The effect of the neonatal Continuous Negative Extrathoracic Pressure (CNEP) trial enquiries on research in the UK

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THE IMPACT OF THE RESEARCH GOVERNANCE FRAMEWORK UPON NEONATAL AND OTHER RESEARCH

The UK Research Governance Framework introduced in 2001,[1] initiated sweeping changes to the regulation of UK research. The framework implements the Medicines for Human Use (Clinical Trials) Regulations 2004, the European Union Clinical Trials Directive (EUCTD) and additional regulatory requirements. Other substantial changes were the establishment of the Comprehensive Clinical Research Network and Medicines for Children Research Network (MCRN) in 2005, and in 2006, a strategy to stimulate patient-focused research and place the National Health Service (NHS) centre, stage was presented in 'Best Research for Best Health'.[2] The Research Governance Framework arose largely in response to the Griffiths Report[3 4] into a neonatal trial, the Continuous Extrathoracic Negative Pressure (CNEP) trial. Among the many consequences was that the intended benefits to patients of placing the NHS at the heart of initiatives to improve clinical research have been seriously compromised by over-regulation.

The first decade of the 21st century saw newborn research in the UK come close to a standstill. In 2002, the British Association of Perinatal Medicine cancelled its annual Trials Group Meeting because of lack of attendance. By 2006, there were only three large multicentre trials in the UK involving medicines in neonates, all led by academic investigators (INIS: International Neonatal Immunotherapy Study; PROGRAMS: A multicentre, randomised controlled trial of PROphylactic GRAnulocyte-Macrophage colony stimulating factor (GM-CSF) to reduce Sepsis in preterm neonates; NIRTURE: Neonatal Insulin Replacement Therapy in Europe). Approximately 8000 applications are reviewed by the UK National Research Ethics Service (NRES) each year. In 2009, research in children of any age represented only around 1 in 10 of all applications, of which less than 10% were trials of an investigational medicinal product (NRES, personal communication) and such trials in newborns were very few indeed. Babies, thus, continue to be at the highest risk of receiving untested, unproven treatments because of the many deterrents to research addressing their needs. European legislation aiming to increase medicines research in children has led to an increase in pharmacokinetic studies, but efficacy and effectiveness research remains scant. The current edition of the British National Formulary for Children lists over 200 medicines for neonatal use; of these only around 7% cover a licensed indication.

Stephenson, in 2000,[5] warned of the adverse impact the Research Governance Framework would have. Investigators today, regardless of specialty, face multiple and lengthy approvals processes, progress reports to different agencies at variable intervals and in different formats, aggressive inspections, poorly trained NHS R&D staff, illogical, unnecessary, unreasonable and inconsistent rulings and the need to find ever-increasing financial support to service regulatory requirements.[6–11] Responsibility for different aspects of research regulation is held by a number of 'arms-length' bodies, adding to the confusion. Delays of several years from funding to first recruitment are by no means rare. Professor Andrew Whitelaw, immediate past-President of the Neonatal Society (a research society) describes "A complexity that requires a taught course. The increasing burden of just applying for permission has completely de-motivated my younger colleagues and driven ambitious young doctors away from patient centred research" (personal communication, 9 September 2009).

The goals of safeguarding patients, creating a research-friendly NHS and delivering more evidence-based treatments are being seriously compromised by a bureaucracy that appears out of control. The UK PROGRAMS trial (ISRCTN42553489) investigating a haemopoietic cytokine for infection prophylaxis in preterm babies spanned the introduction of the Research Governance Framework. Before entry of the EUCTD into UK law recruitment was ahead of schedule, but the imposition of several layers of regulation brought it close to foundering; £100 000 was required in additional funding from the charity Action Medical Research and the Wellcome Trust. Nonetheless it was completed, the primary outcomes published in the *Lancet*[12] and the 5-year follow-up assessments of the children are underway. The clinical aspects were identical before and after the regulation came into effect but the costs and bureaucracy were markedly increased.

