Investigating allegations of research misconduct: the vital need for due process

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On 27 February 1999 the *BMJ* carried a news item reporting that the government had set up an inquiry into a controlled trial of neonatal ventilatory support undertaken at the North Staffordshire Hospital, in Stoke on Trent, from 1990 to 1993.[1] The trial was designed to assess whether continuous negative extrathoracic pressure (CNEP) ventilation could reduce the need for, and problems associated with, tracheal intubation and positive pressure ventilation.

Four years later the parents of one of the children treated with continuous negative extrathoracic pressure in the trial sought advice from a "neo-natal specialist"[2] about the likely aetiology of their child's neurological problems. The local newspaper in Stoke recently reported the mother's account of the consultation as follows: "The doctor examined [child's name] and then said, 'What do you expect from experimental treatment?' I replied,—'What experimental treatment?'—and that was the very first time we discovered [child's name] had taken part in research involving CNEP tanks. I was left in absolute shock."[2] After other parents had made similar allegations, the local member of parliament persuaded the undersecretary of state for health in the House of Lords that a government inquiry was required.

The Griffiths review was set up by the NHS Executive in February 1999 "to look into the general framework for both the approval and monitoring of clinical research projects in North Staffordshire" (paragraph 2.1 of the Griffiths report).[3] The review panel ceased taking evidence in "mid 1999," (para1.6) and the report was published on 8 May this year (document A in appendix A).[3] The panel concluded that enough was amiss to recommend a major overhaul of the way in which all clinical research is conducted in the NHS. The editorial headline of the 13 May issue of the *BMJ* declared: "Babies and consent: yet another NHS scandal."[4]

One day earlier, we had been contacted by the Medical Defence Union and asked to review the papers relating to that scandal. We can still agree that there has been a scandal but suspect that the scandal is what has been done to, not what was done by, the medical and nursing staff in Stoke on Trent. Leaving aside the unanswered question as to whether some consent forms were forged, which the panel said should be referred to the General Medical Council (para 4.6.2),[3] one can still form a view as to whether the research in

Summary points

We believe that almost every statement made about the design, conduct, and reporting of the neonatal continuous negative extrathoracic pressure (CNEP) trial in the Griffiths report was ill informed, misguided, or factually wrong. Errors include:

A false assertion that the trial's design had not been subjected to external peer review

A failure to understand the trial's statistical design, as evinced by their erroneous belief that Professor Southall was single handedly responsible for its size and shape

A failure to recognise the expertise of the nurses involved in the study

A false statement that some of the consent forms could not be found

A false statement that it was not possible to be sure who had completed some of these forms

A false statement that there was no way of checking that consent had been obtained properly

An inaccurate statement that the process of consent was not managed consistently and that no system of management or documentation was in place to prove that it was

A false assertion that parents were not given clear opportunities to withdraw their child from the study at any time

A failure to take sufficiently into account evidence showing that parental recall of events in the newborn period can be fallible

An overreliance on the evidence of the small group of parents who asked to testify to the panel at the expense of contemporaneous evidence from a questionnaire sent to all parents and returned by 79% at discharge

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question was properly conducted. The panel seem to have concluded that it was not. We do not agree.

In reaching their conclusions, the Griffiths panel seem to have relied largely on allegations of poor practice made by an unstated number of unnamed parents of children who received neonatal care within the context of the controlled trial of continuous negative extrathoracic pressure ventilation. However, they state that they "have not sought to determine whether allegations of poor practice are true" (para 1.5).[3] We find this admission extraordinary, given the seriousness of their implied criticism of the staff in Stoke. A detailed list of the documentary evidence on which we have based our conclusions is given in the appendix to our article.

Methods

Our review is based on copies of documents supplied to us by the Medical Defence Union, but we have also sought clarification and additional written information from Professor David Southall. Because the issue of written consent was so central to the inquiry, we asked specifically to be told of all the documents bearing on this issue. The North Staffordshire Hospital NHS Trust has not allowed us see any of the original papers for reasons of patient confidentiality, but we have been able to inspect photocopies of all the key documents and samples of all the relevant consent forms, questionnaires, and data abstraction sheets. Although we have spoken informally to three members of the research team at Stoke, what we have written here is based entirely on documents in our possession.

In approaching this task we have had access to the detailed riposte to the Griffiths report prepared by Professor Southall (document B in appendix A) but have made our own evaluation of the matters in contention. There are clearly many statements in this report to which most of the medical and nursing members of the Stoke research team take exception. We have, however, concentrated on the randomised trial of continuous negative extrathoracic pressure in newborn infants[5] because this was also the focus for almost all the panel's detailed criticism. We have not commented here on any of the other matters covered in the Griffiths report.

