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TGN1412 Remembered: the Scientific Duty of the Ethics Committee

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Abstract

Current guidance to research ethics committees in the United Kingdom instructs them not to conduct their own review of the science. This is an error. Research ethics committees have an ethical responsibility and a present legal duty to review the science. The author re-examines the Northwick Park disaster from this standpoint and demonstrates how the Brent Medical Ethics Committee's review of the TGN1412 protocol followed the operational guidance handed down to them and failed to protect the trial subjects as a consequence. The guidance has not changed much in the time since the accident. TGN1412 is a warning that still has relevance for research ethics committees everywhere. They must insist on seeing an independent review of the science and an independent assessment of the safety of the protocol before delivering their own opinion on the ethics of the research. In future, ethics committees and competent authority must work together to produce a single decision on clinical trials. This has yet to happen in the United Kingdom.

Flat-Pack Ethics: Lord Warner and the Ad Hoc Advisory Group

Research ethics committees (RECs) in England and Wales provide a rather feeble assurance of the risks and benefits of clinical research. Policy and operational practice are mainly to blame for this. The REC is required to leave the assessment of quality in scientific design and method to the funding body and/or the sponsor.[1] The REC is required to leave the assessment of safety

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1 Health Research Authority, *UK Policy Framework for health and social care research, For Comment*, Version 1.0 February 2015, paragraph 8.9; *Governance Arrangements for NHS Research Ethics Committees*, July 2001, paragraphs 9.8 and 9.9; *Governance arrangements for research ethics committees A harmonised edition*, May 2011, paragraph 5.4.2.

to the Medicines and Healthcare products Regulatory Agency.[2] By the time that those components are removed from ethical review, there is not much left that cannot be handled jointly by a lawyer and an insurance expert. This compartmentalisation of ethics is a policy born of administrative convenience. It is not justified by current law or morals. It comes from the Department of Health guidance referenced in this article and the report of Lord Warner's Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees in June 2005. This policy has been applied[3] by the organisations successively responsible for overseeing RECs in the United Kingdom.

The manner of implementation of the *Warner* recommendations played a causal part in what has since become known as the *Northwick Park disaster.*[4] Had the Brent Medical Ethics Committee been given better operational guidance and better access to independent scientific expertise, then the TGN1412 protocol might not have been approved in the form in which it had been submitted. Injury and distress to the trial volunteers might have been avoided or lessened as a consequence.

Back in the days before TGN1412, there was a perception amongst researchers that RECs were too concerned with clinical trial methodologies and were not sufficiently versed in other types of research design.[5] The concern was that an REC might reject a sound research application because it disagreed, rather arbitrarily, with the science of the protocol. The best way to resolve that problem was to have spent substantial amounts of money on expanding the skills base of the ethics committees so that they could perform their own review of a variety of research designs. After all, substantial amounts of money are now being spent on expanding the staffing base of the HRA for its new Assessment and Approval scheme.[6] But there was no political will to improve quality in ethical review, only to speed up research approvals. So the RECs were not given these resources.

Instead, *Warner* proceeded on the unsubstantiated premise that it is not the business of an REC to carry out its own review of the science. *Warner* saw no need for the REC to waste time or money by revisiting science that had already been reviewed by peers. This meant that scientific review and ethical review were to be treated separately in the manner of their performance. It meant that

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2 *Memorandum of Understanding between MHRA, NRES, GTAC and AAPEC*, Version 2 April 2010, paragraph 3.6.

3 COREC, *Building on Improvement Implementing the recommendations of the Report of the Ad Hoc Advisory Group on the Operation of Research Ethics Committees*, August 2006.

4 BBC News, 'Six taken ill after drug trials', http://news.bbc.co.uk/1/hi/england/london/4807042.stm, 15 March 2006, last accessed 7 July 2015.

5 Department of Health, *Report of the Ad Hoc Advisory Group on the Operation of Research Ethics Committees*, paragraph 3.2.

6 HRA, *Summary of Plans for Health Research Authority Assessment and Approval*, March 2014.

scientific peer review should in some way tie the hands of the REC on certain aspects of ethics. This is wrong. But it does at least enable 'corners to be cut'. The Ad Hoc Advisory Group produced this statement on the place of science in ethical review:[7]

'...RECs are not, and should not be, responsible for detailed scientific review. Because it is unethical to conduct scientifically inadequate research, the RECs' role is to be reassured that there has been *adequate scientific review of the design*. For most applications, this review will have taken place before the application reaches the REC. We do not believe RECs should function as a secondary form of scientific review; indeed, to do so would have significant implications for REC membership. *Where peer review has taken place, the RECs should accept this in all but exceptional cases*; if it has not taken place, RECs should be able to refer the application, for scientific review purposes only, to a Scientific Officer based in COREC [emphasis added]'.