The MCRN aims to attract pharmaceutical funding and medicines research to the UK. Yet the inflexibility of the new regulatory processes managed by the Medicines and Healthcare products Regulatory Agency (MHRA), such as the need for NHS pharmacies to obtain a 'manufacturing license' and employ a 'qualified person' to handle 'investigative medical products' even when the same products are being used routinely in clinical practice, has had the opposite effect. These regulations assume the availability of the resources of a large pharmaceutical company and the testing of novel products. This seriously penalises babies where most medicines research evaluates products already in wide off-licence or off-label clinical use. In 2009, a pharmaceutical firm aiming to conduct a pilot study in surgical newborns of a novel amino acid solution in four European centres, two of which were in England, pulled out of the UK after intractable regulatory delays. The UK lead clinician had been involved in the development of the product over 5 years; the company had also intended to proceed to a larger study in preterm infants, a group where the evidence base for intravenous nutrition is particularly lacking.

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The approach in the UK differs markedly from that adopted elsewhere in Europe. The design of a current randomised controlled trial (NEON, ISRCTN29665319) in preterm babies is identical to a study running concurrently in the Netherlands and the interventions are parenteral nutrition formulations in everyday clinical use. In the UK, the classification of the trial as a Clinical Trial of an Investigational Medicinal Product (CTIMP) has led to immense associated bureaucracy, and multiple approvals, including signing at last a count of 22 separate contracts. In contrast, in the Netherlands a single regulatory approval was required.

The damaging effect of the present regulatory climate upon UK research led the then Health Secretary, Andy Burnham, to announce a Government commission in March 2010 for an independent review. This is being undertaken by the Academy of Medical Sciences that had previously highlighted concerns.[13] The children's research community contributed a number of responses that were coordinated by the Science and Research Department of the Royal College of Paediatrics and Child Health. Chief among paediatrician concerns are the escalating costs of research to service bureaucratic requirements and hence a smaller number of studies that can be funded from a shrinking pool of resource, and adoption of an increasingly defensive approach and a risk-based interpretation of regulations that place bureaucracy before patient welfare. A case in point is the requirement to include the statement "If your baby experiences harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that (the institution) is at fault". Even in a study of minimal or no risk, this provokes what Snowden terms "injurious misconception", an exaggerated and inappropriate sense of risk that leads parents to reject trial participation.[14] Public confidence in clinical research will only be improved if it is presented honestly, acknowledging that high-quality clinical research is a hallmark of high-quality care.

The need for repetitive applications to every NHS Trust participating in a study, and multiple layers of approval with different sets of forms and processes, is a deeply dispiriting experience. The delays at NHS Trust level are compounded by the MHRA and the NRES as the addition of a new trial centre for CTIMP studies is considered a substantive amendment, resulting in a minimum 6-week delay to process the associated paperwork. The implications for neonatal trials are not trivial. Neonatal services in England operate as managed clinical networks with infants transferred to a unit providing more intensive care as necessary and then to a 'step-down' unit close to home for ongoing or convalescent care. If a baby recruited at one neonatal unit is transferred, the second unit is also considered a trial centre. As two thirds of babies born before 32 weeks gestation have at least one transfer, for a large national trial every one of the regulatory requirements must be in place in each of the 200 neonatal units in the UK, prior to the recruitment of the first baby. This is impossible, even if costs were no object. Professor Peter Brocklehurst, Director of the National Perinatal Epidemiology Unit, describes an instance in BOOST-II (Benefits of Oxygen Saturation Targeting) UK (ISRCTN008422661) where the research objective is to establish an optimum saturation target for preterm babies requiring supplemental oxygen (the Investigational Medical Product). This trial experienced the withdrawal of a baby transferred to a 'step-down' unit at the insistence of the NHS R&D department because regulatory approvals were not formally in place, despite explanation from the Chief Investigator that oxygen is widely used and was needed by the baby and even though the Research Governance Framework states 'Health and social care organisations are expected to manage risk, minimise bureaucratic process and facilitate high quality research; they are not normally expected to withhold permission when a sponsor offers reasonable assurances of arrangements to carry out the responsibilities set out in this framework'.[1] This baby continued to receive oxygen though not within the objective setting of the trial.

