

Informed Consent in the TeGenero TGN1412 Trial

By Norman M. Goldfarb

A March, 2006 TeGenero Phase I study of the monoclonal antibody TGN1412 superagonist against T cell CD28 receptors sent all six of the exposed subjects to intensive care with severe inflammatory reactions¹, and may have caused long-term physical harm such as damage to their immune systems. As a result, the informed consent form (ICF) and other study documents have become public and can be examined. (In the U.K., the "informed consent form" is separate from the "information sheet," In the U.S., they are combined into a single document. In this article, the term "ICF" refers to the combination.)

These documents are of interest to the injured parties, but they also provide a vivid case study relevant to all clinical research trials. The TeGenero disaster casts a bright spotlight on this ICF. But make no mistake; it is not the only ICF with "issues" that will be signed this year.

Informed Consent Regulatory Requirements

In the U.K., clinical trials are governed by The Medicines for Human Use (Clinical Trials) Regulations 2004 ("MHU" in this article). It gives the following "conditions which apply in relation to an adult able to consent":

- The subject has had an interview with the investigator, or another member of the investigating team, in which he has been given the opportunity to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted.
- The subject has been informed of his right to withdraw from the trial at any time.
- The subject has given his informed consent to taking part in the trial.
- The subject may, without being subject to any resulting detriment, withdraw from the clinical trial at any time by revoking his informed consent.
- The subject has been provided with a contact point where he may obtain further information about the trial.

The study protocol states that the trial was to be conducted "according to the Declaration of Helsinki, revised version of Edinburgh, 1996, and in accordance with local law and Good Clinical Practice." (GCP) The Edinburgh revision of the declaration of Helsinki occurred in 2000, so it is not clear which version applied. However, pertinent language in the most recent version (Edinburgh 2000) includes:

- Medical research involving human subjects must... be based on a thorough knowledge of the scientific literature... and on adequate laboratory and, where appropriate, animal experimentation. (Principle 11)
- Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. (Principle 16)
- Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. (Principle 17)

- The subjects must be volunteers and informed participants in the research project. (Principle 20)
- In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. (Principle 22)

MHU states that “No person shall... conduct a clinical trial; or perform the functions of the sponsor of a clinical trial,... otherwise than in accordance with the conditions and principles of good clinical practice,” including “the International Conference on Harmonisation GCP Guideline.” (ICH) ICH E6 4.8.10 specifies the elements of informed consent. In the U.S., 21 CFR 50.25 and 45 CFR 46.116 are similar but not identical, and provide additional insights into GCP and ethics.

According to a TeGenero spokesperson, “The companies have worked according to strict standards applicable for such type of studies.”² According to the same spokesperson, who prefers to remain unidentified, “The ICF was prepared by Parexel, a highly experienced contract research organisation, in conjunction with TeGenero, and approved by the ethics committee.”³

Table 1 sets forth the applicable MHU and ICH regulatory requirements (along with CFR requirements in the U.S.) for informed consent disclosures.

Table 1. TGN1412 ICF Elements of Informed Consent

Elements	Issues
<p>The trial involves research. The purpose of the trial. The expected duration of the subject's participation in the trial. The trial treatment(s) and the probability for random assignment to each treatment. The trial procedures to be followed, including all invasive procedures. The subject's responsibilities. Those aspects of the trial that are experimental. [ICH] A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental. [CFR]</p>	<p>ICH requires a statement of the randomization probabilities, which is missing. Instead, the statement “...volunteers will be ‘randomized’ to receive either a single dose of the study drug or a placebo” implies a 50:50 randomization ratio. The actual ratio was 3:1 study drug to placebo.</p>
<p>The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant. [ICH] A description of any reasonably foreseeable risks or discomforts to the subject. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable. [CFR]</p>	<p>See “Discussion of Risks” below table.</p>
<p>The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this. [ICH] A description of any benefits to the subject or to</p>	<p>CFR requires a statement of potential benefits to others, which is missing. In this trial, any such statement would probably be condemned in</p>