The Department of Health also seeks to restrict the role of the REC on matters of safety. RECs are instructed that it is their function neither to assess the safety of the protocol nor to commission experts to give advice on matters of safety.[8] The guidance states that RECs may 'generally rely' upon the assessment by the MHRA as the competent authority. As with all generalities, one must ask what the REC is supposed to do when it encounters a situation in which the MHRA has made a safety error and cannot be relied upon. An REC is expected to contact the MHRA to try to resolve any concerns that the REC might have.[9] But the REC operates separately to the MHRA. They do not collaborate in a single decisional process at this time. *So where is the evidence to show that RECs are in a position to make an effective challenge to safety errors by the MHRA? RECs cannot challenge anything if they do not get to see the MHRA assessment.*

Make do and Mend: the patch-work implementation of the Warner report

The crux of *Warner* is the removal of scientific review from the function of the REC. So it is imperative to its successful implementation that the REC be provided with a proper peer review of the science *in every protocol*

7 See note 5, paragraph 3.2.
8 *Governance arrangements for research ethics committees. A harmonised edition*, May 2011, paragraph 5.4.2.
9 *Memorandum of Understanding between MHRA, NRES, GTAC and AAPEC*, Version 2 April 2010, paragraph 3.6.

that it considers. For how else was the REC to decide for itself that the review of the science had been adequately performed? The Central Office of Research Ethics Committees, the National Research Ethics Service and the Health Research Authority have all failed to deliver on this. They are the bodies successively responsible for running the REC system. The HRA made admissions in two distinct circumstances[10] to the effect that, between 2010 and April 2013, *only 4% of REC submissions seemed to include independent scientific review. The figure was 2.5% for medicinal trials.* A more recent analysis showed that two sample RECs received independent scientific review with only 25% of applications. The author assumes that the term 'independent scientific review' embraces MHRA safety assessments as well as peer reviews. It is an admission that the REC system in England and Wales is unfit for purpose.

Warner recommended that Scientific Officers be appointed to provide support to those RECs dealing with applications for which no peer review had taken place.[11] This was not a bad idea. But COREC did not adopt that recommendation. The Chief Executive of what is now the Health Research Authority rejected the use of Scientific Officers in England and Wales on the ground that they could not bring all the competences needed to deal with the full spectrum of research reviewed by an REC.[12] That decision made a bad plan worse. COREC originally intended to use national research ethics advisors *inter alia* to screen studies to make sure that they had been subjected to a sufficient external peer review, to procure specialist scientific review for complex or unusual cases, and to identify low risk studies.[13] In October 2012, plans were announced for a pilot study for 'Ethics Officers' to conduct something resembling this.[14] Ethics Officers are still not in post. Nor has the HRA done anything to establish a standing panel of experts to whom RECs can turn when they need their own advice on scientific matters arising from the ethical review of the protocol.

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10 HRA, *Peer/scientific review of research and the role of NRES research ethics committees*, April 2012, citing NRES review of the Research Ethics Database; Joint Committee on Draft Care and Support Bill Session 2012-2013, 31 January 2013, Q299.

11 Department of Health, *Report of the Ad Hoc Advisory Group on the Operation of Research Ethics Committees*, Recommendation 9.

12 J. Wisely & J. Lilleyman, 'Implementing the district hospital recommendations for the National Health Service National Research Ethics Service in England', *Journal of Medical Ethics* 33 (2007), 168.

13 National Patient Safety Agency, Implementing the Recommendations of the *Ad Hoc Advisory Group: Consultation*, January 2006, paragraph 4.1.2; COREC, Building on Improvement Implementing the Recommendations of the Report of the *Ad Hoc Advisory Group on the Operation of Research Ethics Committees*, August 2006, paragraph 2.1.4.

14 www.hra.nhs.uk/news/2012/10/17/hra-ethics-officer-pilot/, 17 October 2012, last accessed 7 July 2015.