The PIPS trial (a multi-centre, double blind, placebo-controlled randomised trial of probiotic administration in preterm infants), examining neonatal probiotic prophylaxis, was expected to open in January 2007 but did not commence recruitment until July 2010. Regulatory difficulties included prolonged uncertainty by the MHRA concerning the information required to support the application following their decision that the probiotic should be regarded as an Investigational Medical Product rather than a food supplement. Further, the Research Ethics Committee required the statement "It should be made clear that it may be necessary for a baby to

Box 1 An eyewitness account

- In the late 1980s, David Southall, then based at the Brompton Hospital, proposed a clinical trial in preterm babies with respiratory distress syndrome. At that time, only first-generation positive-pressure ventilators were available, surfactant was still undergoing clinical trials and antenatal steroid use was patchy. Even relatively mature babies experienced severe respiratory distress, the features of which would not be recognised by today's trainees.
- In those early days of neonatology working weeks of around 100 h were not uncommon, but it was an intellectually stimulating and rewarding time when the care of sick newborn babies was advancing rapidly. The research ethics committees of most teaching hospitals had requirements that accommodated local circumstances. Good institutions and good researchers would do things well, but independent scrutiny to identify and improve poor-quality research was unusual and there was little uniformity of regulation. In short, there was ample need for reform of a ramshackle system.
- David Southall's trial involved the use of negative pressure applied externally to the baby's chest, an adaptation of the old 'iron-lung'. Given the inadequacies of the then available treatments, it seemed a good approach. The trial had some striking features: a dedicated clinical research team, 24-h off-site randomisation, a sequential matched paired design with predefined interim analyses, stopping criteria that were of greater stringency for benefit than for harm, independent statistical oversight, CI to present results, a process for adverse event review, trial registration and a postrecruitment parent questionnaire. Today these are considered hallmarks of high quality. The CNEP trial was ahead of its time. It was approved by the Research Ethics Committees of all participating institutions and the results, published in a leading international journal in 1996, showed benefit to the infants randomised to the CNEP arm.[26]

CNEP, Continuous Extrathoracic Negative Pressure.

Box 2 A matter of public record

- Following the publication of the CNEP trial results, a group of parents made a series of complaints against the investigators to the General Medical Council (GMC) in an apparently orchestrated campaign.[27] Newspapers published claims that delivery by caesarean section was encouraged so experiments could be performed on premature babies, and made lurid use of the phrase 'Guinea pig babies'. An inquiry was ordered by the health minister in 1989, headed by Professor Rod Griffiths, then West Midland's regional director of public health "to look into the general framework for both the approval and monitoring of clinical research projects in North Staffordshire".[4] Groups of parents insisted on child protection issues being considered[16] and the remit of the enquiry extended to include this,[19] an area in which David Southall was prominent. Penny Mellor, a member of Mothers Against Munchausen syndrome by proxy Allegations; http://www.msbp.com/ made 'a number of very serious allegations'[4] against David Southall. She also commented "Southall's suggestion that those campaigning about the CNEP trial are trying to sabotage his child protection work is outrageous".[28] The Griffith's panel, that included a paediatrician, Professor Terry Stacey, was highly critical of the CNEP trial; they concluded there was justification for a major restructuring of research regulation in the NHS.[3 4] Their report was instrumental in leading to the Research Governance Framework.
- Following a protracted investigation, all allegations made by parents, including the charge that signatures on CNEP trial consent forms had been forged, were found to be false.[27 29] In 2002, Penny Mellor received a jail sentence for conspiracy to commit child abduction.[30] The Griffith's report was shown to be seriously flawed.[31] The CNEP trial was examined seven times in 11 years until finally in 2008, yet another disciplinary panel collapsed when a key witness for the GMC was discredited, Richard Nicholson, editor of the *Bulletin of Medical Ethics*, who had taught for many years on Research Ethics training courses run by the Department of Health. The panel expressed grave reservations about his suitability to give evidence and the reliability of his opinions, noting he had "little or no formal training in medical ethics".[27 32]
- Professor Griffiths became President of the Faculty of Public Health and Professor Stacey, director of the UK Central Office of Research Ethics Committees. Penny Mellor has been appointed by the GMC to an expert group producing guidance for paediatrician's working in child protection.[33] The disillusionment and trauma suffered by the senior research nurses and the loss of their skills to children's research has been described in moving detail.[20] The lead investigators endured prolonged suspension, traumatised personal lives, multiple GMC hearings, loss of income, career destruction and repeated vilification in the press.