Copies of drafts of our report were sent to members of the Griffiths panel on 18 July and to the North Staffordshire NHS Trust more recently, with requests that they identify any errors of fact so that these could be addressed before publication. The Department of Health solicitor has responded on behalf of the panel mentioning two general points (which we have addressed) but advising us that "this does not mean that you may assume that we accept anything or everything else you say" (letter to IC, 25 August 2000).

Findings

Trial design

The Griffiths panel said that they got "unsatisfactory answers" (para 7.1.4)[3] when they asked about the design of the CNEP trial, but it is surprising they did not pursue this issue further. In fact the trial's design was of high quality and extremely well chosen. The sequential design involved matching infants in pairs at randomisation. Professor Southall and Dr Martin Samuels, who were based in London when the study started, shared the responsibility for matching and randomisation, but day to day responsibility for recruitment rested with Dr Andrew Spencer and the ward staff in the hospital in Stoke, as the local ethics committee's documentation makes clear (document C). As Professor Richard Lilford reminded the panel in his expert testimony, it was essential that "those responsible for randomisation should be absolutely separate from the researchers" (para 15.4.7).[3] The panel's concern that Professor Southall "was not providing much supervision" (para 9.4.2)[3] was therefore misplaced. There is no doubt that the conduct of the study needed to be supervised closely, but responsibility for this fell on the local "lead clinician," Dr Spencer, in Stoke.

The panel expressed concern that "Parents were subjected to the natural enthusiasm of the researcher, and parents later felt that they had been unduly pressured by this" (para 14.3.6).[3] It is not clear to whom the panel are referring when they speak of "the researcher." If they mean any of the authors of the final published trial report[5] their criticism is misplaced, because these people were involved in obtaining parental consent from only four of the 224 children recruited to the study in Stoke. As Professor Lilford reminded the panel, any good trial will, by its design, try "to separate the task of obtaining consent from the researchers involved in the trial" (para 15.4.4).[3] Such an ideal can be hard to achieve and, as Professor Lilford stressed, much must inevitably be left to the integrity of the research worker involved. However, the design of the CNEP trial minimised this potential conflict of interest in Stoke to an unusual degree.

Statistical issues

The panel stated: "It should not have been Professor Southall who was making the decision as to the size and shape of the trial on his own" (para 9.4.4)[3]—a statement showing that they had not understood the basic design of the trial. This single statement, on its own, could well serve to discredit the panel's whole standing in the eyes of the research community. The size of the trial was fixed in advance by the nature of the rules built into the use of Armitage's triangular design strategy,[6] and the trial's independent statistical adviser must be given much credit for recommending the use of this long established, but little used, trial approach (D).

As a further refinement, non-symmetrical closure rules were agreed. The trial would be stopped at the first sign that continuous negative extrathoracic pressure might be doing more harm than good, but otherwise could be stopped early only if it was offering substantial benefit. Professor Lilford spoke to the panel about "The value of a data monitoring committee … to set statistical criteria … for the termination of the trial if the hypothesis is proved, or the results are better than expected, or if the subjects suffered harm, particularly unexpected harm" (para 15.4.7).[3] The CNEP trial was ahead of its time in having set criteria and a mechanism for dealing with these issues. The panel (like the anonymous *Lancet* editorialist,[7] on whose views they may have placed undue faith) did not seem to understand that this was the whole purpose of the

"clinical outcomes score" (para 7.1.1)[3] over which they questioned clinical staff so closely. The score was not used in the subsequent analysis of any of the study outcomes after the trial closed, but its existence made the setting up of a separate data monitoring committee unnecessary, as would have been recognised by those who peer reviewed the full trial protocol before the study started.

Peer review

The panel stated that there had been "no external peer review of the project" (para 7.1.5),[3] but this is not true. Before the study started in Stoke its design strategy was presented at three international meetings and also discussed with more than 70 senior medical and nursing colleagues at more than 10 centres in Britain over a 12 month period (E), including experts at the Perinatal Trials Service of the National Perinatal Epidemiology Unit in Oxford (F). Information about the trial was also, ahead of its time, registered prospectively and made publicly available through the *Oxford Database of Perinatal Trials*.

The panel also stated that the trial's design underwent "no peer review by experts" (para 7.1.3)[3] before the study was funded or before recruitment was approved by the research ethics committee in Stoke, but this is also not true. We find it extremely disturbing that the panel should make such firm statements that turn out to be inaccurate.

