

6. Trials and tribulations

Reference has been made in the preceding chapter to the period during which Ted Freeman had an association with the Westmead Hospital as chief investigator in a research project into severe brain injury. This association was a consequence of the award of a substantial financial grant from the NSW Government Insurance Office (GIO) intended to test his ideas for procedures to facilitate awakening patients from coma after brain injury and their subsequent rehabilitation. Freeman's association with the hospital and its receipt of the GIO grant were both terminated abruptly during the course of preparing for a clinical trial.

This chapter has two discrete parts. In the first, the story of that clinical trial and its failure to progress beyond the feasibility study is told. In the course of its telling, several issues that loomed large during this trial, but which also raise important general questions, will be identified. When the story of the trial is complete, attention is directed to these more general questions about clinical trials, which events at Westmead raise.

It should be recognised in the planning stage that double-blind randomised control trials of procedures, the outcome of which may be dependent on interpersonal relationships between research subjects and those responsible for undertaking procedures with them, may be impossible to implement. The absence from the literature of trials of coma arousal procedures that meet all the 'control' criteria may reflect this. Career implications for researchers may exist in any trial and the utmost care should be taken to anticipate them and to ensure that research aspirations do not displace clinical obligations, especially in the case of very vulnerable research subjects. Whether allocation of patient-subjects to 'non-treatment' control groups should have been considered ethically acceptable late in the twentieth century, and an associated question—namely, whether it is permissible to impose foreseeable risks on a *control* group—are considered.

Background to the 'Westmead experience'

Prior to his association with Westmead Hospital, Freeman had been receiving support from the GIO to investigate the possible use of stimulation in order to facilitate the emergence of people with brain injuries from coma and then to continue their rehabilitation. In 1983, earlier discussion about a possible trial led to the development of a protocol for it. Whilst the hospital administration was receptive to accepting the funding to undertake the study, Freeman sensed

possible difficulties. He attributed these to widespread adherence to the opinion prevalent among Australian rehabilitation practitioners that sensory input to comatose patients should be minimised. This opinion held not only that it was not helpful, but also that it might disadvantage a patient. Freeman recalled:

Stimulation of the person in coma was diametrically opposed to the thinking prevailing at that time with regard to the treatment of brain injury, but it was obvious to me that providing an input to the comatose patient through vision, hearing and touch, as long as it was kept within normal sensations, could not be dangerous.

Reinforcing opposition to the use of stimulation, concerns existed among many professionals about allowing (non-professional) family members to provide that stimulation. As will be apparent from earlier chapters, especially the patients' stories, Freeman's experiences had convinced him that assisting and/or detecting returning consciousness could be facilitated with assistance from family members at the earliest possible stage. He found that this was not generally accepted:

The head of a department at one hospital was quoted as saying, 'You might as well hang a bunch of bananas at the end of the bed. It would have the same effect as this coma arousal!' I thought that remark was hardly a scientific approach to the imperative of finding new ways to solve a major problem!

The 'banana' remedy proved not to be an isolated incident, as Freeman soon realised. Doctors who would have clinical responsibility for patients admitted to the trial were frequently unwilling to monitor their progress on a regular basis. Some hospital staff expressed anxiety that the trial would attract premature and unwelcome media attention. Access to patients was not always forthcoming. Notwithstanding these impediments, a financial solution, even if only temporary, was at hand. Acceptance by the hospital of the study was settled when the GIO offered to donate \$20 000, which the hospital needed for the purchase of equipment unrelated to the study.

Setting up the feasibility study

By the end of 1983, the protocol had been scrutinised and passed by the Ethics and Research Committee of the Westmead Hospital and the GIO decided to fund a feasibility study on coma arousal at the hospital as a preliminary to a full-scale exercise. Freeman anticipated some difficulties in mounting the trial because of the number of different hospital departments whose cooperation would be essential. While the research protocol for administration of therapy to patients

was thorough, there were no clear, existing guidelines outlining the method by which the research could be integrated with the normal functioning of the hospital. Apart from difficulties peculiar to the specific trial, there were probably some general obstacles that may have arisen with any large trial in a hospital unaccustomed to trials. Freeman recalls that little effort was made within the hospital to integrate the trial requirements into a number of different departments.

The feasibility study was intended to be the prelude for a full-scale investigation of Freeman's procedures, provided it appeared to support his contention that there were obvious gains in the use of coma arousal. He anticipated some management difficulties:

Whilst arousal procedures had previously been implemented intuitively and informally by some families in the hospital or the patient's home by laypersons (not hospital employees), it was considered that they could potentially be disruptive for the care of patients, both those in the study and others coincidentally located close to them.

