EXECUTIVE SUMMARY

1. Investigators in Clinical Trials should do no harm to the subjects they recruit. Investigators should also preserve and maintain the public’s confidence in medical research by offering care and adequate compensation for adverse events arising from their studies.

2. The number of Phase I clinical trials being done in Singapore has risen considerably over the past 3 years, in keeping with Singapore’s aim to be a leading clinical trials centre. Since Phase I trials are tests of new agents in human beings and are almost always done in healthy volunteers, no health benefits are expected in the trial participants. On the contrary, although the agents would have undergone safety testing in animals, they may still produce unpredictable effects in man. Such unpredictable effects may occur with new agents with novel mechanisms of action, with biological agents, and with those that act via the immune system. Phase I trials include studies in which new agents are used for the first time in man, so unforeseen adverse events cannot be ruled out.

3. In the light of recent adverse events in the UK TGN1412 trial, the National Medical Ethics Committee (NMEC) has reviewed current procedures for the approval and conduct of Phase I clinical trials in Singapore, and the recommendations in this document are specifically for participants in these trials - i.e. volunteers who usually are not patients. The TGN 1412 trial was a Phase I study of a humanized monoclonal antibody, in which all the six healthy volunteers who received that antibody became critically ill within hours of receiving the first dose.

4. The issue of costs of acute and continuing medical care required for medically significant adverse events in all volunteers in Phase I clinical trials in Singapore needs to be addressed specifically because, unlike the UK, Singapore has no free national health service. The individual’s own medical insurance cover may not apply to injuries sustained in a clinical trial and, even if it did, it should not be called upon in such events, nor should the individual suffer the recurring increase in annual premiums that would arise therefrom.

Recommendations for prevention of injuries due to unexpected adverse events

5. Before ethical approval of new agents, especially those with novel modes of action, and including those acting via the immune system, expert advice should be sought on the likelihood of unexpected events.
6. Phase I trials of agents with significant risk of unexpected serious adverse events, and all first-in-man trials should be conducted in centres with appropriate facilities for emergency treatment and intensive care.

7. Local drug developers, research-funding bodies, and regulatory authorities should actively seek and share information from unpublished preclinical studies and from Phase I trials on the test agent being conducted outside Singapore, and they should insist on being notified in a timely manner of serious unexpected adverse reactions arising from the latter.

**Recommendations on recruitment of subjects and informed consent**

8. Efforts should be made to ensure that all such volunteers understand:

- the potential risks, expected and unexpected, of the trial;
- their right to compensation for adverse events;
- the limitations of the compensation offered;
- avenues for arbitration should there be disputes over compensation.

9. Payments for participation in Phase I trials should be commensurate with the burden of participation. However, excessive remuneration or other forms of benefit are improper if they are such as to persuade people to volunteer against their better judgment.

**Recommendations on compensation and medical bills**

10. Sponsors of Phase I trials, commercial or non-commercial, should make adequate and separate provisions for medical costs and for compensation of non-medical costs resulting from injuries sustained as a result of the clinical intervention or procedures provided for by the research protocol.

11. Institutions that allow non-physician investigators to do clinical studies should take out specific insurance cover for liabilities that these investigators may incur.

12. Research ethics committees should ensure that there are no gaps in responsibilities for providing for compensation for relevant non-medical costs and for medical bills that arise from adverse events, and that responsibilities are spelt out clearly in the protocol and information sheet.

13. Medical costs and relevant compensation should be awarded on a no-fault basis.

14. Volunteers know that the trials they participate in are not treatments, and medical costs for adverse events from the trial should be settled on their behalf without delay. The party that should first settle the costs should be specified (e.g., the drug developer, contract research organisation, research institution; or an insurance company contracted by any of these). Any disputes as to who should bear the cost of the compensation should be resolved subsequently by the parties concerned.
PART I: BACKGROUND

1. In March 2006, in a Phase I clinical trial done in the UK of TGN1412, a humanized monoclonal antibody, all six healthy volunteers who received the antibody became critically ill within hours of receiving the first dose of the antibody intravenously. The effects were reported to have been unpredictable from the preclinical tests of the antibody.

2. This incident led to questions being raised on whether volunteers in Phase I clinical trials might not have been made sufficiently aware of the risks of participation in the trials and of the limitations of compensation available; whether the insurance cover was sufficient for the trial; whether people might be induced to enter clinical trials for financial gain; and what lessons can be learnt by regulators and ethics bodies about the conduct of the trial.

