ESG remit. These included topics such as the process of informed consent, insurance cover, the role of Research Ethics Committees, and clinical follow-up of trial subjects who had experienced an adverse reaction. Although beyond the ESG remit, these wider concerns are all extremely important, and it was recommended that they should be considered in detail by the appropriate agencies.

The recommendations have been accepted in the UK, and the EU is in the process of developing very compatible new guidance for the design and conduct of first-in-human clinical trials of innovative agents where special consideration may be needed in risk assessment and risk management. New guidance along similar lines will also be available from The Association of the British Pharmaceutical Industry (ABPI). It is important that a similar approach is adopted at international level to ensure that equal protection is given to clinical trial participants worldwide.

Biological advances are providing an ever-increasing number of pharmacological targets for the development of new and better medicines that are vital for the public health. There is no single answer to the question of how to optimise the safety of first-in-human clinical trials. Each new potential medicine must be considered on a case-by-case basis by appropriately trained and experienced teams taking account of all the available information.

Summary

First-in-human Phase 1 studies are the gateway between scientific research and clinical practice, and we must ensure that such clinical trials are safe for the human subjects, whether healthy volunteers or patients, and efficient in gaining new knowledge.

The safety of clinical trial subjects must always be the primary concern. The ESG made 22 recommendations to increase the safety of first human exposures to new agents that require special consideration because of their novelty or intended pharmacological target. The recommendations, while aimed at increasing safety, should not unduly inhibit innovation.

The Expert Group on Phase One Clinical Trials: Final report is available free of charge on the DH web-site: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_063117 and can be purchased as a bound paper version (600 pages) from: TSO Publications Centre, PO Box 29, Norwich NR3 1GN. Tel: 0870 600 55 22 Fax: 0870 600 55 33

Clinical trials and the MRC Clinical Trials Unit

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Clinical trials are the foundation of evidence based medicine and underpin the evaluation of all new interventions which prevent or treat disease, such as vaccines or drugs. Once they have been shown to be safe and have activity in laboratory and animal experiments most interventions will go through a series of clinical trials which start by testing it in a small number of volunteers, usually healthy individuals but sometimes patients, to assess safety known as a Phase I trial. If there is no evidence of serious toxicity it will then be tested in a larger number of people with the disease (or normal people if it is a preventive intervention such as a vaccine) to assess both safety and activity, a Phase II trial. If the trial is successful then much larger trials referred to as Phase III, are undertaken to assess the benefits and risks of the treatment, and its role in clinical care.

Most of these trials are:

- randomised (that is treatment is allocated by a chance process) to avoid bias in the selection of treatment
- controlled, which means they compare the new treatment with the best current treatment to assess its role in clinical care
- and are often blinded by using a placebo, which is inert but indistinguishable from the new drug so that participants and their doctors do not know what treatment they are getting to avoid biases in the management of the participants and decisions about the outcome of the treatment.

The final stage is to set the results of a trial in the context of all other similar trials by bringing together the evidence in a systematic review or meta analysis to provide the most robust evidence base for decisions about the role of the new intervention.

In the MRC Clinical Trials Unit (CTU) our main focus is on clinically important questions which will not be of interest to Pharma as their primary purpose in setting up trials is to lead to licensure of a drug or vaccine. These may include different approaches to using drugs in combination for cancer chemotherapy, the use of surgical procedures or other modalities of therapy or prevention such as radiotherapy or behavioural interventions. Our research programme is centred on a limited number of disease areas, primarily cancer and HIV, which are both major causes of morbidity and mortality. Benefits from new interventions may be greater efficacy, less toxicity or improvement in quality of life – ideally all three.

Two recently completed trials in cancer demonstrate the importance of exploring different approaches to the treatment of cancer. The first, the MAGIC trial, showed that by giving a standard chemotherapy course before and after surgery for cancer of the stomach and lower oesophagus 5-year survival could be increased to 36% compared with 23% in those who had surgery alone. In the second, there was no evidence that the surgical removal of pelvic lymph nodes (lymphadenectomy) in women with endometrial cancer confined to the uterus improved overall survival and there was a tendency for recurrence free survival to be poorer and side effects to be worse in those who had lymphadenectomy.