The aims of the feasibility study were

1. to determine if coma arousal could be carried out in the wards of a general hospital
2. to find out if the relatives of patients with brain injury could provide the arousal program
3. to determine whether, on the basis of probability, there was some advantage to be gained for the patients.

Once the go-ahead for the study had been obtained, it was necessary to recruit the best available personnel to undertake the dual function of supervising the programs and maintaining good rapport with the ward staff. Freeman explained the basis for his decision as follows:

It was necessary to select a team leader. The choice was a nurse, physiotherapist, occupational therapist or social worker. I chose a nurse because, in my experience, the nurse is multi-skilled while the other disciplines tend to specialise in one area. The nursing professionals are generally competent when dealing with a mess. If the patient vomits or defecates or passes urine, the nurse is not fazed but will clean the patient and continue with the work. The other professionals will call for a nurse to remedy the situation. I also thought that it was important for the therapist to be able to touch the patient and this excluded a social worker.

In the event, he appointed a nurse with experience of neurosurgery wards who was highly recommended by the hospital director of nursing. She was a very practical nurse, with a great capacity for hard work, the ability to understand the objectives of the research, and to apply the research in a practical working situation. She established excellent rapport with relatives. Having once made up her mind, she was committed to her way of carrying out the therapy unless there were good reasons to change. This determination on her part ensured a standard of high quality for both the patients and the families.

Freeman was soon to become aware of the difficulties that were likely to arise when management that had empirically been found to benefit a particular group of patients was to be submitted to the scientific requirements of a randomised trial. Perhaps even sooner, he encountered the demarcations underlying the operation of any large hospital. He was aware of the potential for rivalry between different professional disciplines and for territorial disputes within hospitals. His choice of a nurse triggered such a dispute, with at least one of the occupational therapists vowing to get one of his own as team leader.

An issue that is of primary importance in consideration of any clinical trial is that of possible harm to the patient. The clinical trial at Westmead was most unusual in that it was necessary to consider not only risks of harm to participating patients but also the risks of adverse effects on their (equally participating) families. The possibility that families might be adversely affected by participation in a trial was one of which Freeman was well aware.

Some observations made at an early stage during the feasibility study, by two of the social workers in the research team, were relevant to assessing this risk. These observations concerned the adverse effects, already triggered by the event of the brain injury per se, on family members, antedating entry into the trial. Before any attempt to identify adverse consequences of participation in the trial could be undertaken, it was necessary to assess the residual impact of the event of the brain injury itself. Two social workers in the team evaluated the attitudes of families who were about to enter the trial. These were invariably heavily influenced by the event that had occasioned the brain injury to their family member. The social workers in the coma arousal team reported:

This event was often reported as the most tragic event in their lives. There were deep fears for their relative's survival, and for survival in what state; guilt for wondering whether their relative would be better off dead than the possibility of remaining in the vegetative state; guilt about their inability to stop the accident happening—'If only I had not let her go out with them'; bargaining—'Why not me, I've lived longer?'; disbelief, shock, numbness; bewilderment at a hospital and intensive care unit; fear and anger; days merging into one; terror when the phone rings at night; insomnia.

Commenting upon the ability of family members to cope with, and adjust to, the catastrophe that had befallen their family member, Freeman reflected:

Over the years I have found that generally the women in the family cope better than the men when their relative is in the early stages of brain injury. Men, especially those who have been in positions where they are required to take charge of situations, often suffer the typical stress reaction of 'fight or flight' because they suddenly feel powerless in the face of this terrible event that has befallen their family.

The practicality of conducting a trial in hospital wards without disrupting normal operations was affirmed as early as May 1984 by the Director of Nursing, who wrote to Freeman in the following terms:

I wish to advise, following discussions with the nursing staff, that the Coma Arousal Study has caused no disruption to the ward involved. The presence of family members has not interfered in any way with the nursing care and the only effect the study has had on the nursing staff has been advantageous. All of the staff are extremely interested in the program and the favourable responses to therapy from the patient.

By September 1984, another potential adverse consequence for participating families appeared not to be a cause for concern. The social workers who had previously evaluated the residual impact on families of the injury to the patients reported:

Families were unanimous that the program had been positive for them. The families believed the coma arousal team gave help to the patient as well as understanding to the families of the changes as the patient progressed. These things gave a sense of control. It took away their feelings of isolation and hopelessness and demystified the medical system. It removed many of their misconceptions and fears and unified the family with a common purpose and approach. The only criticism of the program was that it should have started earlier.