3. The NMEC’s 1997 Ethical Guidelines on Research Involving Human Subjects does address recruitment, risks and safety, and compensation. Nevertheless, the seriousness and unexpected nature of the injuries, as well as Singapore’s aim to be a leading centre for biomedical research and clinical trials, and the increasing number of Phase I trials being conducted in Singapore (Appendix A), has prompted the NMEC to examine:
   - How to minimise the likelihood of similar disasters occurring in Phase I clinical trials conducted in Singapore;
   - Whether provisions for compensation for harm arising from the trial are adequate for participants in Phase I clinical trials in Singapore;
   - Whether limitations of compensation provisions are clearly conveyed to participants;
   - Whether the remuneration and other benefits being offered to potential participants are such as to induce them into volunteering for Phase I trials against their initial judgment.

4. Phase I clinical trials are tests of new therapeutic agents in man (Appendix B). They are almost always done in healthy volunteers, who are not expected to derive any health benefit from the trial. An additional ethical and moral difficulty with Phase I trials is that, although these agents would have undergone extensive preclinical testing in animals, there is always the possibility of unpredictable adverse effects when they are given to man. Unforeseen effects are especially likely to occur with agents that act by novel mechanisms, with biological agents, with those that act on the immune system, and with those that are being tested for the first time in man.

The TGN 1412 clinical trial

5. The clinical trial was conducted by Parexel International Ltd, a contract research organization, for TeGenero AG, a German biopharmaceutical company that focused on immunotherapeutics (and which has since filed for insolvency proceedings on grounds that the incident has made it impossible for it to attract the investments needed to operate). The monoclonal antibody was manufactured by Boehringer Ingelheim, Germany.
6. The trial was conducted at the Parexel Clinical Pharmacology Unit based at Northwick Park Hospital in North London, an established clinical research centre.

7. Volunteers would receive £2000 UK for completing the trial.

8. In the trial six volunteers were to receive the antibody, and two to receive a placebo. Within 90 minutes of receiving an intravenous dose of TGN1412, all six volunteers had a systemic inflammatory response, and within 12-16 hours they started to have pulmonary and renal failure, and disseminated intravascular dissemination. Two patients required mechanical ventilation, all six received renal-replacement therapy (haemodialysis) for several days, all had severe hypotension, and one required surgery for peripheral ischaemia. The recovery phase from the acute effects began between 3 and 20 days, but in the first 30 days there were also other symptoms, such as generalized desquamation, myalgia, difficulties finding words, hyperalgesia, and peripheral numbness. Five patients went home within a month of the incident, and the sixth remained in hospital for about 100 days.

9. Pathogenesis of adverse reactions

9. TGN1412 is a biologically derived CD28 agonist. CD28 agonists stimulate the creation and activation of T lymphocytes. What happened in the volunteers was the development of a cytokine-release syndrome, a severe inflammatory reaction with shock-like symptoms. However, the exact pathogenesis of the reaction has yet to be determined.

Investigations by UK’s Medicine and Healthcare Products Regulatory Agency (MHRA)

10. The MHRA investigated whether there were any errors in the conduct of the trial that might have caused the serious adverse events. The agency reported (May 25, 2006) that there had not been errors in the manufacture of TGN1412 or in its formulation, dilution, or administration to the trial participants. Its conclusion was that the events were most likely caused by a biological action not predicted by apparently adequate preclinical testing.

11. The MHRA had also found some deficiencies in Good Clinical Practice by Parexel, but that none of these would have contributed to the adverse events. Among these deficiencies were that Parexel did not review TeGenero’s insurance policy on cover for the volunteers and the absence of a formal system for 24-hour medical cover for the participants.

12. In its interim report (April 5, 2006), the MHRA had also advised that, pending the report of an expert group set up by the UK Secretary of State for Health to review the TGN1412 incident and recommend any necessary changes to the conduct of clinical trials, a precautionary approach be taken for all first-in-man clinical trials of monoclonal antibodies or other novel molecules targeting the immune system that act via a novel mechanism - i.e. that such trials not be authorized without seeking additional expert opinion on whether the experience with TGN1412 might be repeated.
13. The group made 22 recommendations\textsuperscript{14} for first-in-man trials of higher risk medicines, essentially in the following groups: biological molecules with novel mechanisms of action, new agents with highly species-specific action, and new drugs directed towards immune system targets.