Over the last 10 years antiretroviral therapy (ART) using combinations of drugs has led to dramatic improvements in survival and quality of life in people with HIV infection in the UK and many other countries which can afford both the drugs and the cost of monitoring the therapy. With the reduction in cost of drugs and the commitment to roll out ART in resource poor countries an important question is whether the intensive and expensive monitoring

undertaken in resource rich countries is necessary.

The DART trial, funded by MRC, DFID and the Rockefeller Foundation, co-ordinated by MRC CTU and Imperial College, was set up to address this question by comparing clinical plus laboratory monitoring with clinical monitoring alone in patients who all receive a standard 3-drug ART regimen. It has recruited over 3,000 patients in two sites in Uganda and one in Zimbabwe who will be followed up for 6 years. Already the impact of ART in these sites has been demonstrated by comparing the survival with a similar group of patients who were followed up before ART became available; the 2-year survival rates were over 90% compared with about 25% respectively.

Sometimes there are areas which are less attractive to Pharma where new interventions come from small companies or academic departments and in these areas the MRC CTU is involved in the whole development process working closely with the company or group which developed the drug or vaccine. A current example here is the MRC/DFID funded Microbicides Development Programme led jointly by the MRC CTU and Imperial College which is working with a small biotech company (Indevus) to evaluate a vaginal gel as a potential microbicide product to prevent HIV transmission. This is a major international collaboration with many partners in Africa, the UK and Spain in which nearly 10,000 women will take part and over 4,000 have been recruited already. The challenges of developing a microbicide and concerns about the likely return on investment make it an area which is not attractive to Pharma.

Most of the trials that the MRC CTU undertakes are large trials exploring better ways of using existing treatments or part of a development programme in areas of limited interest to Pharma. When the MRC CTU was established in 1998 it was also given the remit to work in areas outside cancer and HIV where there are important questions but no strong tradition of clinical trials. Collaboration in trials in musculoskeletal disease have been set up with the Arthritis Research Campaign and with the National Blood Service and trials in a number of other areas such as tuberculosis and diabetes set up with clinical colleagues at University College Hospital.

Underpinning the clinical trials are a number of other areas of research, which contribute to the design, conduct and analysis of the trials to ensure that the results are reliable and timely. Observational epidemiological studies tell us about the outcome of disease in a population on current treatment and therefore help to estimate the size of trials needed to demonstrate reliably whether a new intervention is better. Methodological research is important both to address problems encountered in trials, such as how to handle missing data, and to improve trial design so that answers can be obtained more quickly. Systematic reviews and meta analyses can both assess what the results of a new trial add to the current knowledge or bring together all the information in a clinical area to identify questions which new trials are needed to answer.

Clinical trials units such as the MRC CTU which have expertise and experience in designing, conducting and analysing clinical trials and related clinical and epidemiological research studies are a key part of the 'whole system' which underpins clinical research in the UK with the goal of improving health care. Other key components are the clinical infrastructure in the NHS which enables the recruitment of patients and healthy volunteers to the studies and the funders, whether Government, medical charities or industry which provide the resources. Equally important are the involvement of patients and the public at all stages of the research process, and academic and clinical investigators to identify research questions and priorities and, working with the CTUs, turn these into successful trials.

Cancer trials in the UK have a long and successful track record but in 2000 were struggling to recruit rapidly because of insufficient clinical time of doctors and nurses. The National Cancer Research Network (NCRN) was set up by NHS R&D in 2001 to provide infrastructure support through local research networks across England, with parallel developments in Scotland, Northern Ireland and Wales. By 2006 the proportion of newly diagnosed cancer patients recruited to trials had increased from less than 4% in 2000/1 to 12.5% in 2006/7. Building on the success of NCRN, further networks have been set up under the UK Clinical Research Network in mental health, diabetes, stroke, dementia and other neurodegenerative diseases, medicines for children and primary care.

Currently the UKCRN is being extended to cover all areas of health care and disease by the establishment of the NIHR Comprehensive Research Network across the whole of England with parallel activities in the Devolved Administrations. The ultimate goal is to achieve benefits for patients through the more rapid introduction of better treatments including the industry pipeline and resources and by dissemination of excellence in clinical care through the research process.