On the basis of the social workers' report, and of his personal observations, Freeman concluded that families could successfully participate in a trial:

The relatives acknowledged that sharing information with members of other families was beneficial because, knowing what it was like to be in this terrible predicament, they became a source of mutual support for each other, especially as they found it difficult to talk to the neurosurgeons, all of whom appeared to be too busy after the first week. This was understandable as the neurosurgeons were involved in life-saving surgery and were constantly in demand for the next acute admissions.

This was positive news, implying not only that families were unlikely to be adversely affected by their involvement in a program, but also that they gained encouragement from it. Another finding—namely, that families provided mutual support to each other—foreshadowed complications for implementing a randomised control trial. It hardly required penetrating insight to appreciate that daily communication between families would render it both morally and humanely indefensible to allow some families (in the ‘experimental’—that is, active—group) to participate in ‘hands-on’ involvement for their family members whilst others (the ‘control’, passive, group) were precluded from doing so.

By October 1984, it was possible to summarise some of the findings with the 12 patients in the feasibility study. One had died, three were at home, four were ready to go to the rehabilitation department, three were still on the program, one of whom was out of coma, and one other patient had not responded and had been taken off the program.

Alongside this positive preliminary finding, the feasibility study had exposed, as such studies are intended to do, some major potential complications inherent in upgrading to a full-scale trial. Freeman summarised these as:

- 1. There was no clinical document in use to assess the small but important changes in the early stages as the person aroused from coma.*
- 2. Drugs were sometimes used excessively or for too long. While necessary in the acute stage of treatment, many were given in high doses for weeks and months. Many of these drugs were highly sedative—enough to prevent the patient from waking.*
- 3. Tubes were left in the nose and into the trachea far longer than necessary.*

Freeman regarded this as totally unacceptable and a violation of the intimate personal space of the patient. He recalled:

The team was dismayed to find patients with their arms tied to the armrests on the chairs because they ‘tried to pull their tubes out’. If the patient tried to pull out the tubes, their body language implied that it was time to check if the tubes could be removed safely.

- 4. The physiotherapists sometimes applied plasters (plaster of Paris) similar to those that are used to treat people with broken bones. This was done in an attempt to prevent muscle contraction; but the problem of muscle contraction following a brain injury was totally different from that of broken bones and required a totally different method of treatment. The team wanted to provide a dynamic approach to the restoration of body function, but the plasters prevented the application of stimulation to the*

skin by touch or vibration or pressure or the application of ice. They also prevented any attempts to rotate, extend or flex the arm or leg through its normal range of movements.

Mounting a trial

Responding to the results of the feasibility study early in 1985, the GIO decided to offer funding for a more extensive study. This was to be a full-scale prospective study running over three years. GIO offered to provide \$1 million to Westmead and \$500 000 for development of a research protocol by the Commonwealth Institutes of Health in the University of Sydney. In the GIO letter offering this funding, it was specified that the money was to be used to establish a Coma Arousal Unit in Westmead Hospital, as described by Dr Freeman, in which treatment was to be provided under his supervision. GIO funds went directly to the finance section of the Westmead Hospital. Freeman was not involved in their disbursement.

The unit envisaged would be the first of its kind in a major Australian teaching hospital. There were some specialised units overseas, such as the Royal Hospital for Neurodisability in London, specifically concerned with coma arousal, but these were not located within general teaching hospitals. The GIO expressed the hope that the new unit would lead the way to a dynamic approach to the management of severe brain injury. The hospital accepted the GIO offer in February 1985, indicating that it was seeking to provide optimal physical facilities for the project within the constraints of resources available. The awarding of the grant was announced in the NSW Parliament and attracted considerable media attention.

Two weeks after the announcement of the grant, Freeman was speaking with an American friend, who remarked, somewhat prophetically, 'Ted, with money like that, your problems are now about to begin. You will have a battle to keep the research under your control.' True to forecast, the arrangement was to become completely unworkable before the end of the year.

The first problem to arise concerned the proposed structure of the trial. Epidemiological input from the School of Public Health at the university favoured a double-blind randomised control trial as the most rigorous design. In this type of trial, subjects who have 'matched' medical conditions are randomly allocated to one of two treatment groups. One group will receive the treatment regimen that the trial is intended to test. The other receives the alternative (control) treatment with which it is to be compared. In a double-blind trial,

neither the medical personnel responsible for treatment of the two groups nor others responsible for assessing the results should be aware of which group any patient is in.

Freeman expressed ethical concerns. The allocation of some patients to a control group, which meant in practice 'no treatment', was unacceptable to him. He expressed a preference for a trial in which each patient acted as his/her own control. He considered that

[w]here the patient outcome is acknowledged internationally to be disastrous, the withholding of such a non-invasive, atraumatic, non-surgical treatment was unwarranted. Today it is recognised that at times the epidemiological demands may jeopardise the optimum treatment of the patient, in which case most clinicians see the patient's treatment as taking absolute priority.