The Fundamental Principle: *science and ethics cannot be separated*

Contrast the statement by the Ad Hoc Advisory Group with that made by CIOMS in 2002, in guidance that is currently under revision but which the author considers to be the dominant international statement on the role of ethics committees in research:[15]

'The ethical review committee is responsible for safeguarding the rights, safety, and well-being of the research subjects. *Scientific review and ethical review cannot be separated*: scientifically unsound research involving humans as subjects is ipso facto unethical in that *it may expose them to risk* or inconvenience to no purpose; even if there is no risk of injury, wasting of subjects' and researchers' time in unproductive activities represents loss of a valuable resource. *Normally, therefore, an ethical review committee considers both the scientific and the ethical aspects of proposed research*. It must either carry out or arrange for a proper scientific review or verify that a competent expert body has determined that the research is scientifically sound. Also, it considers provisions for monitoring of data and *safety* [emphasis added].'

For CIOMS, reliance on a peer review is merely a power, as the ethics committee retains the right to conduct its own review of the science. But for *Warner*, the separation of scientific review from the function of the REC is nearly absolute. For *Warner*, there are exceptional circumstances in which the REC could reject the peer review of the science, but tellingly these are not spelt out. This suggests slack reasoning on the part of the Ad Hoc Advisory Group as to when a UK REC *is* permitted to reject the peer review. CIOMS states that it is permissible for the ethics committee to *commission* a scientific review by a third party, provided that this review is 'proper'. This might then stand in substitution for their own review of the science. *Warner* seems to require the REC to accept what they are given by the sponsor or funder of the research, provided that the REC can be reassured that what it has been given amounts to an adequate review of the design. CIOMS requires the ethics committee to have the first and last word as to who it will appoint to perform a scientific review. For *Warner*, the matter appears to have been put outside the REC's control. If the ethics committee seeks to *rely* on a statement from outside the committee that the research is scientifically sound, then CIOMS requires that this statement be determined by a 'competent expert body'. The ethics committee must *verify* that a competent expert body has determined the science to be sound. This

15 Council for International Organisations of Medical Sciences (CIOMS) in collaboration with the World Health Organisation (WHO), *International Ethical Guidelines for Biomedical Research involving Human Subjects*, 2002, Commentary on Guideline 2, at 24.

means that the ethics committee must do its own checking, by communicating with the expert body if need be. And what constitutes a competent body of experts? Does it mean a regulatory body with the responsibility for matters of safety in research? Does it mean a designated pool of independent experts who can be tapped for their scientific opinion? Or both? CIOMS does not resolve this question. Nor does *Warner*. Current HRA guidance[16] suggests that different sorts of research might require different sorts of peer review to support it. The given examples feature peer review by funders and sponsors. But this guidance is even less clear on the circumstances in which the REC can reject the peer review of the science.

The linkage that joins science to ethics is the question of risk to the research subject. This is how the conflict between *Warner* and CIOMS must be resolved. CIOMS posits that scientifically unsound research is unethical because it may expose the human subject to risk. Therefore it is normal for the ethics committee to consider the science. CIOMS also requires the ethics committee to examine the provisions for monitoring safety. CIOMS is correct in this. A study may be impeccable in its design because it determines valid end-points, yet may be wholly unethical because it slays all its patients. Therefore it is the ethics committee's function to consider the science with regard to the risk that it poses to the human subject in research. But *Warner* requires RECs merely to be reassured of 'adequate scientific review of the *design*'. It is pre-occupied with stopping RECs interfering with the *method*. The need for ethics committees to examine risk and benefit by reference to the design, method and *the wider scientific background* is not communicated in *Warner*. So *Warner* must be rejected. It is not a proper statement on science in ethics.

The legal duty of the ethics committee with regard to the science

The 2001 Clinical Trials Directive sets out the legal duties of the ethics committee. The Directive requires those duties to be transposed to domestic law. In the United Kingdom, transposition occurs in The Medicines for Human Use (Clinical Trials) Regulations 2004. This is the law at the date of writing. Domestic law must be read in a way that is compatible with the Directive that it purports to implement. Even when it is repealed, the Directive must still be used to interpret the UK Regulations because the latter derive their meaning and purpose from the former. The new EU Clinical Trials Regulation will repeal the Directive. Domestic law relating to national ethics committees

16 HRA, *Peer/scientific review of research and the role of NRES research ethics committees*, April 2012.

will remain unaffected if it is deemed to be already compatible with the Regulation. National Governments are free to repeal domestic law and make new laws in response to the Regulation.