14. Some of their recommendations are:

   a. Efforts by drug developers, research funding bodies, and regulators to expedite collection of data on unpublished preclinical studies and Phase I trials, and on serious unexpected adverse reactions in Phase I trials, and to explore the feasibility of open access to these databases.

   b. A consideration of whether first-in-man trials should be done in healthy volunteers or volunteer patients.

   c. A broader approach to dose calculation, beyond “no effect level” or “no adverse effect level” in animal studies.

   d. The use of the lowest value, with a margin of safety, as starting point in first-in-man trials.

   e. Sequential administration of the trial agent to participants, with appropriate period of observation between individual participants.

   f. Having a treatment strategy in place where there is a predictable risk of certain types of severe adverse reaction.

   g. Having an appropriate clinical environment for the trial, with immediate access to facilities for the treatment of acute emergencies and prearranged availability of intensive-care facilities, with possibly the development of specialist centres for Phase I trials of high-risk agents.

   h. Consultation with independent specialists knowledgeable in areas relevant to the trial before approval is given for the trial.

Results of survey of practice in Singapore

15. For this NMEC examination of compensation and remuneration in clinical trials, six clinical trial centres in Singapore (some run by drug companies, and others part of the Singapore health service) were asked for information on:

   a. The principles of remuneration and compensation should trial participants experience adverse events during the trial;
b. The incentives used for attracting trial participants;
c. The guiding principles adopted to balance proper remuneration for time and inconvenience, against incentives to participate.

16. The results (Appendix C) show that

a. Most of the centres themselves or the sponsors of the trial follow the guidelines of the Association of British Pharmaceutical Industry (ABPI) on compensation for adverse events resulting from participation in a clinical trial.

b. Participants are reimbursed at modest rates for time, transport, and inconvenience. Free medical assessment and comfortable accommodation for overnight stays are sometimes offered.

c. The centres are guided by principles to avoid encouraging people to participate in trials for financial gain.

ABPI guidelines

17. Some of the points stated in the ABPI Guidelines for Medical Experiments in Non-patient Human Volunteers \(^\text{15}\) are that:

a. “Any risk, either known or suspected, and any inconvenience, discomfort or pain likely to be experienced should be made clear to prospective volunteers…”. There is no mention of the possibility of serious unexpected effects.

b. No excessive use should be made of any volunteer, and volunteers should be counselled about the dangers of excessive volunteering.

c. Rewards to volunteers should be reasonable and related to the nature and degree of inconvenience and discomfort involved, but payment should never be offered for undergoing risk.

d. Compensation for injury should be on a no-fault basis.

e. When pharmaceutical companies sponsor studies to be conducted in outside research establishments, the contract with the volunteer should clarify which organisation is responsible for paying compensation.

18. The ABPI’s Clinical Trial Compensation Guidelines \(^\text{16}\) refer to Phase II and III trials, and, among other things, it points out that:
a. “Compensation should only be paid for the more serious injury of an enduring and disabling character (including exacerbation of an existing condition) and not for temporary pain or discomfort or less serious or curable complaints”

b. The patients should not be excluded from consideration for compensation on grounds that the adverse reaction causing the injury was foreseeable or predictable, or that the patient had freely consented to participation in the trial. However, the compensation may be abated or excluded depending on:
   - “the seriousness of the disease being treated, the degree of probability that adverse reactions will occur, and any warnings given” and
   - “the risks and benefits of established treatments relative to those known or suspected of the trial medicine”.

c. No compensation should be paid (or it should be abated as the case may be) to the extent that the injury has arisen from significant departure from the agreed protocol, through the wrongful act of default of a third party (including a doctor’s failure to deal adequately with an adverse reaction), and through contributory negligence by the patient.

d. The amount of compensation paid should in general terms be consistent with the quantum of damages awarded for similar injuries by an English court in cases where legal liability is admitted.

e. Compensation should be given on a no-fault basis.

f. The investigator should be encouraged to make clear to the patients that the trial is following the ABPI guidelines on compensation for injury arising in the course of the trial, and that the investigator should have available copies of the guidelines should they be requested.

19. In the ABPI guidance note on Patient Information and Consents for Clinical Trials, which applies to Phase II and III trials, the statement on risks that should be explained to patients refers to “risks (as reasonably foreseen)”. It also suggests that patients be informed that a copy of the ABPI’s Clinical Trial Compensation Guidelines can be made available on request.