Two other envisaged features of the trial were at odds with Freeman's philosophy. How was the management of people who had 'emerged', consistently or intermittently, albeit remaining 'locked in' and unable to communicate, to be accommodated within any trial? How sound, ethically and scientifically, was the termination of stimulation procedures for the 'experimental' group after 10 weeks, irrespective of the condition of the subject at that time, in order to create a 'clean' universal cut-off point for data analysis? In relation to the second question, Freeman was informed by a hospital administrator in April 1985 that:

One major problem seems to be in defining when the patient comes out of coma and hence an endpoint to the need of coma arousal. My impression is that you now wish to continue a treatment program beyond the point of arousal from coma and into the rehabilitation phase of patient care. This is outside the scope of your present research proposal and is being seen to impinge on the responsibilities of other hospital staff.

Apparently, this difficulty was not directly concerned with requirements imposed by the trial but, rather, with the territorial instincts that are a common feature of healthcare communities. Continuation of a program was considered to trespass on the responsibilities of the hospital's rehabilitation practitioners. While, most importantly, premature termination could cut across patients' opportunities for later improvement, it could also preclude chances of the trial actually discovering something. The emerging complications were considered by hospital personnel, who then contacted Freeman:

It is clear that the program is beset with a number of problems and that it will not be possible to enter the next stage of the study, the controlled clinical trial, until these have been resolved. Much of our present problem results from the fact that the treatment conducted in

the feasibility study extended beyond your original brief. What was originally presented as coma arousal therapy has extended to prolonged intensive rehabilitation.

It was recorded above that a study undertaken by social workers in the 'coma arousal' team as part of the feasibility study had emphasised the beneficial manner in which patients' families interacted with each other to provide mutual support. This interaction, however, was identified in a report to the hospital's Research and Ethics Committee as a hazard to the research. This report warned that such interaction

would lead to a serious contamination of the treatment and control groups because of the fact that relatives often spend long times in the hospital in a highly emotional state ... There is considerable interchange between the different sets of relatives while they are waiting at this hospital and given the situation and the fact that they are seeking information about possibilities of improvement from any source possible, it is impossible to stop leakage of the treatment procedures.

'Contamination' was an unfortunate choice of terms, perhaps unintentionally disclosing where the balance between subject welfare and research needs lay. It indicated quite unequivocally where the priorities of the author(s) of the report to the Research and Ethics Committee lay. A further unfortunate, albeit revealing, choice of vocabulary appeared in correspondence, in this instance, from hospital personnel to the university. A senior doctor wrote, on 16 May 1985, concerning 'the firm opinion that this study cannot be allowed to proceed unless both control and treated patients are from Westmead Hospital'.

If this were not done, he was of the view that 'no self respecting editor [of a journal] would allow a study with such a basic design fault to be published'.

This opinion inevitably raises the issue of for *whose* benefit the trial was to be undertaken. Potential conflict between the personal interests of the participating subjects (that is, patients) and the career aspirations of the researchers may arise in any study and should, it seems reasonable to argue, invariably be resolved in favour of the former. Freeman's account of the media presentation of the awarding of the GIO grant suggested that considerable kudos was attached to the receipt of such a large grant on the part of both recipient institutions.

As a means of avoiding 'contamination' because of contact between families, it was suggested by some of the Westmead practitioners that 'control' (passive) patients be at that hospital while the trial (active) group should be located at Parramatta Hospital. Another suggested approach intended to assist with undertaking the trial entailed the replacement of the control group with data drawn from an existing source, such as the US National Coma Data Bank.

Accompanying this alternative was a proposal to replace family members with professional therapists whose input could be more readily standardised, perhaps assisting the process of outcome measurement. This proposal indicated a failure to grasp the manner in which a family's intimate knowledge of their patient could equip its ability to tailor procedures to provide the best chances of success for that individual. This is clearly a situation in which one size does not fit all. Not unexpectedly, Freeman disagreed forcefully with the proposal to use professional therapists. As he argued:

It was my belief that the relatives had so much to offer the patient because they knew the patient intimately and were highly motivated to do the work. 'No-one is more motivated than me to get my child better,' exclaimed one father when I asked him if the demands of the therapy on him were too great.

Freeman's intuitive belief that family participation in programs is highly desirable receives considerable support from the recent electrical studies of brain function described in Chapter 4. For instance, these studies demonstrated that, when an investigator spoke about people and topics with personal relevance to the unconscious patient, unique electrical responses could be detected.