In discussion the following points were made:

A third speaker (see below) had been invited to represent the Medical Healthcare products Regulatory Agency who was unfortunately unable to attend.

If the Northwick Park trial was unethical it would not have been approved. Would it have been possible to devise a prior experiment to prove the safety of the planned trial? Were there any prior indications or warnings that the experiment was likely to be unusual in any way? No-one knew previously about the cross-linking effect. It took 60 scientists working for six months knowing what they were looking for to work out what had happened. There were four companies involved in the trial, each one making their own contribution to different stages of the trial. In future it will be vitally important for some one individual person to be responsible for knowing everything that it is relevant to know in a drug trial involving first-in-human exposure.

In the past, work was performed in test-tubes but experimental medicine requires testing on human beings. This creates a huge demand for increased training of new researchers to undertake this work, involving new challenges, new biology, and new knowledge, and there are not nearly enough people to do the work at present. Much more exchange and collaboration will be required in the future between commercial organisations such as drug companies and academic institutions such as universities.

Some first-in-human tests may give a very steep, explosive, and apparently all-or-nothing response to a marginally small dose increase. Such dramatic responses over a narrow dosage interval can be very difficult to predict in advance. The only way to perform such tests safely therefore is to develop an experimental model and perform the initial experiments on primates. In addition, risk must be managed within the clinical trial by giving a dose to the first person and then waiting before giving a similar dose to the second person. Do not treat everyone simultaneously. An Expert Advisory Group has now been established, chaired by Sir Gordon Duff, for consultation on the design of first-in-human trials.

With patents running out on many drugs, biosimilars manufactured by other companies may differ slightly from the originally patented drug. These may behave differently under trial conditions which may require very careful consideration in case of unpredictable responses. However biosimilars may become very important economically as they will increasingly form the basis for health care in the future.

THE DESIGN AND REGULATION OF MODERN CLINICAL TRIALS

Medicinal Products for Paediatric Use

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(Dr Julia Dunne was unable to be present at the meeting but has submitted the following article for publication)

Background

Before any medicine is authorised for use in adults, the product must have undergone extensive testing including pre-clinical tests and clinical trials to ensure that it is safe, of high quality and effective. The same may not be true for medicines used to treat children. Over 50% of the medicines used in children may not have been studied in this age group. In the European Union, the paediatric population (0-18 years) represents about 75 million people, that is 20% of the total population. This is a vulnerable group with developmental, physiological and psychological differences from adults, which makes age and development related research particularly important.

The absence of suitable authorised medicinal products to treat conditions in children is an issue that has been of concern for some time. Pharmaceutical companies have been reluctant to invest in developing specific treatments or adapting existing medicines to meet the needs of the paediatric population, mainly because the market is small and therefore of lower commercial interest and the studies can be difficult, long and expensive. In addition, developing a suitable formulation which can provide an exact dose, for example a syrup, may be technically difficult and expensive on an industrial scale. This often leaves no alternative to the prescriber than to use 'off-label' and unauthorised products, without evidence-based information to guide prescribing and give information about the risk-benefit assessment.

The need to conduct trials in the paediatric population

The paediatric population is not a homogeneous group; it ranges from pre-term newborns, through toddlers and children to adolescents. They are not miniature versions of adults. Specific clinical trials in paediatric populations are normally required due to age-related differences in the drug handling or drug effects which may lead to different dose requirements to achieve efficacy or to avoid adverse effects. Paediatric studies conducted in response to US legislation led to the introduction of new paediatric information in around 130 labels for established medicines between July 1998 and June 2007. The new information includes new dosing information or a dose change in recommended dose, new safety data, advice that safety and efficacy are not established in the paediatric population and new dosing instructions in younger populations. These changes have an impact on the safe and effective use of the medicine in the paediatric population. Further information is available on the US

Food and Drug Administration (FDA) website (http://www.fda.gov/oc/opt/default.htm). Without such specific studies in the paediatric population this important information would not be available. In addition, the US legislation led to the development of age-appropriate formulations to avoid difficulties in swallowing or, more significantly, serious calculation errors when using adult formulations to obtain paediatric dosages.