This is what the Directive states.[17] The duty of the ethics committee is to protect the rights, safety and wellbeing of human subjects in a clinical trial. The ethics committee shall give its opinion on any issue requested of it. The ethics committee shall consider the trial design in the context of the relevance of the clinical trial as a whole. The protocol must be considered. A clinical trial may only be undertaken 'if the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients'. A clinical trial may be initiated '*only if the Ethics Committee and/or the competent authority* comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored [emphasis added]'. In preparing its opinion, the ethics committee shall consider 'whether the evaluation of the anticipated benefits and risks [meaning the evaluation carried out by the ethics committee and/or the competent authority] is *satisfactory* and whether the conclusions *are justified* [emphasis added]'. What the Directive states must be taken at face value.

Warner stipulated that the REC should not function as a secondary review of the science of the protocol. There is no support for that proposition in the Directive. The Directive requires the ethics committee to consider whether the design will generate relevant data and end-points for the study. That is, to consider the science. The Directive also requires the ethics committee to express an opinion upon the protocol as a whole, *not just parts of it*. The crux of the ethics committee's opinion is its decision on the risk and benefit of the research. The ethics committee can use a scientific peer review to *inform* its own assessment of the risks and benefits, but only if it wishes. The Directive also permits the ethics committees to *rely* upon an assessment of risk and benefit carried out by the competent authority. They can rely on the latter because the Directive enables assessment to be made by each or either body. But in order to be relied upon, the competent authority's assessment of risk and benefit must logically *precede* the deliberation of the ethics committee and *be communicated to it* in time for it to produce an opinion. Ultimately, it is the ethics committee's own assessment of risk and benefit that needs to be satisfactory and justified, or else that of the competent authority. But the Directive is clear that it falls to the ethics committee to have the last word on risk and benefit, no matter who has made this earlier assessment. This means that the ethics committee must check

17 2001/20/EC Article 2(k), Article 6(2), Article 6(3)(a), Article 6(3)(c), Article 3(2)(a), Article 6(3)(b); compare SI 2004/1031 Schedule 1 Part 2 paragraph 14.

over its own assessment on risk and benefit, or that of the competent authority, before giving its opinion.

The UK Regulations make a brief statement on the duty of the REC with regard to the science: both the REC *and* the MHRA must make a decision as to whether the risks of the research are justified by the benefits to the patient and to the public. The UK Regulations do not state that the REC must rely upon the findings of the MHRA or *vice versa*. All that is required is that both of them make their own decision and reach the same conclusion. Apart from this, the UK Regulations follow the Directive.

How the ethics committee should approach risk and benefit in research

The ethics committee must decide whether it or the competent authority has made a 'satisfactory' assessment of risk and benefit. In the United Kingdom, the REC's assessment of risk and benefit might be based upon a peer review submitted by the sponsor or applicant to the REC. More likely, the REC's assessment will be based upon an abbreviated description of the study method and a statement on risk and benefit in the IRAS application form. In the author's experience it is rare for the REC to be furnished with an assessment from the MHRA, especially in Phase II and III studies. The author posits that the REC's assessment of risk and benefit can be deemed to be satisfactory if the REC relies upon a scientific method that is recognised to be sound and also judged on the facts to be free from bias. A conclusion on risk and benefit should be treated as a result derived from the application of a method. Method and result must be capable of being reproduced before either can be held to be valid. Therefore, before accepting a third party's assessment of risk and benefit, the REC must be able to *reproduce the method* that underpins that assessment in order *to arrive at the same result*. If it takes time and money to supply the REC with independent expertise and scientific support to help them reproduce assessments of risk and benefit, then the time and money must be expended.

In specifying no bias, the author has regard to the requirement in the Directive that the ethics committee be independent. He interprets this to mean independence from the other actors in research. There must be a risk to the independence and quality of the decisional powers of the REC when it is required to accept a peer review that has been procured by the sponsor or funder and submitted as part of the application for research approval. Therefore an assessment of risk and benefit cannot be satisfactory to an REC unless it is based, at least in part, upon an assessment that is independent of the research team, the sponsor and the funding body behind that research. In other words, the REC can take peer review into account, but it should not give a favourable opinion on a clinical trial protocol *unless anduntil it has seen an assessment from the MHRAor a report of an independent scientific expert* appointed from a pool of ex-

perts designated for that purpose. This is how the CIOMS requirement for a competent expert body to assess the science should be interpreted in the United Kingdom.