They stated that "extensive peer review … is a quality characteristic of research funded by the MRC and the major medical charities" (para 7.1.5) and concluded that, if the neonatal CNEP trial "had been subject to external peer review there would have been several aspects of its design and operation that might have been modified" (para 7.1.6).[3] Not only did the panel fail to indicate which aspects of the study might have been modified, they also failed to ascertain that the full trial protocol had been seen and peer reviewed by the MRC as well as by the research committee of the National Heart and Chest Hospitals in London (G). In March 1990, although referees might have had some suggestions about ways in which the protocol could be modified, the MRC awarded the study an alpha rating, defined as "Research of high scientific merit, ie of such novelty or timeliness and promise as is likely to make a significant contribution to knowledge and/or clinical practice" (H). Unfortunately, although the MRC feedback stated that "all 'alpha' and 'beta' applications are considered to be of a standard which merits support if funds are available," there was insufficient money to support the CNEP study.

Nursing input to the study

The panel asserted: "Nursing staff, and the sister in particular, had not been trained, or had adequate research experience, for the job that they were being asked to do" (para 9.3.5).[3] They provided no evidence to back this statement. We say it is not true. It is also an unwarranted slur on the professionalism and skill of all the nurses concerned. The experienced, H grade neonatal nursing sister referred to had spent more than a year making herself conversant with the nursing techniques involved in giving continuous negative extrathoracic pressure to vulnerable small babies before the trial started in Stoke, and staff in the unit had built up considerable experience in the care of such babies (I, J). The nursing sister also had previous research and audit experience. The panel's demeaning reference to her as "the nursing sister assigned to the project" (para 9.3.5)[3] shows that they also failed to realise that the study was, from the outset, a partnership between the medical and nursing staff involved. Skilled professional nursing care was central to the conduct, and success, of the study—as evinced by the nurse researcher's name featuring third in the list of authors of the published report of the trial.[5]

The panel stated that staff "did not appear to have been provided with a protocol or system of documentation which made sure that everything was complete for all patients" (para 9.3.5).[3] It is not clear whether they asked if such a protocol existed. We have been shown an extensive array of trial documents (C, K, L, M, N), and these establish beyond all doubt that the day to day care delivered to the babies in this trial was of an extremely high standard and that record keeping by the nursing staff involved was exemplary. We were particularly impressed by the fact that a detailed, 47 page care protocol drawn up and used by nursing staff during the trial (O) was still traceable after an interval of 10 years (along with copies of almost all the other trial documents). The panel's statement about the lack of any nursing protocol is therefore misleading.

Case documents

All the relevant research documents seem to have been found without difficulty seven years after the study finished. In contrast, for their audit in March 1999, the hospital trust had great difficulty gaining access to its own clinical case records of children who had participated in the study. Sixteen sets of notes were unavailable to the trust's audit team, and a further 104 were available only on microfiche. The trust's audit of the timing of trial consent was eventually based on a study of less than half the clinical case records (96/219) (P).

Obtaining parental consent

Some of the most damning criticism in the panel's report relates to the seeking of parental consent. The panel stated that "some of the consent forms could not be found" (para 14.3.8), and that there seemed to be "no way of checking that consent had been obtained properly" (para 9.3.4).[3] Both these statements are untrue. Furthermore, the hospital trust knows that all the forms could be found because it conducted its own independent internal audit of this in March 1999. This showed that a consent document existed among the research records for every child in the study (P, Q). The reasons why a further 28 families did not take part were also well documented (R).

The panel stated that "it is not possible now to be sure who completed some of these consent forms" (para 9.3.6).[3] This is also untrue. This issue did not seem to have been investigated, so we asked for this to be done and have been shown a list naming all the staff involved (34 in total) (S). Consultants in Stoke approached two families, three quarters of the families were approached by a paediatric registrar or senior registrar and a quarter by a senior house officer. Allegations that "some consent forms purported to have been signed by individuals had not been so signed" (para 4.2.3) and that treatment was still instituted in one child even though the mother "had

vigorously refused consent" (para 14.3.3)[3] can therefore be investigated further. As far as we have been able to discover, no attempt has yet been made to do this. We have been told by the trust that they now have this in hand.

Keeping families informed about the conduct of the study

Other criticisms of the day to day conduct of the study are equally unsustainable. The panel stated: "There should have been an effective process in place which ensured that … there were clear opportunities for the parents to withdraw" (para 9.4.5).[3] The inference is that there was not. We consider this to be untrue. A patient information sheet was in existence which stated: "Should you decide that you do not wish your baby to be studied that is perfectly all right, and your baby will receive the usual form of treatment for his or her condition …. Should you decide to consent to this study and then later change your mind you may withdraw your baby from the study. If your baby was in the negative pressure ventilation group we will go back to the usual positive pressure ventilation treatment" (T). The senior nursing sister referred to earlier also produced, on her own initiative and in collaboration with another senior nursing colleague, an illustrated, 12 page information booklet for parents which contained the same statement prominently on the back page (U). Every parent also signed a form that said: "I understand that participation in this study is voluntary … and withdrawal does not effect the future care that he/she will receive from his/her doctors" (V).