Guidelines of Royal College of Physicians, London

20. Like the ABPI guidelines, the College’s Guidelines on the Practice of Ethical Committees in Medical Research involving Human Subjects (3rd edn, 1996) points out that when medical research on healthy volunteers is undertaken by contract companies on behalf of a pharmaceutical company, it should be made clear, in the protocol and in the agreement with
the volunteer, which of the companies is responsible for compensation. Liability for injuries during research should be accepted regardless of fault.

21. The College report points out that the legal situation for healthy volunteers in research funded by state bodies or originated by individual investigators is less satisfactory than that sponsored by pharmaceutical companies. It acknowledges that many of these bodies have third-party insurance to cover negligence, and recommends that the policies be extended to cover non-negligent incidents. The report says, “The number of claims is likely to be small and the extra insurance premium should be acceptable”.

Liability

22. Liability will depend on the reason for the adverse events.

23. In general, sponsors will be liable for adverse events due to innate properties of the trial drug or effects of procedures associated with the conduct of the trial, whereas liability due to errors in the formulation, dilution, or administration of the drug or errors in conduct of the trial will fall on the parties that erred.

24. The ABPI guidelines on experiments in non-patient human volunteers and the guidelines of the Royal College of Physicians, London, state that responsibilities for paying compensation should be clarified in the contractual document with the volunteer.

Insurance cover

25. An insurance policy was taken out by one local organization to cover for injury due unexpected adverse events (i.e. those not listed in the information sheet) during trials of drugs or procedures. This cover was for all clinical trials (i.e. Phases I-IV).

26. Generally compensation due to doctor-investigator’s errors (“negligence”) is sought from the doctor’s medical protection insurance company. Non-physician investigators do not have similar insurance cover from a medical protection insurance company, and they will require separate insurance cover if they are principal investigators in clinical trials.

Compensation provision for injuries due to clinical trials in other countries

27. In the USA, there are no national regulations requiring sponsors and institutions to provide free medical care or compensation for injuries due to clinical trials, but some institutions have specific policies on compensation. In Europe, the 2001 European directive on the conduct of clinical trials requires that provision be made for insurance or indemnity to cover the liability of the investigator and the sponsor before a trial can be undertaken.
Legal/regulatory framework in Singapore

28. The Medicines (Clinical Trials) Regulations requires that all clinical trials be conducted in accordance with the Singapore Guidelines for Good Clinical Practice (SGGCP).\textsuperscript{19} The SGGCP thus has the force of law.

29. The SGGCP does not state specifically that trial participants must be compensated for non-negligent harm, although this point is implied in its requirement for sponsors of clinical trials to provide no-fault insurance.

30. The SGGCP also implies that sponsors should provide medical care for adverse events since it requires the sponsor’s policies and procedures to address the costs of treatment for trial-related injuries.

31. The SGGCP does not specify the extent of compensation or medical costs to be provided.
PART II: CONCLUSIONS AND RECOMMENDATIONS

32. The NMEC believes that an investigator should do no harm to the subjects he recruits. It also believes that investigators should preserve and maintain the public’s confidence in medical research by offering care and adequate compensation for adverse reactions.

33. Our survey of clinical trials centres in Singapore indicates that they or their sponsors follow guidelines of the Association of the British Pharmaceutical Industry on compensation for injury resulting from participation in clinical trials. However, these guidelines are based on the assumption that the injured in the UK (unlike their Singapore counterparts) have access to free and continuing medical care within the National Health Service. The survey also showed that clinical trial centres in Singapore are guided by principles to avoid inducing people to participate in trials for financial gain.

34. Nevertheless, the NMEC notes the increasing number of Phase I clinical trials being done in Singapore (Appendix A). The numbers of such trials are likely to increase in line with Singapore’s efforts to be a leading clinical trials centre.

35. The NMEC has thus drawn up recommendations to try to minimise the occurrence of unexpected events that might arise with new drugs, and to ensure that participants in Phase I trials, i.e. volunteers who are usually not patients, receive adequate care and compensation for injuries sustained during the trial.

36. The issue of costs of acute medical care required for serious adverse events in Phase I clinical trials in Singapore needs to be addressed specifically because, unlike the UK, Singapore has no free national health service. The individual’s own medical insurance cover may not apply to injuries sustained in a clinical trial, and even if it did it would not be right for sponsors of clinical research to draw upon this source of insurance for injuries due to their studies, nor should the participants suffer the recurring increase in annual premiums that would result therefrom.