The ethics committee must 'justify' its own conclusion on risk and benefit, or that provided by the competent authority and upon which the ethics committee might seek to rely. Reproduction of a method and a result is not a justification of each or either. Justification requires more. It is the 'special ingredient' that ought to make ethical review indispensable in the regulation of research. 'Justification' should be defined by reference to the legal duties put upon the ethics committee by the Directive. The ethics committee has a legal duty to protect the rights, safety and wellbeing of the human subjects in a clinical trial. Therefore the ethics committee must scrutinise the assessment of risk and benefit to decide if the acceptance of that conclusion would serve to protect the rights, safety and wellbeing of the trial subjects. If it does, then the assessment of risk and benefit can be said to be justified.

In the United Kingdom, the guidance set down for RECs has been slow even to contemplate that it is the function of the REC to protect legal rights of the subjects in research.[18] Infringed rights might result in data protection breaches or non-consensual research amounting to assault or battery in law. Trial subjects might be under-compensated for harm suffered in the research, as was alleged of the TGN1412 study. The REC must also consider how clinical and diagnostic procedures in the protocol might impact upon wellbeing and safety. This could require the REC to substitute its own judgement on the design for that of the sponsor or the peer review. The list of factors for the REC to consider defies precise classification. It should be a reflexive process. But the point to note is that the REC cannot justify its own decision on risk and benefit unless it examines the legality of the protocol and the science behind the method.

How the REC should deal with the peer review of the science

When *Warner* requires the REC to accept a scientific peer review, and to have a very limited discretion to reject it, it is a restrictive rule of practice that is not supported in law. Nevertheless, RECs should not chop and change the protocol just because the REC thinks that it could do a better job than the person who designed it. If the REC has access to a peer review then

18 C.L. Roy-Toole, 'Illegality in the research protocol: the duty of the research ethics committee under the 2001 Clinical Trials Directive', *Research Ethics Review* 4:3 (2008), 111-116; C.L. Roy-Toole, 'Research ethics committees and the legality of the protocol: a rejoinder and a challenge to the Department of Health', *Research Ethics Review* 5:1 (2009), 34-37.

there should be some limits set to the way in which the REC can deal with it in the interests of rationality and procedural fairness. A legal analysis could resolve the problem left by *Warner* as to when the REC can properly reject a peer review submitted by a third party.

The author posits that the REC's conclusion on risk and benefit must be justifiable to a hypothetical REC that is properly constituted and which acts *rationally* in the exercise of its powers. It requires the determining REC to apply an objective test about how an REC might *properly* approach the risk and benefit assessment and to abide by this. This also helps to explain how an REC should deal with a peer review. If the peer review's assessment of risk and benefit could be justified by an REC acting in a proper manner, then the determining REC should not reject the peer review. When *Warner* speaks of exceptional circumstances, the author interprets this to be circumstances in which the REC is confronted by a peer review that is so deficient in its assessment of risk and benefit that no REC could properly justify it. Rationality should be used in its legal sense, connoting the need for the REC to consider that which is relevant, to ignore the irrelevant, to eschew bias and to act as a reasonable tribunal of fact would be expected to act. RECs are public bodies susceptible to judicial review, so they must adhere to these principles of public law.

TGN1412: *An accident waiting to happen in the UK REC system?*

The disaster at the Northwick Park Hospital occurred approximately 11 months after the publication of the *Warner* review. So an independent public inquiry into what TGN1412 meant for the UK REC system would have tested the assumption that *Warner* was correct and going as planned. If not, then the implementation of *Warner* should have been revised or scrapped. The Expert Scientific Group on Phase One Clinical Trials recommended that the role of RECs in the clinical trial process be examined as a matter of priority.[19] But there was no independent public inquiry. So there has been no conclusive statement on the role played by the ethics committee in the Northwick Park Hospital disaster.

COREC/NRES carried out an internal investigation into what the Brent Medical Ethics Committee (MEC) had done. The finding was incorporated into

19 *Expert Scientific Group on Phase One Clinical Trials Final Report*, 30 November 2006.

a learning and actions report.[20] There was a separate report to the UKECA.[21] The author found these documents on a legacy website of the now defunct National Patient Safety Agency, along with a letter showing that these reports were released into the public domain pursuant to a Freedom of Information request.[22] The actions report shows that an 'initial review' was conducted by the NRES Ethics Advisor, himself a former Chairman of the Brent MEC and responsible at that time for REC training. More formal enquiries reportedly followed but these are not described in the report. COREC/NRES stated that it 'was able to establish very quickly that Brent REC had followed appropriate procedures according to published standard operating procedures in their review of the research application'. The actions report concluded that 'no issues of concern were raised [in] this and subsequent enquiries regarding the REC deliberations'. So whatever the Brent MEC did right or wrong, their actions complied with the operational guidance for RECs, and specifically in the way that they should deal with the science and safety of the TGN1412 protocol. But the cheery conclusion does not fit with other commentaries on the role of the Brent MEC in the TGN1412 episode.