Furthermore, a questionnaire was later sent to all the 173 families from Stoke whose babies survived to discharge. It was designed jointly with the nursing staff (W, X) but was sent from the National Heart and Lung Institute in London by the research registrar responsible for the London end of the collaborative study at around the time each baby was discharged from hospital (Y). Replies were received from 137 families (79%). These seem to have revealed general satisfaction with the conduct of the study. The nurses, in particular, received praise in this regard. Twenty two families took up the invitation to append more general comments, and eight of these wrote about the provision of information and the way they were approached for consent. Six mentioned the care taken by staff over these issues. One wrote: "We felt that the initial contact to gain our consent for [child's name] to be on the CNEP trial could not have been handled in a more sympathetic manner." Only one was critical—a parent whose baby received conventional treatment wrote: "We would have liked more information/discussion with the doctors … and an explanation as to why our baby received standard treatment" (Z).

The picture to emerge from these near-contemporaneous questionnaires is in stark contrast to the one painted by the small group of parents who were interviewed by (or for) the panel seven years later. Some of these claimed that "they were not aware they were consenting for entry into a research trial" (para 14.3.2).[3] Parents may have found it difficult to remember what happened on the day their child was born, but the letter that accompanied the questionnaire sent to them subsequently said: "You will remember that shortly after [child's name] was born you kindly agreed to enroll him/her into our study comparing negative pressure respiratory support with standard treatment. As part of this study we have devised a questionnaire which attempts to compare the effect of these two methods of treatment on the way you were able to relate to your baby. We would greatly appreciate your completing this questionnaire and returning it to the nursing staff. The information from the questionnaires is confidential and will only be used for the purposes of the study. We would also be very grateful for any suggestions that you may have which would improve our treatment for future babies" (Y). This could not have failed to remind the parents of the existence of the trial.

The panel's reporting of these issues was extremely one sided. They repeated, in considerable detail, the accusations now being made by several parents but failed to set these in the context of the large amount of documentary evidence available showing that consent was obtained with considerable diligence. Indeed, it is our impression that the conduct of the CNEP trial was exemplary. It was certainly up to the standard of most neonatal trials that were recruiting patients in Britain in the early 1990s.

The panel's concluding statement that "the process was not managed consistently and no system of management and documentation was in place to prove that it was" (para 14.3.8)[3] seems to rely exclusively on what they were told by the small, self selected group of parents on whose testimony they chose to rely. Why was the substantial documentary evidence to the contrary not made available for review by the panel? Their implied criticism of the diligence of the local research ethics committee is equally unjustified.

Issues of recall

The panel seemed reluctant to accept that recall in such matters can be extremely unreliable, despite the clear evidence they were given to this effect from those responsible for the recent national neonatal ECMO trial (para 14.3.7).[3] Other testimony points to a similar conclusion. Dr Ben Stenson and Professor Neil McIntosh from Edinburgh recently wrote: "Our experience 18 months after a trial of clinical monitoring in 199 newborn infants, where consent was obtained shortly after birth by a single researcher (BS), showed that, at follow up, 12% could not remember being asked to give consent for a research study. In all cases signed consent had been obtained from the parents and a printed information sheet had been given out. Of those that remembered giving their consent, 20% could not remember receiving an information sheet."[8]

Subsequent publication

The panel made much of the claim that the CNEP study was never "subjected to external peer review" (para 7.1.6).[3] Indeed their main recommendation to the NHS Executive—that there is an urgent need to issue "new guidance on research governance" (para 4.1.2)[3]—clearly stemmed from this belief. We find the panel to have been factually wrong in this regard and believe that the CNEP study was actually subjected to more than the usual amount of peer review both before it was funded and before ethical approval was given for the study to start. It faced further review

before the findings of the study appeared in print, and again after publication.

In particular the panel failed to note that the report of the study underwent thorough peer review before publication in 1996 in the world's highest rated paediatric journal and that since then it has also survived the final and most important element of scientific peer review—scrutiny by the world's clinical science community—unscathed to date. These four elements of peer review have served the scientific world well for a long time. The panel's proposals for research in the NHS to be subject to further levels of management scrutiny rest on the demonstrably false premise that the CNEP study somehow bypassed the community's existing scrutiny hurdles.