Reinforcing the hospital's arguments that family participation introduced risks of 'contamination' and of variability in the way in which different families implemented stimulation procedures, it was also contended that prolonged involvement could have adverse effects on family members. Similar arguments suggesting that stimulation procedures risked introducing 'false hope' were regularly raised, independently of the trial, by those critical of Freeman's approach. This was at odds with the observations of the social workers in the team noted above, but in response to the objection Freeman suggested to the hospital management that an independent examination of the effects on families of participation in arousal programs should be undertaken. His request did not receive any response in the rapidly deteriorating interactions with hospital authorities.

Whereas Westmead was unresponsive to Freeman's suggestion of examination of the possible effects of the trial on families, in 1986, after the project at Westmead had been discontinued, the GIO proceeded to fund an independent study by the Unit for Rehabilitation Studies at Macquarie University.¹ A few extracts from the resulting report are provided below. They represent an assessment, from the perspective of families, that was consistent with the thrust of the small questionnaire undertaken by Freeman (mentioned in Chapter 3) and of the descriptions, noted above, of the project's social workers.

1 Cecilia Gray, Tony J. Koop & Trevor Parmenter (1986) *Coma Care Family Survey*. Report commissioned by the Government Insurance Office of New South Wales.

One conclusion contained in the Macquarie unit's report in relation to the participating families was: 'They felt that the Coma Care staff explained fully the nature of this experimental program to them giving them no false hopes but a great deal of support, encouragement and understanding.'

The Macquarie researchers considered that participation had brought positive psychological benefits for families. They reported:

The involvement in the Coma Arousal Program and thus contributing to the care of the patient, in the vast majority of cases, helped to relieve many of the feelings of frustration and of helplessness experienced by close relatives and friends.

Close involvement of families in programs was seen as assisting them to cope: 'This provided emotional support mitigating in part the destructive effects the patient's accident has upon their lives.' Perhaps the most revealing indication of families' attitudes towards participation in a program was elicited in response to the researchers' questioning about whether they would recommend participation to other families. They commented in the report on the response to this question as follows:

The fact that 97% of respondents answered 'yes' to the question of whether they would advise other people to be involved in a program such as this one seems to indicate that not only was it deemed worth it for the patient but also for themselves (3% didn't respond to the question).

Of 32 respondents who were asked whether they felt like withdrawing from the program, all but one answered 'no' or, more emphatically, 'never'. All respondents to the question of whether the Coma Care Team was a support answered emphatically in the affirmative: 'Extremely supportive. He wasn't just a patient, he was an identity.'

Although the primary purpose of the survey was to assess the impact of the program's staff on families, responses provided a wider perspective. One conclusion drawn in the report was:

Overall there was a fairly even mixture of positive and negative reactions by respondents to hospital staff, nursing staff, physiotherapists, occupational therapists, social workers and the doctors in intensive care. However, while there was unanimous agreement about the excellent quality of the Coma Care staff's treatment and support, the vast majority reported negative reactions to and relationships with neurosurgeons.

By August 1985, an approach from a senior hospital administrator to the GIO sought to retain the funding for the project while effectively sidelining

Ted Freeman from the research. This communication asserted in support of continuing the trial in this way that '[n]o-one has yet put coma arousal to the test and it should be done before demand rises to such an extent that it will be impossible to get patients in a "no treatment" condition'.

In another unfortunate, but revealing, choice of vocabulary, the writer equated the 'control' group with a 'no treatment' one. Concern was also expressed in this letter that media attention might increase demand for entry to the 'treatment' group.

A report to the GIO Board on 30 September 1985 from Kevin Beckton, the GIO person responsible for oversight of the trial, recommended that the funding be removed from the hospital. Beckton, who had by this time been closely involved with the aims of the trial from its earliest stage, supported his recommendation on two principal grounds. He regarded the hospital's proposal to remove Freeman from direct involvement as completely unacceptable. Second, he did not accept the hospital management's change in attitude to limit the trial duration to 10 weeks:

[T]here is no doubt that the recommended duration of therapy will be 10 weeks or thereabouts, as this is the item upon which the differences of opinion most clearly have manifested themselves. Both Freeman and I agree ten weeks was inadequate and that the greatest improvements occurred after this period. I draw your attention to the fact that the proposal contained in the letter from Westmead Administration of 21st August 1985 does not attack the continuation of the scheme on the basis of harm to the patient but suggests relatives are at risk. As most of the patients have been obtained from the human scrap heap any change is probably an improvement.