To illustrate the deficient state of the COREC/NRES internal investigation, the author points to the Brent MEC's decision regarding the insurance and compensation arrangements for the trial volunteers. This decision has been questioned more than once.[23] The Association of the British Pharmaceutical Industry commented that the insured amount was between a half and a third of the sum that the ABPI would *probably* have proposed at the time.[24] The ABPI statement was already public before COREC/NRES finalised their report. Yet the actions report and the report to the UKECA omitted to answer the question of whether the Brent MEC had erred in its approach to insurance and compensation in TGN1412.

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20 National Research Ethics Service (NRES), *Learning and actions taken in response to the clinical trial of TGN1412*, September 2007, www.npsa.nhs.uk/easysiteweb/getresource.axd?assetid=62159&type=full&servicetype=att, last accessed 8 July 2015.

21 NRES, *Report to the UKECA on learning and actions taken in response to Northwick Park*, July 2007, http://webcache.googleusercontent.com/search?q=cache:1SWtigZ-nXsJ:www.npsa.nhs.uk/EasysiteWeb/getresource.axd%3FAssetID%3D62160%26type%3DFull%26servicetype%3DAttachment+&cd=1&hl=en&ct=clnk&gl=uk, last accessed 8 July 2015.

22 Dr. Janet Wisely, Director NRES, *Freedom of Information Act request: Clinical Trial-TGN1412-Parexcel-March 2006*, 24 April 2009, http://npsa.nhs.uk/EasysiteWeb/getresource.axd?AssetID=62158&type=Full&servicetype=Attachment, last accessed 8 July 2015.

23 Desmond Laurence, 'Ethics Committees and Drug Trials', *The Guardian*, 2 May 2006; Reynolds Porter Chamberlain LLP, 'TGN1412 – Calm after the cytokine storm', *Health Update*, March 2007.

24 NPSA NRES, *Research Ethics Committees in the News*, Issue 33, March/April 2007.

Professor Adam Hedgecoe examined the working of the Brent MEC in his illuminating monograph on the TGN1412 episode.[25] Hedgecoe saw the incident as a manifestation at a systemic level of acquired bad habits by researchers and regulators. Practices that were not in accordance with the rulebook were treated as acceptable because that was the way that things were done and nothing had yet gone wrong with them. Central to this study of 'organisational deviance' was the use of short interval dosing (SID) as a near-ubiquitous regimen for Phase I studies. This near-simultaneous dosing of the volunteers was not questioned by the industry or the regulators, yet it precipitated extreme drug reactions in close order for the six volunteers dosed with the TGN1412 compound. Hedgecoe also points to the assumptions made by RECs about the researchers that come before them and the trust that the REC must place in the assurances that they are given. In TGN1412, the sponsor's immunologist was not a clinician and the principal investigator was not himself an immunologist. Yet the Brent MEC was swayed by the familiar relationship that it had with the contract research organisation in charge of the study and made assumptions about the clinical competencies of the sponsor's representative that were not correct. The Brent MEC also made assumptions about the sponsor's resources that were more appropriate to a large pharmaceutical company than the small 'spin-off' company that it was. For Hedgecoe, all these were causal factors in the Brent MEC's decision to approve the TGN1412 protocol without questioning the use of SID as part of the design.

A Royal Statistical Society (RSS) working party, chaired by Professor Stephen Senn, produced the only independent report to consider the ethical dimension to the Northwick Park Hospital disaster.[26] The RSS noted that the sponsor's statistician had been involved in drafting the protocol, but the Brent MEC had no statistician itself, only individual members with experience of research design and who conducted their own statistical analyses. The Brent MEC felt constrained to ask for an independent report from a clinical immunologist before giving a favourable opinion. But of the three immunologists' responses available to the Brent MEC, only that of the sponsor dealt with the design of the protocol. This described the risk of cytokine release syndrome (CRS) as 'low, although it cannot be completely excluded'. An assessor provided a summary to the MHRA that followed the format of the protocol and deemed the assessment of risk and benefit to be favourable, but did not deal with the risk of CRS. The Brent MEC arrived separately at a favourable conclusion on risk and benefit, but did not query the use of the practice of SID in the study design.