It is true that the issues raised in the *Lancet* editorial of 27 February 1999 have not yet been addressed.[7] This is because the senior principal investigator in the Stoke research team has been advised by the trust that employs him not to become involved in public debate about the conduct of the study. We have therefore taken the liberty of addressing them here on behalf of those who have been advised that it would be unwise to speak up in their own defence. Both the *Lancet*[7] and the *BMJ*[4] have recently suggested that they would not now publish the observational study[9] that led to the start of this controlled trial since it was not reviewed by an ethics committee before it began. All that can be said about this is that no other recent development in neonatal ventilation—such as routine paralysis and sedation,[10] patient-triggered ventilation,[11] high frequency (oscillatory) ventilation,[12] or flow driven nasal continuous positive airway pressure[13]—was taken to an ethics committee before its innovative use was first explored by experienced clinicians. Formal evaluative research followed early pragmatic clinical exploration, as here. The hope behind each of these innovations has been that they would reduce the amount of chronic lung damage caused by the need to impose high pressure ventilation on an already injured organ. The length of time a baby continues to need supplemental oxygen is a potent marker of this.

Finding that continuous negative extrathoracic pressure resulted in a statistically significant increase in the number of babies who avoided laryngeal intubation (14 *v* 9 %) and a significant halving of the average time the babies spent in supplemental oxygen (18 *v* 34 days), the authors of the 1996 paper concluded that "CNEP improves respiratory outcome."[5] The *Lancet* questioned the validity of this conclusion, noting that there were more pneumothoraces, significant cranial ultrasound abnormalities, and deaths among the babies given continuous negative extrathoracic pressure.[7] However, all the differences in these important outcomes could easily have arisen by chance, and are thus compatible with continuous negative extrathoracic pressure having beneficial effects on these outcomes as well. Unlike the panel (para 7.1.4),[3] we therefore find nothing inappropriate or improper in the way the findings of this trial were analysed or reported. Randomisation halved the chance that the baby would benefit from this new medical development, but it also halved the chance of unpredictable harm. The findings are consistent with those revealed by a Cochrane review of other trials of continuous distending airway pressure for neonatal respiratory distress.[14]

The *Lancet* expressed concern that recruitment to the trial had to be effected within four hours of birth,[7] a misunderstanding that probably arose because of a flawed sentence in the 1996 paper, which reflected policy at the start of the study in London.[5] None of the infants from Stoke were entered into the study until they were at least four hours old, as is clear from the local trial protocol (O). Nearly all were entered when between five and 10 hours old, as the trust was in a position to ascertain when it conducted its own internal inquiry into these issues (S). The belief that there was excessive pressure to effect early entry is, therefore, misguided. The panel failed to explore and clarify this issue.

Comment

We are driven by the above analysis to conclude that almost every statement made about the design, conduct, and reporting of the neonatal CNEP trial in the Griffiths report was ill informed, misguided, or factually wrong. Despite the limited time at our disposal, we have identified and highlighted several extremely important errors of fact that are central to the conclusions reached by the panel. In our view, these wholly avoidable errors call into question the reliability of the whole Griffiths report. Since we are told that the panel ceased taking evidence for the report almost a year before it was eventually released by the NHS Executive (para 1.6),[3] we expect that these errors could have been avoided had the panel seen the documents we were shown or obtained comments from the people they criticised before publication. This is particularly surprising in view of the fact that one member of the panel has extensive clinical, research, and ethics expertise (A).

The panel's purported focus on research management issues within the North Staffordshire Hospital NHS Trust has, in effect, been turned into a clumsily conducted scrutiny of the scientific probity of work done by the whole of the paediatric research team at Stoke. What is more, that scrutiny was not conducted to anything approaching the standard to be expected of any reputable inquiry into allegations of research misconduct.[15]

The panel's focus on the thoroughness with which informed consent was obtained before treatment was given to the babies in the CNEP study also contrasts starkly with the complacency that exists about the quality of consent to treatment in most other clinical situations. There are the most flagrant double standards operating here.[16] We found clear documentary evidence that the staff in Stoke went to unusual lengths to ensure that families were as informed as possible about the nature of the care on offer, both before and after entry to the study. The role of the nursing staff in this regard was particularly praiseworthy. We cannot understand why the clinical community, and NHS management, accept much lower standards than this when obtaining consent to treatment in a routine clinical setting.

An unknown number of unnamed parents made serious allegations to the panel about the failure of the ward staff in Stoke to obtain properly informed

consent to their child's inclusion in the CNEP study. By repeating these untested allegations in the report and then recommending major changes in the governance of clinical research in the NHS, the panel have clearly led readers to believe that they consider many of these unchecked assertions to be correct. The disclaimer that "The Review Panel have not sought to determine whether allegations of poor practice are true" (para 1.5; 14.1.6)[3] contrasts implausibly with the whole thrust of the report, which is to the effect that what went on in Stoke was obviously unacceptable. Since these "flaws" went unremarked at the time, the panel seem to believe that the whole conduct of research needs urgent managerial review. We doubt whether the intellectual activity that has underpinned most medical progress within the NHS in the past 50 years is well served by change of the type the panel are now proposing. Such a radical departure from a basic presumption of professional self accountability needs to be supported by better evidence than this.