The account of the preparations for the study does not mention the process that was envisaged in gaining informed consent for participation in the double-blind randomised control trial. Clearly, consent would necessarily have to be obtained from families as representatives of the patients. Equally clearly, this process would necessitate the provision to the families of an information document for a study that was to be undertaken under the auspices of two institutions of high standing in the Sydney community. An essential part of such an information sheet for a control trial would be the disclosure that only half of the patients were to be entered in a 'Freeman program'. Given that all of the patients had entered the study *because of* the regard in which they held the man and his philosophy, it beggars credulity to anticipate that *any* of the families would have opted to enter such a lottery had they been adequately informed.

Consistent with the commitment of those on Freeman's team to assisting the patients with whom they would be working, they regarded withholding of the trial therapy from any patient as unthinkable. On the other hand, the hospital clinicians envisaged having a concurrent control group. The information sheet for families of potential participants was prepared by the team and did not include any mention of a control or non-treatment group.

Apart from the unacceptability of a trial in which their family member had a 50 per cent chance of missing out on attempts at arousal (that is, the 'random' aspect of the trial), the concept of the trial being 'double blind' should have been perceived from the beginning to be entirely fatuous. An essential component of double blinding is that *neither* the doctors responsible for supervising the treatment modality under test and its control *nor* those (others) responsible for measuring the responses of the two groups should be aware of which patients were in which group. Whilst this double-blinding requirement may be readily achievable when the trial sets out to compare two pharmaceutical preparations, it becomes a nonsense to claim that the supervising doctors can remain blinded when the experimental group is to receive intensive stimulation. Supervising doctors may be suitably blinded when each group is to receive an unmarked pill, but not when a team of therapists is hovering in the background.

With hindsight, it appears almost inevitable that the Westmead trial would encounter major obstacles. There was hostility towards Freeman's ideas, and perhaps towards him personally, from some of the hospital's medical staff. There was apparently dissension within the hospital over which professional specialties should be responsible for trial conduct, and this disagreement intruded into its planning. The substantial financial support, which may have been larger than any research funding that the hospital administration had been required to manage to that time, could have fuelled some of these difficulties inherent in the trial. Leaving 'Westmead-specific' issues to the side for the moment, it is worth considering, at the distance of a quarter-century, some of the innate difficulties in clinical trials, in any location, which the coma arousal trial exemplified.

Clinical trials: Ethical considerations

The Cochrane Collaboration is an organisation established to evaluate clinical trials of drugs and treatment procedures. Its goal is to facilitate the introduction and retention in practice of treatments the scientific basis for which has been validated in the course of clinical trials. It does not undertake trials itself but conducts comprehensive searches of medical databases to assess the scientific

and statistical values of published results and then to collate those which attain the required standard and to subject the aggregated data from the acceptable trials to further analysis.

In 2009, the Cochrane Library published a review entitled *Sensory Stimulation for Brain Injured Individuals in Coma or Vegetative State*.² The authors identified 25 published articles on this subject, but only three of these satisfied the Cochrane criteria of being randomised, double-blind trials. The assessors expressed considerable reservations even about these three. When compared with 'standard' double-blind randomised trials of new drugs, they did not measure up well.

It has always been a requirement that the information provided to people who are considering entry to a clinical trial clearly indicates that they may not personally benefit from participation. The primary goal of a clinical trial has historically been to establish whether the new treatment that is to be examined is superior to existing options and, consequently, the envisaged beneficiaries will be *other* people affected by the condition for which the new treatment is a potential remedy. More recently, research ethics committees have been required to consider trials the declared aim of which has not been to demonstrate *superiority* but only to establish *non-inferiority* of the new therapy when compared with existing ones. Committees are increasingly required to distinguish genuine trials from marketing exercises.

The largest trials are generally concerned with testing the efficacy of a pharmacological agent and hence the pharmaceutical industry is numerically by far the largest sponsor of trials. This has now developed to the extent where double-blind randomised control trials have become a major income-generating industry in themselves, with their sponsoring corporations being the major beneficiaries.

A 2011 Australian Government publication was titled *Clinically Competitive: Boosting the Business of Clinical Trials in Australia*. At its launch, the Ministers for Health and Ageing and for Innovation, Industry, Science and Research were quite explicit in emphasising the commercial benefits of trials for participating institutions: 'It is an industry that brings hundreds of millions of dollars annually into Australia's health system.'³ Subjects participating in a trial are the heroes. Apart from potential benefits for society at large, the major beneficiaries may include the manufacturers of tested products and the medical personnel

2 Francesco F. L. Lombardi, Mariangela Taricco, Antonio de Tanti, Elena Talaro & Alessandro Liberari (2009) *Sensory Stimulation for Brain Injured Individuals in Coma or Vegetative State (Review)*. The Cochrane Collaboration. John Wiley & Sons Ltd, London.