Recommendations for prevention of injuries due to unexpected adverse events

37. Before ethical approval of new agents, especially those with novel modes of action, including those acting via the immune system, expert advice should be sought on the likelihood of unexpected events.

38. Phase I trials of agents with significant risk of unexpected serious adverse events should be conducted in centres with appropriate facilities for emergency treatment and intensive care. All first-in-man trials should be conducted in such centres.

39. Local drug developers, research-funding bodies, and regulatory authorities should actively seek and share information from unpublished preclinical studies and Phase I trials of the
test agent being conducted outside Singapore, and insist on being notified in a timely manner of serious unexpected adverse reactions from these trials.

**Recommendations on recruitment of subjects and informed consent**

40. Effort should be made to ensure that all volunteers understand:
   - the potential risks, expected and unexpected, of the trial,
   - their right to compensation for adverse events,
   - the limitations of the compensation offered,
   - avenues for arbitration should there be disputes over compensation.

41. Payments for participation in trials should be commensurate with the burden of participation. The remuneration and other benefits offered should not be such as to induce people to volunteer against their initial judgment.

**Recommendations on compensation and medical bills**

42. Sponsors of Phase I trials, commercial or non-commercial, should make adequate and separate provisions for medical costs, and for compensation for non-medical costs for injuries sustained as a result of the clinical intervention or procedures provided for by the research protocol.

43. Institutions that allow non-physician investigators to do clinical studies should take out specific insurance cover for liabilities that these investigators may incur.

44. Research ethics committees should ensure that there are no gaps in responsibilities for providing for compensation for relevant non-medical costs and medical bills that arise from adverse events, and that responsibilities are spelt out clearly in the protocol and information sheet.

45. Medical costs and relevant compensation should be awarded on a no-fault basis.

46. Volunteers know that the trials they participate in are not treatments, and medical costs for adverse events from the trial should be settled on their behalf without delay. The party that should first settle the costs should be specified (e.g., the drug developer, contract research organisation, research institution; or an insurance company contracted by any of these). Any disputes as to who should bear the cost of the compensation should be resolved subsequently by the parties concerned.
## Number of clinical trial certificates issued in Singapore since year 2000

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*Source: Health Sciences Authority  
*Jan-Jun 2006
Appendix B

Clinical trial phases

New biomedical agents undergo tests in human beings, or “clinical trials”, in four phases:

**Phase I** clinical trials study pharmacology and toxicology. The agent is usually given to small groups of healthy volunteers, unless the intrinsic side-effects of the agent is such that phase I testing should instead be done directly in patients (in which case the trials are sometimes referred to as Phase I/II or Phase 1.5 trials). In either case, the purpose is to evaluate safety, to determine a safe dosage range, and to identify side-effects.

**Phase II** clinical trials are clinical investigations of treatment effect. They are done in relatively small, defined groups of patients (usually less than 100-200), to determine efficacy and to further evaluate safety.

**Phase III** clinical trials are intended for full-scale evaluation of treatment after the agent has already been shown to be reasonably effective. They further document the efficacy of the agent in large defined groups of patients (from several hundred to several thousand) by comparing the agent to other standard or experimental agents, as well as to monitor adverse effects, and to collect information that will allow the agent to be used safely. To some people the term “clinical trial” is synonymous with a full-scale Phase III trial, which is the most rigorous and extensive type of scientific clinical investigation of a new treatment.

**Phase IV** clinical trials are sometimes referred to as “post-marketing surveillance”. Such studies are conducted after the agent has already been approved for registration and been marketed, to monitor its effectiveness in the general population of patients and to collect information about relatively infrequent adverse effects that can be detected only by widespread use. (The term “Phase IV trials” is sometimes used to describe promotional exercises aimed at bringing the drug to the attention of a large number of clinicians, typically those in general practice. Trials of this type have limited scientific value and hence should not be considered part of clinical trial research.)
Confidential information was obtained in a survey
REFERENCES

2. Dyer C, Carvel J, Curtis P. Victims could lose out after doubts about insurance cover. Guardian Apr 17, 2006 www.guardian.co.uk
10. FAQs re TGN1412. TeGenero AG. www.tegenero.com