We do believe that the panel's report will have performed a service if it leads to more thought being given to the way in which informed consent for treatment is obtained, and to the care with which this important activity is monitored and supervised (para 10.5.10).[3] However, such issues relate just as much to the process of gaining consent to routine clinical treatment as to consent to treatment in a research context. It is not a matter meriting closer "governance" only in a research context.

We applaud the open approach taken by the Medical Defence Union in agreeing unconditionally that we could report our findings to this journal, whatever our conclusions, before we started work on this review. Our work for them has been unpaid and was completed on 4 July 2000. We acknowledge the helpful advice of the paper's referees. We also thank Kath Sidoli for checking the factual accuracy of the report on behalf of the North Staffordshire Hospital NHS Trust. She has assured us that the complaints lodged by individual families regarding the conduct of the CNEP trial are now under active investigation. The views expressed in this article represent those of the authors and are not necessarily the views or the official policy of the Cochrane Collaboration.

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Competing interests: Both authors admit to a concern that clinical research to safeguard the interests of people using health services is in serious jeopardy. At the time Professor Southall sought advice from the National Perinatal Epidemiology Unit in 1990, IC was director of that unit, but the issue was dealt with by the specialist staff at the perinatal trials service. Neither author knew any member of the research team at Stoke when asked to undertake this work for the Medical Defence Union.

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Appendix A: Key CNEP trial documents

(A) NHS Executive West Midlands Regional Office. *Report of a review of the research framework in North Staffordshire Hospital NHS Trust* (Griffiths report). Leeds: NHS Executive, 2000. (www.doh.gov.uk/wmro/northstaffs.htm, updated 8 May 2000.) Chair: Professor Rod Griffiths, director of public health, NHS Executive West Midlands Regional Office; Professor Terry Stacey, director of research and development, NHS Executive South East Regional Office; Mrs Joyce Struthers, chairwoman, Association of Community Health Councils of England and Wales.

(B) Southall D. "Response to the Griffiths report." Rebuttal prepared by Professor Southall and lodged with Medical Defence Union 3 August 2000. Available at www.baspcan.org.uk/

(C) Full version of the proposal submitted to the Stoke Ethics Committee for the neonatal CNEP Trial ("A randomised controlled trial of continuous subatmospheric (negative) extra thoracic pressure (CNEP) in neonatal respiratory failure") by Dr Andrew Spencer with a covering letter dated 29 November 1989, together with a copy of the full 12 page CNEP trial protocol and a letter giving committee approval dated 11 January 1990.

(D) Untitled research document outlining the rules for matching and randomising babies into the neonatal CNEP trial.

(E) Letter from Martin Samuels to EH, July 2000.

(F) Correspondence with the Perinatal Trials Service at the National Perinatal Epidemiology Unit in Oxford between February and May 1990.

(G) Correspondence with the Clinical Research Committee of the National Heart and Chest Hospitals regarding their funding for the multicentre neonatal CNEP trial 1990-2.

(H) Letter from the MRC dated 22 March 1990 reporting that the CNEP trial had been awarded an alpha rating but had not been rated highly enough for the MRC to be able to offer funding.

(I) Job specification for the post of clinical nurse specialist and respiratory research coordinator at the National Heart and Lung Institute in London and North Staffordshire Hospital. Grade H. Dated July 1990.

(J) Curriculum vitae of the nurse who took up the post outlined in I. The only version we have was probably prepared in early 1993.

(K) Sample pages from the central "Trial Randomisation Log Book" for both the CNEP in RDS and the CNEP in bronchiolitis trials.

(L) Photocopies of five samples of the research folder opened for each baby entering the neonatal CNEP