3 Clinical Trials Action Group Report (2011) *Clinically Competitive: Boosting the Business of Clinical trials in Australia*. Ministers' foreword. Australian Government Publishing Office, Canberra.

undertaking the trial for the manufacturers. Seen in this light, the opportunity to participate in the randomised control trial of coma arousal may be considered as less of a notable win for comatose patients than for those professionals conducting the trial.

Potential exists for any trial to prejudice the clinical care of an individual patient. In designing any trial, this risk should be identified and then minimised. A survey of 500 Australian physicians and paediatricians published in 2005 concluded that '[r]elationships with patients were valued over research accomplishments and most felt that their patients' right to select treatment took precedence over advancing knowledge'.⁴ It was inferred that the doctors surveyed were generally clinician oriented rather than research oriented. Judging from the conditions that were introduced into the proposed trial during the preliminary discussions, the balance between the entitlements of the comatose Westmead group as *patients* and their liabilities as *research subjects* does not appear to have been a major consideration in planning for application of the substantial GIO grant.

Whilst the issue of striking a fair balance between the interests of patients and subjects has not always been thoroughly considered, it is interesting to observe current developments in trials of new drugs. An array of the highest-profile US oncologists has divided in arguing about this balance as it relates to trialling PLX 4032, a new agent that appears to offer the possibility of significant improvement in the control of disseminated melanoma tumours. Whilst this new agent is currently the subject of a nationwide random controlled trial, many clinicians have asserted that patients who have been 'randomised' to serve as controls and consequently denied treatment with it should have access to the drug. The counterargument runs: 'Without the hard proof the trials can provide, doctors are left to prescribe unsubstantiated hope—and an overstretched health service is left to pay for it.'⁵

The common feature of the 'Westmead' trial and the PLX 4032 one is the dubious ethical acceptability of exclusion of participants in the control group from treatment that may potentially be beneficial for them. When a trial is intended to establish whether a new treatment is superior to an established procedure for which some level of efficacy has already been demonstrated, this concern about exclusion can be much less than is the case in a situation in which the control is, realistically, 'no treatment' or patently futile treatment. When an

4 Patrina H. Y. Caldwell, Jonathan C. Craig & Phyllis N. Butow (2005) Barriers to Australian physicians' and paediatricians' involvement in randomised control trials. *Medical Journal of Australia*, 182, 59.

5 Amy Hermon (2010) New drugs stir debate on basic rules of clinical trials. *The New York Times*, 19 September.

established treatment offering some benefit is available, the ethical concern may relate more to any possibility of adverse effects of the new treatment on subjects randomised to the experimental group.

Reverting to the 1985 trial of coma arousal therapy, a number of other issues deserve specific consideration. The assumption, implicit in any comparative trial, that each of the subjects randomised between the two groups has an equivalent pathology, remains highly questionable. Clinical similarity between two patients each of whom has sustained a brain injury can certainly not be presumed automatically to equate with identity of structural damage.

To illustrate the nature of 'treatment' on offer to the control group, it will suffice to direct attention to the description of patient management at Weemala in an earlier chapter. Trials in which treatment is withheld from, or not available to, the control group have a disreputable history. Examples of withholding treatment that was considered to have some value in order to observe the consequences have attained permanence in the bioethical literature. Such examples include the withholding of the (admittedly imperfect) treatment then available from patients with primary-stage syphilis in Tuskegee, USA, and of minor prophylactic surgery from women with early stage cervical cancer in Auckland.⁶

The locating of a mid-1990s trial of a putatively improved treatment for neonatal AIDS in a Third-World location in which the available treatment was nil attracted much opprobrium (it was not permissible to mount such a trial capable of providing a statistically satisfactory outcome in developed nations where affordable, effective treatment was available).

Perhaps rather simplistically, the issue of whether the Westmead control group was a non-treatment group raises the question of what is treatment? In a rather revealing comment, a letter to the GIO from the epidemiologist participating in the trial (who, it was proposed, would replace Freeman as chief investigator), which sought to preserve the funding, minus Freeman, described the 'control' group as the 'no treatment group'.