CNEP, Continuous Extrathoracic Negative Pressure; NHS, National Health Service.

be withdrawn from the study if the baby is transferred between sites but that this would not impact negatively on the care that would be offered. It would be acceptable to note that this was a result of various regulatory conditions" to be included in the Parent Information Sheet. The investigators challenged this, responding "It cannot be right that we accept a major protocol violation because of the slow response time of NHS R&D bureaucracy." This exchange illustrates a bizarre paradox; the REC (Research Ethics Committee) considered it acceptable to withdraw a baby from a trial solely for reasons of bureaucracy, but the researchers successfully challenged this as unethical. Lead investigator and Neonatal Society President, Professor Kate Costeloe describes "terrible confusion" and "very limited insight by the staff in R&D offices" and concludes "contributing to studies has simply become so much more difficult in terms of the approvals needed that many people just choose to pass" (personal communication, 8 July 2009).

Pressure upon consultants to recruit to portfolio studies by NHS Trusts scrabbling to claw-back monies is in danger of damaging the doctor-patient relationship. Many consultants also report being prohibited by their Trusts from participating in research until they can demonstrate that funding will be forthcoming. Research that is unfunded, funded by local research charities or funded from investigator unrestricted funds is becoming relegated to second place. Yet these sorts of studies often provide pilot data or the serendipitous observations that have been so rewarding in science.

Parents would be aghast if they knew the difficulties faced by researchers trying to improve the evidence base for newborn care. Brocklehurst reflects "many of the consequences of creating this Research Governance Framework could have been predicted if there had been greater consultation with researchers so that the people responsible could discuss the potential consequences of these changes. If such a meaningful process had taken place, the Research Governance Framework would have been rather different" (personal communication, 7 August 2009).

The Research Governance Framework, born from a flawed evaluation of an exemplary trial (Box 1), possibly even the need to find a scapegoat to camouflage long-standing failure to introduce research regulation,[3] emerged as a heavy handed, restrictive, 'one size fits all' approach. Had the Griffith's Panel conducted a proper investigation they would have concluded that the CNEP trial was a model of good research practice that could serve as a template for a new national framework for research governance. Instead, the investigators and their families suffered grave personal harm. The damage caused to the public perception of clinical research, reinforced by false allegations, poor investigation and irresponsible media reporting, remains a tragedy. Investigators have to contend with a bureaucracy that has little bearing on patient safety. The cost of servicing this bureaucracy has led to an escalation in overall research costs and a smaller number of studies that can be supported. Babies have been harmed by the slowing in the development of the clinical evidence base. All this might have been averted by addressing the need for national research governance in a positive and proactive, not a reactive and retributive context. Rod Griffiths, has described his experience of leading the CNEP review as 'drinking from a poisoned chalice'[15] and writing in 2006, acknowledged "...I believe that the implementation of research governance has been disappointing ...over-bureaucratic, clumsy and restrictive. Some of those responsible seem to think that the only safe research is no research."[16]

THE WAY FORWARD

We believe it important that there is a historical record of the events and actions that led to the present position. The story of the CNEP trial is a matter of public record (Box 2) and has been documented in a series of articles in the *Journal of the Royal Society of*