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25 A. Hedgecoe, 'A deviation from standard design? Clinical trials, research ethics committees, and the regulatory co-construction of organisational deviance', *Social Studies of Science* 44:1 (2014), 59-81.

26 Royal Statistical Society, *Report of the Working Party on Statistical Issues in First-in-Man Studies*, March 2007.

The RSS working party were critical of the design of the TGN1412 protocol and also identified failings on the part of the MHRA and the Brent MEC. For the RSS, the protocol was deficient as a design to test safety and was dubious even to test tolerability. SID only had one thing to recommend it and that was the speed with which data could be collected. Yet the MHRA medical assessor had challenged neither the dosing regimen, nor planned clinical interventions in response to particular clinical risks, nor the composition of the Data Monitoring Board. Furthermore, the protocol design and statistical content complied with the specimen applications published as guidance on the MHRA website. These revealed deficient statistical reporting standards. The RSS conjectured that had better statistical methods been applied, the confidence in the starting dose would have been less and different outcomes might have resulted. The RSS states that the Brent MEC did not query the emergency procedures and facilities available to the volunteers in the event of a cytokine release storm. The Brent MEC approved the final version of the volunteer information leaflet that was deficient in numerous aspects. Specifically, this final version omitted to mention that a similar antibody had caused CRS before and that CRS was a possible consequence of this trial. To the author, this omission suggests that the Brent MEC had erred in its assessment of risk and benefit by attaching too little importance to CRS.

It might be tempting to dismiss the TGN1412 study as a freak accident, but this would be unwise. *In some respects, TGN1412 is a rather typical example of how RECs operate now.* A marked feature of the TGN1412 case is the absence of independent scientific support available to the Brent MEC. It was reliant on peer reviews from outside its own number. There were no in-house Scientific Officers to assist them because COREC did not appear to want to recruit any. The expert review that arguably mattered most to the outcome, the immunological report on the design, came from the sponsor. The Brent MEC did not have an independent immunological opinion on the design of the study and one must therefore question why it went ahead without one. The Brent MEC might have looked to the MHRA to lend them its expertise, but the author questions how readily available such expertise was in a system where the REC and competent authority were, as they are now, institutionally separate. And even if the Brent MEC chose to rely on the MHRA's assurance, the latter appears to have erred in its assessment of the risks inherent in the design and to have placed too close a reliance on the format of the protocol. When one recalls the HRA's admissions as to the small percentage of RECs that are sent an independent scientific review with the protocol, and add to that the absence of scientific support from other quarters, it will be seen that not much has changed for RECs since 2006.

The TGN1412 incident should also be seen as an example of the *Warner* recommendations in action. The Brent MEC was working to an earlier version

of the operational guidance when it considered the TGN1412 protocol.[27] The wording of this guidance was subtly different to that of *Warner* on the matter of how the REC should approach the science. This operational guidance required the REC to *satisfy* itself that there had been a prior scientific review and that it was adequate for the nature of the study under consideration. If an REC were not satisfied about this, then the application had to be sent back. The operational guidance stated that RECs were not constituted to carry out 'additional scientific review', nor was this their task. Their primary task was to conduct an ethical review of the proposal and documentation, with special attention *to be given to the nature of any interventionand its safety implicationsfor the trial subjects*. But *Warner* had by that time gone beyond the letter of this operational guidance by suggesting that, once a peer review had been carried out, the REC should not reject it unless exceptional circumstances applied. If that dictum were followed to the letter, an REC might cease to rely upon its own critical examination of the design and come to rely instead upon a 'gut feeling' that all was well with a peer review based on assumptions about the competency of the reviewer and the performance of sponsor's representatives at the REC meeting. RECs might then get into a habit of making assumptions about the adequacy of research design based on their prior experience of the applicant. According to Hedgecoe, this is what happened in the Brent MEC's approval of the TGN1412 protocol.

The Brent MEC's uncritical acceptance of SID within the design of the TGN1412 protocol demonstrates what happens when an REC is subjected to operational guidance that separates scientific review from the domain of the REC. No doubt, the Brent MEC believed that it had received credible assurances about the state of the science. It had received three immunologists' responses and a polished presentation from the sponsor's representative at the meeting. None of these had seen fit to challenge the use of SID despite the risk of CRS. The Brent MEC's failure to challenge SID might seem now to be a gross error. But it should be remembered that this was a logical consequence of operational guidance holding that it is not the function of the REC to conduct a secondary review of the science. SID was widely accepted in the design of Phase I studies. That is how the industry operated. A strict reading of *Warner* would *preclude an REC from challenging the use of SID if reviews of the design appeared to be adequate and these did not see fit to question its use*. One might counter this seemingly bizarre proposition by asserting that TGN1412 was an exceptional case that warranted the rejection of the reviews of the science. But that is to be wise after the event. Even *Warner* could not define the exceptional circumstances in which an REC should reject a peer review.