others which may reasonably be expected from the research. [CFR]	retrospect as manipulative.
The anticipated prorated payment, if any, to the subject for participating in the trial. [ICH]	The calculation of the prorated payment is not disclosed in the statement "If you withdraw from the study prior to completion, you will be paid on a proportional basis."
The anticipated expenses, if any, to the subject for participating in the trial. [ICH] Any additional costs to the subject that may result from participation in the research. [CFR]	The ICF says the stipend is to "compensate for any inconvenience," without mentioning transportation and other costs related to regular and extra visits, which, however, should be obvious to the subject. As of April 9, 2006, one of the injured Subjects, Rob O., has been paying his own £50 cab fares for follow-up medical care visits without reimbursement. ² See also compensation for injury below.
The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks. [ICH] A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. [CFR]	Not applicable
The compensation and/or treatment available to the subject in the event of trial-related injury. [ICH] For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. [CFR]	According to guidelines laid down by the Association of the British Pharmaceutical Industry, Sponsor compensates "for any significant deterioration in health or well-being caused directly by your participation in the study." The National Health Service presumably provides free treatment for minor medical care and injuries that are indirectly caused by the study. Foreign nationals (who, according the protocol, are not excluded from participating) may not be covered by the National Health Service and therefore may not have coverage for minor medical care.
A contact point where [the subject] may obtain further information about the trial. [MHU] The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury. [ICH] An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject. [CFR]	The statement "If you have any point of concern, before during or after the study, you can discuss this with the Principal Investigator or Unit Medical Director, <i>then</i> you may approach the Ethics Committee..." [Italics added] potentially puts the subject in a very awkward situation if he/she wants to contact the Ethics Committee, which is unidentified in the ICF.
The subject [may] withdraw from the trial at any time. [MHU] The subject's participation in the trial is voluntary and the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled. [ICH] Participation is voluntary, refusal to participate will involve no	The statement "If you leave the study and exercise your right not to give a reason,... no payment need be made to you" is a significant penalty for subjects who are participating for financial compensation. Of course, the Subject can provide a false reason. Paying the stipend at completion of the study may coerce the Subject

<p>penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject. [CFR]</p>	<p>to stay to the end of a study that may have a duration as long as "approximately 10 weeks."</p>
<p>The subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial. [ICH] A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject. [CFR]</p>	<p>None</p>
<p>The monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access. Records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential. [ICH] A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. [45 CFR 46.116] A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records. [21 CFR 50.25]</p>	<p>The statement, "Your information.... will be kept no longer than necessary" may be true in the U.K., but is false for most studies conducted in the United States because sites are required, explicitly or in effect, to store study records until sponsors authorize their destruction, and sponsors almost never authorize destruction of study records, despite the requirement in ICH guidelines (E6 4.9.5) and the cost and inconvenience to study sites of perpetual storage.</p>
<p>The approximate number of subjects involved in the trial. [ICH] The approximate number of subjects involved in the study. [CFR]</p>	<p>None</p>
<p>The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. [ICH] Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent. [CFR]</p>	<p>None</p>

Discussion of Risks

The ICF states that "A description of all reasonably foreseeable risks or discomforts is contained within this information sheet." How foreseeable was the risk of the serious reactions that did occur?

The title of the ICF states that the purpose of the trial was "to investigate... a new drug for the potential treatment of various inflammatory diseases." It further states that "This study is a First Time Into Human study and will test the safety and the effects on the body with varying doses of the study drug." One of the subjects, Rob O., told a reporter that he thought he "was participating in a fairly standard trial of a painkiller like ibuprofen, for arthritis... I had no idea it altered the immune system."²

Although recent reports (described below) indicate that there may have been previous human tests with two antibodies similar to TGN1412, TeGenero's study materials do not mention them and the company apparently believed that TGN1412 was the first superMAB tested in humans. The ICF does not mention this understanding.¹ TGN1412 belongs to a new class of synthetic antibodies that are potentially so powerful that TeGenero trademarked the name "superMAB."² ("MAB" is the acronym for "monoclonal antibody.")