Table 1 Wider suggestions for improving research regulation

Consult widely and test processes in small pilots prior to implementation.
Strive to create a positive, rather than a defensive climate (eg, by explaining that even though risk may not be totally eliminated, it is minimised by good design, processes to identify harm (eg, independent review of interim analyses, adverse event reporting) and predefined stopping rules).
Encourage investigators to provide concise, not lengthy, information; when coupled with verbal explanation this improves understanding.[34]
Encourage investigators to explain that participation in a well-designed randomised trial is in a patient's best interests as this provides an equal chance of receiving the (as yet unknown) better treatment; the requirement to provide the false reassurance 'If you do not wish to participate, your baby will still receive the best possible care' should be dropped because the justification for the research is that this is not known.
Reduce inconsistency in rulings (eg, in relation to research in emergency situations) by establishing review boards expert in infant's and children's research.
Update attitudes to infant's and children's research by clearly distinguishing between interventional and observational research (eg, the Research Governance Framework statement "Unless the risk to them is negligible, it is unethical to involve...minors in research that could have no therapeutic benefit"[1] is confusing; a clinical trial aims to demonstrate one treatment to be superior to another; though one randomised group will receive less, or even no therapeutic benefit, this is not unethical because if the research were not done many patients would continue to be given an inferior treatment. It required many years of painstaking research that also had to face the charge 'unethical', to recognise that the routine use of oxygen for resuscitating babies at birth is harmful.[35] Had these trials not been performed babies would continue to receive the accepted standard treatment (routine oxygen for resuscitation at birth) and many would die or suffer harm as a consequence).
Apply consistent criteria for quantifying risk and harm in infant's and children's research (eg, in relation to blood sampling).
Ensure regulatory reviewers are competent to understand the science of the research and/or the quality and adequacy of expert independent peer review, as well as address the ethical issues; bad science is unethical.
Provide training for NHS R&D staff to a national standard (eg, consistency in assigning NHS costs).
Eliminate the requirement for multiple, repetitive processes for approval by NHS Trusts; introduce enforceable time lines for responses.
Abolish multiple requirements for progress reports to different agencies, to different criteria, employing different reference numbers.
Obtain independent scientific review once; at present this is often required at multiple levels (eg, institutional approval, funding, research ethics review, Comprehensive Local Research Network adoption); Research Ethics Committees often require investigators to submit peer review reports, even though a funded application may have been through considerable prior peer review and it is difficult to understand how additional review by a person or persons chosen by the investigators is helpful.
Develop a reasonable and proportional approach by the MHRA for trials involving off-licence indications of licensed medicines or comparisons of medicines in regular use and distinguish these from the testing of novel products.
Provide transparent, consistent support through Clinical Research Networks regardless of whether a study is commercially sponsored or investigator-led, and address the confusion around how support for adopted studies may be accessed.

MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service.

Medicine.[17–22] We hope that recognition of the mistakes that have been made will help improve attitudes, governance and regulation in the future. There have been excellent changes such as the introduction of the national Integrated Research Application System with associated clear timelines, eliminating the requirement for multiple applications for research ethics approval. We applaud the Best Research for Best Health implementation plan to 'bust bureaucracy' in NHS Trusts and their R&D Departments.[23] The original remit of the current review of research regulation by the Academy of Medical Sciences[13] was to identify key problems in the regulatory and governance environment for medical research in the UK, and make recommendations aimed at reducing complexity and eliminating bureaucracy. Following the Department of Health's review of Arms Length Bodies,[24] this has been extended by the incoming coalition government to the consideration of creating a single UK research regulator. We hope the recommendations will fully address the needs of infants and will bring about substantial and fundamental change for the better.

Aggressive regulation and purposeless bureaucracy neither encourage researchers nor reassure patients. A supportive research climate must encompass more than regulation (table 1). The greatest danger is to lose sight of the purpose of regulation, which is not only to protect 'the rights, safety, dignity and well-being of research participants' but also 'to facilitate ethical research which is of potential benefit to participants, science and society'.[25] Babies are among our most vulnerable; their right, as that of children, young people and adults, to participate in and benefit from high-quality research must be upheld.

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