trial (containing the consent form, the main data coding sheet, blood gas chart, temperature chart, parental questionnaire, and ultrasound information).
(M) Letters between Professor Southall and the local lead clinician, Dr Andrew Spencer, between November 1989 and September 1991, including a trial protocol modification to incorporate the use of artificial surfactant dated May 1991.
(N) Letter from Mr John Alexander (statistician to the neonatal CNEP trial) dated 23 March 2000 outlining the trial's design and the way the randomisation process was conducted as faxed to Professor Griffiths and Lord Hunt.
(O) Manual on the use of "Negative pressure ventilation in infants and children (as used in North Staffordshire Hospital)" by Samuels M, Jones K, Noyes J, Southall D, April 1990. An illustrated 47 page document outlining, in detail, both nursing and medical management.
(P) "Audit of consent documentation for the CNEP trial." A confidential report prepared for Mr David Fillingham, chief executive, North Staffordshire Hospital NHS Trust, by the hospital's clinical audit department, March 1999.
(Q) Nursing document giving details of the 147 babies who were considered ineligible for the neonatal CNEP trial, and the 15 cases where suitability for trial entry was overlooked and who were thus not invited to participate.
(R) Document outlining why 28 eligible patients were not recruited into the CNEP trial. This forms appendix 4 of an unknown document prepared by the Stoke Hospital Clinical Audit Department at about the same time as document P.
(S) Further audit of the CNEP trial consent forms undertaken in June 2000 at the request of EH in order to identify the staff involved and the exact time of trial entry, and of a further audit of the CNEP trial post-discharge questionnaires (document Z) also undertaken in June 2000 at the request of EH.
(T) Information for parents about the neonatal CNEP ventilation study (the information sheet designed for use when informed consent was obtained). A copy appears as part of appendix 1 to the trust's own internal audit report (document P).
(U) "Negative pressure trial. An information booklet for parents." Developed by Katy Lockyer and Teresa Wright after study W. Illustrated 12 page booklet, undated.
(V) Copy of the North Staffordshire Health Authority Ethical Committee's standard consent form ("Consent by proxy to conduct of a research investigation"). This is the form the CNEP research team were required to use when obtaining parental consent in Stoke despite the acknowledged limitations imposed by its very general, untailored nature.
(W) Report of a nursing study into parental understanding of the use of CNEP in neonatal respiratory failure undertaken by Katy Lockyer in late 1992. Document undated. (A study based on questionnaires sent to 12 families whose babies had been entered into the neonatal CNEP trial.)
(X) Analysis of an audit of the way consent was obtained for the trial of CNEP in bronchiolitis using a post-recovery questionnaire sent to parents in their own homes (a randomised controlled trial being undertaken in Stoke at the same time as the neonatal CNEP trial). Replies were received from 21 of the 26 families.
(Y) Copy of the covering letter sent to all the parents along with the post-trial questionnaire referred to in Z.
(Z) Pages from a subsidiary confidential internal trust report after the audit of consent documented for the CNEP research trial. This contains copies of all the verbatim comments parents attached to the questionnaire which was sent to the parents of all surviving babies. Forms are said to have been returned by the parents of 137 of the 173 survivors. Supplementary comments were made by 22 families. An undated report prepared after the report referred to in P.

Appendix B: Recent published articles relating to neonatal CNEP

- Samuels MP, Southall DP. Negative extrathoracic pressure in treatment of respiratory failure in infants and young children. *BMJ* 1989;299:1253-7.
- Noyes J. Respiratory failure in infants. *Nurs Stand* 1990;4:28-30.
- Raine J, Wright TAM, Samuels MP, Southall DP, Modi N, Harvey D, et al. The use of continuous extrathoracic pressure in neonatal respiratory failure. In: Lafeber HN, ed. *Fetal and neonatal physiological measurements*. Amsterdam: Excerpta Medica, 1991:265-70.
- Boase C, Samuels M. Negative pressure ventilation in newborn infants. *Int Rev Adv Neonatology* 1992:5-8.
- Raine J, Redington AN, Benatar A, Samuels MP, Southall DP. Continuous negative extrathoracic pressure and cardiac output—a pilot study. *Eur J Pediatr* 1993;152:595-8.
- Raine J, Cowan F, Samuels MP, Wertheim D, Southall DP. Continuous negative extrathoracic pressure and cerebral blood flow velocity: a pilot study. *Acta Paediatr* 1994;83:438-9.
- Palmer K, Spencer SA, Wikramasinghe Y, Wright T, Samuels M, Rolfe P. Negative extrathoracic pressure ventilation—evaluation of the neck seal. *Early Hum Dev* 1994;37:67-72.
- Gappa M, Costeloe K, Southall DP, Rabbette S, Stocks J. Effect of continuous negative extrathoracic pressure on respiratory mechanics and timing in infants recovering from neonatal respiratory distress syndrome. *Pediatr Res* 1994;36:364-72.
- Palmer KS, Spencer SA, Wikramasinghe YA, Wright T, Southall DP, Rolfe P. Effects of positive and negative pressure ventilation on cerebral blood volume of newborn infants. *Acta Paediatr* 1995;84:132-9.
- Samuels MP, Raine J, Wright T, Alexander JA, Lockyer K, Spencer SA, et al. Continuous negative extrathoracic pressure in neonatal respiratory failure. *Pediatrics* 1996;98:1154-60.
- Thomson A. The role of negative pressure ventilation. *Arch Dis Child* 1997;77:454-8.
- Samuels M, Southall D. The role of negative pressure ventilation. *Arch Dis Child* 1998;79:94.
- The perils of paediatric research [editorial]. *Lancet* 1999;353:685.
- Venkataraman ST. Noninvasive mechanical ventilation and respiratory care. *New horizons: the science and practice of acute medicine* 1999;7:353-8.
- Smith R. Babies and consent: yet another NHS scandal [editorial]. *BMJ* 2000;320:1285-6.