The study protocol states that, after administration of TGN1412, a "cytokine storm," defined as a "massive cytokine release," "may theoretically be encountered." In the ICF, the "cytokine storm" is downgraded to a "cytokine release," a much less intimidating term. The ICF states that "...unintended effects may theoretically" include "...cytokine release (causing a hives-like allergic reaction)...," a clear understatement of the risk. For unknown reasons, this risk is followed by "anaphylaxis (a generalised allergic reaction that can be life-threatening)," without mentioning that a "cytokine storm or "massive cytokine release" is the most likely cause.

The dosage of TGN1412 was set at 1/500th the dosage given to animals in preclinical testing. However, given the novelty and potential power TGN1412, there were good reasons for caution:

- TGN1412 "was designed to circumvent the usual checks and balances that prevent T cells from overreacting in the course of their normal duties."¹
- It is well-known that antibody therapy can cause complex and unpredictable results. For example, antibodies can attach to unanticipated types of cells, and they rarely show a linear dose-response effect.⁴ The study Investigator's Brochure states that "CD28 binding sites appeared to be very quickly saturated after dosing of animals with TGN1412." In other words, a small dose can have the same effect as a dose 1000-times the size.
- TGN1412 was intended for use in patients with compromised immune systems; a more powerful effect is not surprising in individuals with intact immune systems.
- According to the TGN1412 protocol, "Concomitant triggering via anti-TCR and anti-CD28 antibodies leads to proliferation and secretion of pro-inflammatory cytokines in vitro but not in vivo." TGN1412 operates by, in effect, performing the functions of both antibodies simultaneously.
- According to the protocol, swollen lymph nodes after administration of the study drug "may be indicative... for "an excessive T cell reaction..."
- A 1990 report in the journal "Transplantation" stated that an unmodified superagonist monoclonal antibody similar to TGN141 against related C3 receptors caused uncontrolled cytokine releases in immunodepleted mice.¹ After modifications, the C3 antibody proved effective and is now marketed as a treatment for transplant patients.¹

- A study, titled "Tumour regression in patients with metastatic renal cancer treated with a monoclonal antibody to CTLA4 (MDX-010)," used the MDX-010 monoclonal antibody agonist to the CTLA4 receptor, which relates to CD28 receptor activity. Adverse events, including enteritis, hypophysitis and meningitis, were observed in 12 of the 20 subjects.⁵
- A 2002 article in the Journal of Clinical Immunology warned that "caution should be taken in the development of immunotherapies targeting [T cell] costimulatory pathways" such as the CD28 receptor.⁶

The statement "Preliminary data from animal studies demonstrated that the study drug was safe and well tolerated." perhaps should have been clarified as follows:

Experiments with animals have some predictive value for human safety. Preliminary data from animal studies demonstrated that the study drug was safe and well tolerated in the experimental animals. However, the experimental animals experienced swollen lymph nodes after administration of the study drug.

Similarly, the statement "Drugs of this type can also cause swelling of the lymph glands, so you will be regularly checked for this." may have taken on more significance if the pre-clinical results had been mentioned.

Serious side-effects in most clinical trials are infrequent; some subjects may experience them but most do not. There is no clue in the risk disclosure that the risk of a cytokine blast might have been – and was – 100% for subjects receiving the study drug.

The discussion of possible side-effects states "As this is only the first time this drug will be given to man, this study may involve risks that are currently unforeseen." However, in the list of key points on the first page that the Subject initials, the statement is "... the procedures being tested in this First Time in Man study may involve risks to me, which are currently unforeseeable." In fact, there is nothing experimental about the study procedures, only the study drug.

Statements such as "Risk of anaphylaxis applies to all studies at PAREXEL, with drugs at every stage of development" and "any drug can cause a serious allergic reaction in susceptible individuals. For example, penicillin and even aspirin can be life-threatening to some people." may be factually correct but tend to downplay these risks.

Design of the Study

The study was designed to be conducted in four stages, with eight subjects in each stage exposed to an increasing dose of the study drug: 0.1 0.5, 2.0 and 5.0 mg/kg body weight. It was halted after administration of the study drug in the first stage. It is standard practice to spread out administration of the study drug within each stage to detect any potential problems with the first subjects before all subjects in that stage receive the drug.⁴ In some studies, an additional safety measure is taken by administering a tiny "test dose" before the regular dose.⁴ However, TGN1412 study personnel administered the study drug in quick order without test doses, at about ten-minute intervals. As it turned out, obvious negative reactions to the drug appeared in the first subjects before the study drug was administered to the last subjects.² The question is thus why administration continued despite the initial negative reactions.