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27 Department of Health, *Governance arrangements for Research Ethics Committees 2001*, paragraph 9.

The COREC/NRES internal investigation was correct to conclude that the Brent MEC complied with its operational guidance. That is the problem. It is therefore impossible to accept the conclusion that no issues of concern arose from the Brent MEC's handling of the TGN1412 protocol. TGN1412 shows that it is not enough for an REC to rely on mere assurances that there has been an adequate peer review because a peer review can be dangerously inadequate *despite every appearance to the contrary*. TGN1412 shows that REC members can determine 'adequacy' in a peer review only by considering the science for themselves. TGN1412 shows that sometimes the REC cannot even rely on the MHRA. TGN1412 affirms that scientific review cannot be separated from ethical review and that the ethics committee must have the last word on risk and benefit. Hedgecoe stated that SID appears dangerous only with the benefit of hindsight. For him, the causes of the Northwick Park Hospital disaster were systemic and no one person or organisation was specifically at fault. But that statement is incomplete. His monograph on TGN1412 did not discuss whether REC operational guidance and policy were at least partly to blame. They are.

RECs need to adopt alternative approaches to peer review. Had the Brent MEC approached the matter in the way recommended by this article, then it might have rejected those peer reviews that advocated SID and sent back the TGN1412 protocol for re-drafting. SID conferred merely a benefit of administrative convenience upon the conduct of the study. It conferred no compensating benefit on the volunteers in the study. It exposed all of them to a risk of harm because no 'sentinel' subject had been selected to monitor for dose effect in a trial where the risk of CRS could not be excluded. Therefore SID was unjustified as a matter of risk and benefit. SID was an element of a design that no REC could properly have accepted in a protocol to recruit young and healthy volunteers for a trial of a novel compound with some risk of CRS. Most likely, an independent pool of experts would have been needed to support the Brent MEC in identifying SID as a 'deviant norm' that exposed volunteers to risk. Much more important was the need for the Brent MEC to have examined the science for itself by reference to the risk that it posed to the subjects. The ethics committee must therefore be prepared to question the customary practices of the industry and the regulators, despite making itself unpopular. It is significant that the use of SID in Phase I studies was eventually discouraged by a government-sponsored inquiry, not an ethics committee.[28]

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28 *Expert Scientific Group on Phase One Clinical Trials Final Report*, 30 November 2006, recommendation 15.

Half Measures: The regulatory legacy of TGN1412

In the immediate aftermath of the Northwick Park Hospital disaster, the MHRA adopted a precautionary approach to first-in-man (Phase I) trials of monoclonal antibodies or novel compounds targeting the immune system in novel ways. Henceforth additional expert support would be provided via the Commission on Human Medicines to assist the MHRA and the REC in their assessments of risk. There was also a Memorandum of Understanding in which RECs undertaking the review other Phase I, II and III protocols were promised the benefit of information-sharing with the MHRA and other regulators.[29] But how many RECs get the support that they need from the Memorandum of Understanding on matters of safety and the assessment of risk and benefit? The author is aware of no published studies to show how well this arrangement is being applied in practice.

Conclusions

If the United Kingdom delivers an REC opinion in enviably quick time, it is only because the HRA has 'cut corners' by not providing RECs with the support that they need to work their way through the science of the protocol. It is crucial to ask whether the HRA could afford the cost of providing RECs with some sort of independent scientific review for *all* clinical research studies that they review and still manage to comply with the statutory and operational deadlines for an REC opinion. If the HRA cannot do this, then radical organisational change is required for the UK REC system. If RECs overseen by the HRA are incompetent to consider the science or to challenge the MHRA assessment, then they are next to useless and might as well be abolished in their current form. There must then follow, at the very least, a radical reduction in the role of the Health Research Authority. What should come next is a new regulator based on a single decisional process for the authorisation of a clinical trial that encompasses both the science and the ethics of a protocol. The author hopes to explore this question in a later publication.

29 *Memorandum of Understanding between MHRA, NRES, GTAC and AAPEC*, Version 2 April 2010, paragraph 4.1.