Commentary: Response from members of the Griffiths inquiry

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It is difficult to accept Hey and Chalmers' conclusions for several reasons. Most importantly, they seem to have entirely misunderstood the terms of reference and the main thrust of the review of the research framework in North Staffordshire. Secondly, they attempt to dismiss a 50 page report by attacking isolated phrases, often out of context, and ignoring the main substance of the report.

The most important conclusion of the review was that there needed to be a new research governance framework. It is surprising if Hey and Chalmers disagree with this. We were well aware that the Department of Health was already working on the production of a new framework. A simple examination of best practice—for example, the rules that the Medical Research Council lays on its grant holders compared with the current rules governing research in NHS trusts—is sufficient to show that the current NHS rules could be considerably improved and nothing that Hey and Chalmers say changes our view. We remain convinced of the need for researchers to operate within an improved governance system. The public cannot be reassured about the safety and probity of research unless such a system is in place. Furthermore such a system would be a protection for the researchers themselves. The report pointed out, in defence of Professor Southall and the trust, that a number of witnesses of considerable eminence said that research governance in North Staffordshire in the early 1990s was probably no different from that in many other trusts. That is why a national governance framework is needed.

We took evidence from 60 people, some of whom also provided written material. There were repeated calls for everyone who had relevant material to come forward. We could do no more than ask every witness to provide material that they thought was relevant. Professor Southall was interviewed twice, and he provided written material. Furthermore, he added to his statement at a later date and then sent further material. He has now made additional material available,[1] but none of this would change our recommendations.

Of course Hey and Chalmers are correct in calling for due process in investigating issues of personal conduct. That is why there is a disciplinary hearing in the trust looking at two aspects of Professor Southall's conduct, and that is why the General Medical Council is also carrying out its investigation. These disciplinary proceedings were instigated by the trust before the review reported, and indeed Professor Southall was suspended before the review reported. Any criticism real or imagined in the report had nothing to do with these proceedings.

Some points of detail

We are given to understand[1] that by reference to the nursing record, the consent forms, and Professor Southall's own logs (which he did not provide to the panel) it is possible to work out who obtained consent and when they did so. All of that information should have been on every consent form and it was not. It was difficult for us to conclude that all was well when the consent forms do not all contain all the information that they should and when it requires tortuous detective work from non-public sources to determine what happened.

We are now told that nearly all children were entered into the trial at between five and 10 hours old, whereas the paper in *Pediatrics* reporting the trial said, "Parental consent was obtained between 2 and 4 hours of age" and "Randomisation was performed at 4 hours of age on the basis that the earlier CNEP [continuous negative extrathoracic pressure] was commenced the more beneficial it was likely to be."[2] Clearly both cannot be right.

We asked Professor Southall at length about the external input that had gone into the design of the trial. Hey and Chalmers make much of the fact that others, including one of them, were consulted about the design of the trial. Professor Southall did not mention any of this when directly asked by the panel; he did not add this to his evidence later, as he did with other material; and none of this input was acknowledged in the published paper in *Pediatrics*.[2]

We specifically reject the suggestion that our comments about the nursing input were a slur. The nursing sister involved said that she had never undertaken research before the trial and had received limited support. She was accompanied by her husband and a professional representative when she gave evidence, and we expressed in our report considerable sympathy for her position.

We specifically referred to research on issues of recall and were only too well aware of the risk that some of the witnesses may have been pursuing their own agenda, but this does not mean that all parents are wrong and all researchers are right. It means that a governance framework must be in place so that everyone can have confidence, whatever their recall.

It is not in our view desirable or appropriate to debate through this journal all of the points that have been made; much of the matter is still sub judice with the trust and the GMC. We consider our job to be done and will not engage in further debate. The report is a Department of Health report, and that department will be dealing with any further issues arising from it.

Competing interests: None declared.

1 Southall D response to the Griffiths report. Rebuttal prepared by Professor Southall and lodged with Medical Defence Union 3 August 2000. www.baspcan.org.uk/
2 Samuels MP, Raine J, Wright T, Alexander JA, Lockyer K, Spencer SA, Brookfield DS, Modi N, Harvey D, Bose C, Southall DP. Continuous negative extrathoracic pressure in neonatal respiratory failure. *Pediatrics* 1996;98:1154-60.