ICF Readability

CRF and ICH regulations require that "the information is given to the subject or the representative shall be in language understandable to the subject or the representative." In

the U.S., the average English-speaking adult reads at the seventh-grade level. On average adults read about two grade levels below their educational attainment.

The TGN1412 ICF is written at the 14th-grade (2nd-year of college) level. 29% of the sentences are written at a graduate school level.⁷

Biased Language

The following adjectives and adverbs (*italics added*) in the ICF may bias the presentation if they are not accurate:

- *Expert* advice from immunologists has been sought in designing the protocol to minimise your risks, including a *robust* screening process that takes into account your immune status, and repeated *thorough* assessments of immune function.
- ...the following unintended effects may *theoretically* be encountered during *any* trial with a monoclonal antibody drug...
- At the end of the study (on Day 43) you will be asked to return to the Unit to give blood and urine samples for *routine* analysis.
- This study has been *carefully* reviewed and approved by an Independent Research Ethics Committee.

Informed Consent Process

As we all know, informed consent is not a document; it is a process that begins with study advertisements or initial discussions and ends when the study concludes.

The TGN1412 study's subject recruitment posting at www.drugtrial.co.uk stated, "You'll have plenty of time to read or study or just relax – with digital TV, pool table, videogames, DVD player and now FREE Internet access! You can even just catch up on some sleep!"⁸

The TGN1412 ICF is over 5,000 words long, and should take 20 to 30 minutes to read.⁷ It states "Please take time to read the following information carefully and discuss it with others if you wish." and "Take time to decide whether or not you wish to take part." One subject told the Associated Press that he "was pressured to complete the form within 10-15 minutes."⁸ According to Raste Khan (who may have been the same subject, who received the placebo, and has expressed the intention to sue for damages), "The guy said, 'We're in a bit of a push. Can you sign it now, and I'll explain it all to you.'"⁹ According to a news report, "Two of the volunteers told British reporters that they were warned to expect only headaches and nausea."¹⁰

In 2005, U.K.'s National Patient Safety Agency's Central Office for Research Ethics Committees published "Standard Operating Procedures for Research Ethics Committees, Version 3.0." It states that "...Principal Investigators should normally retain full responsibility for the informed consent process, in particular for answering participants' questions about the research and taking written consent..." "Full responsibility" allows the Principal Investigator to delegate the process of obtaining informed consent to qualified personnel. However, the Principal Investigator, at minimum, usually stops by to answer questions and assess the potential subject's understanding of the trial. The author has found nothing in the news reports to indicate whether the TGN1412 Principal Investigator participated in the informed consent process.

Other Issues

The ICF uses the words “understand” and “understood” several times, e.g., “I confirm that I have read and understood the informed consent form...” Many IRBs in the U.S. reject use of these words because it is impossible for the subject to know what he/she understands.

Conclusion

Given the number of clinical trials conducted every year, periodic disasters are probably unavoidable, even with the best of intentions. Although we cannot eliminate risk entirely, at least we can set high standards for the quality of informed consent forms. One approach to “perfecting” ICFs is, in essence, to make them incomprehensible – longer and longer, with more and more legal and medical jargon. However, as the preceding analysis of the TGN1412 ICF reveals, simple adjustments may suffice.

Caveats

TeGenero reviewed a manuscript of the article and provided comments; the article is consistent with the comments received. PAREXEL also received a copy of the manuscript, but did not provide comments. The author has not verified that quotations from news reports accurately reflect the facts. The ICF is available at http://www.firstclinical.com/journal/2006/0605_TGN1412_ICF.pdf.

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Author

Norman M. Goldfarb is Managing Member of First Clinical Research LLC, a provider of clinical research best practices information, consulting and training services. Contact him at 1.650.465.0119 or ngoldfarb@firstclinical.com.