EU Regulation on paediatric medicines

The EU Regulation on Paediatric Medicines was adopted on 12 December 2006 and came into force on 26 January 2007. The Regulation establishes a legislative framework that will fulfil the following main objectives:

- increased availability of medicines specifically adapted and licensed for use in the paediatric population
- increased information available to the patient/carer and prescriber about the use of medicines in children, including clinical trial data
- increase in high quality research into medicines for children.

These will be achieved through a system of requirements and incentives. Work began on the draft texts in the Council Working Group in late October 2004. Achieving progress on the Regulation was a priority of the UK Presidency of the EU and political agreement on a text was reached in December 2005. A second reading agreement between the Council, the European Parliament, and the European Commission was achieved in June 2006. The main elements of the finalised Regulation include:

- the establishment of a new body, the Paediatric Committee, sited at the European Medicines Agency (EMEA)
- for new products and certain changes to the marketing authorisation for products still covered by patent protection
    - o a requirement for paediatric data based on a paediatric investigation plan (PIP)*
    - o a six-month extension of the supplementary protection certificate (SPC) if information arising from a completed PIP is incorporated into the Summary of Product Characteristics (SmPC)
- for orphan medicinal products
    - o a two-year extension of market exclusivity if information arising from a completed PIP is incorporated into the Summary of Product Characteristics (SmPC)
- for off-patent products
    - o a new category of marketing authorisation called the paediatric use marketing authorisation which will be associated with a ten-year period of data and market protection
- a European database of paediatric clinical trials, part of which will be publicly accessible including trial results
- co-ordination of a European Paediatric Clinical Trials Network
- funding for the study of off-patent medicines provided through the Community framework programmes
- an identifying symbol on the package of all products authorised for use in children.

UK Medicines for children research network (MCRN)

The EU Regulation will lead to more paediatric clinical trials being conducted in the EU. The Medicines for Children Research Network (MCRN) was created in 2006 to provide the best possible framework for such trials in the UK. The network aims to improve the co-ordination, speed and quality of randomised controlled trials and other well designed studies of medicines for children and adolescents, including those for prevention, diagnosis and treatment. The network has extensive knowledge and experience of paediatric research, and supports non-commercial, pharmaceutical/biotech-sponsored and investigator-led partnership studies in over 100 NHS sites that serve approximately 6 million children. The MCRN supports studies though its infrastructure, which includes the MCRN Co-ordinating Centre, Clinical Studies Groups (CSGs), Local Research Networks (LRNs), Clinical Trial Units (CTUs) and a Neonatal Network.

The MCRN Co-ordinating Centre is led by a consortium comprising the University of Liverpool, Royal Liverpool Children's Hospital, Imperial College London, National Perinatal Epidemiology Unit (NPEU; University of Oxford), Liverpool Women's Hospital and the National Children's Bureau. The MCRN is funded by the Department of Health and works in partnership with the UK Clinical Research Network (UKCRN) to improve the UK's clinical research environment and maximise the development of safe and effective medicines and formulations for children.

Protection of children in trials

Although there may be ethical concerns about conducting trials in the paediatric population, this has to be balanced by the ethical concerns about giving medicines to a population in which they have not been tested.

There is a complementary framework of European and national legislation, implementing texts and national and international guidelines aimed at protecting children involved in clinical trials. The European Clinical Trials Directive sets out the provisions which must be followed if minors are to be studied in a clinical trial. The directive covers the protection of all clinical trial subjects and includes additional protection for minors. This includes informed consent from a parental/legal representative; provision of information to the minor on benefits and risks in language that he/she can understand; respect for the explicit wish of the minor to refuse to enter a trial or withdraw from a study; compensation is allowed but no financial or other inducements; the group of subjects involved in the trial should derive a direct benefit from involvement; trials should be designed to minimise pain, discomfort, fear; the Ethics Committee approving the trial should have paediatric expertise or input and the patient's interests should always be considered above the interests of society. The directive is reinforced by the Regulation on Paediatric Medicines which contains provisions to prevent unnecessary studies or duplication of studies. In addition the European Commission is co-ordinating the preparation of a document on *Ethical Considerations for Clinical Trials Performed in Children – Recommendations of the Ad Hoc Group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use.* This was released for public consultation in 2006 with comments requested by 31 January 2007.

*This does not become law until 18 months after entry into force of the Regulation