One communication from the epidemiologist pressed the case for inclusion of the 'no treatment' group on the basis that media publicity about 'coma arousal' could make it impossible in the future to recruit starters for a trial in which 50 per cent of patients would effectively remain untreated. This might be read as an expedient call to undertake a trial before the provision of adequate information to participating families about what was involved would, quite reasonably, inhibit recruitment. Whilst one could acknowledge that this may have been

6 Phillida Bunkle (1988) *Second Opinion: The Politics of Women's Health in New Zealand*. Oxford University Press, Auckland.

epidemiologically sound, it would be difficult to provide the same unqualified reassurance about its ethical soundness. A ‘worst case’ interpretation could read this concern as acknowledging that ignorance of the details, among those giving consent for entry of patients into the trial, was a prerequisite.

Media coverage of any medical issue frequently tends to go ‘over the top’, and the perceptions of those responsible for making decisions about entry into a trial may have been distorted as a result. On the other hand, the decision-makers considering entry of a relative into any trial are entitled to be fully informed about every aspect of that trial which could affect their decision. As a minimum requirement, some reasonable attempt to balance epidemiological and ethical imperatives should have been undertaken.

Historically, the provision of basic nursing care with the administration of food and water would not generally have been designated as ‘treatment’. In the past two decades, however, considerable efforts have been made to reclassify the administration of food and water to patients in prolonged coma as ‘treatment’, with the explicit intent of thereby reclassifying it as something that could be withheld. Advocates of this interpretation have included the US President’s Commission. A 1983 paper from this august group deemed the expression ‘life-sustaining treatment’ as extending from the use of ventilators to ‘home physical therapy, nursing support for activities of daily living and special feeding procedures’.⁷ The acknowledged purpose of this new classification was to achieve legal sanction for the withdrawal of hydration and nutrition.

Clinical trials of new therapies have two main roles. Almost all attention has so far been directed to establishing efficacy of a new therapy. The second role—probably more important—is that of confirming the safety of the new treatment. It is difficult to postulate that coma arousal procedures as espoused by Freeman would be dangerous for the patient and the absence from the scientific literature of research reports of harm to patients supports this conclusion. Nevertheless, it was claimed at the time that families of patients might be psychologically harmed, a suggestion which the Macquarie University study, described above, effectively refuted.

In the absence of any documented evidence of harm to comatose individuals from heightened contact with family members, it seems equally unlikely that comatose patients would be harmed by increased family contact. In short, the risk of harm consequent upon receiving the ‘experimental’ protocol appears to have been nil.

⁷ President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioural Research (1983) *Deciding to Forgo Life-sustaining Treatment: A Report on the Ethical, Medical and Legal Issues in Treatment Decisions*. Government Printing Office, Washington, DC.

In describing the recent dispute over the US randomised control trial of melanoma therapy, the very large costs to the healthcare system of allowing widespread use of PLX 4032 as an unproven drug were cited. In the case of coma arousal therapy, it is difficult to foresee any significant new impositions on the healthcare budget if the procedure of coma arousal, as practised by families, became widespread, as the labour input would be voluntary. While this should effectively disable arguments against considering the introduction of stimulation procedures into coma arousal and ongoing rehabilitation on the grounds of imposing additional costs on 'the system', it certainly should not be taken as excusing that system from acknowledging voluntary support by reasonable budgetary compensation.

Whilst the healthcare budget is spared if a family opts for domiciliary rehabilitation, this will invariably be at the expense of the family budget. The patient stories recounted above include instances in which the primary carer was a wife, a husband, a mother or a father. Frequently, both of the last two were heavily committed. Apart from the current income forgone, the future re-employment prospects of family members who leave the workforce, either partially or completely, may be adversely affected. Women may be more adversely affected in this respect if the family decides that a man is earning a higher income, which it is preferable to retain.

Assuming, at least for the purpose of comparing costs, that a decent level of care were to be provided to those patients who were being placed in aged care, terminal, or whatever other description is applied, facilities it is difficult to see what extra costs would be imposed by caring for patients in a situation that permitted ongoing access by relatives involved in coma arousal programs.

The imposition of substantial costs on a community as a result of adoption of an untested therapy can be a valid reason for withholding an expensive new agent from widespread use before its efficacy has been established. It is, however, difficult to dress this argument up as a reason for requiring a randomised control trial before endorsing attempts by a patient's relatives to adopt an arousal program.

An economic rationalist might claim that participation in such a program was diverting resources away from productive use in the community. Productive use could occur if the family was free to make other contributions. If anyone were prepared seriously to present this argument, I believe that it might serve primarily to highlight the similarities between economic rationalism and coma.

A cynic might query whether opportunities for career advancement were coming into play as an outcome of the Westmead trial. The brief discussion above of the potential conflict between care of one's patient and inclusion of that

patient in a trial may be relevant. It is worth noting that the majority of articles describing attempts to test the value of coma arousal programs retrieved in the Cochrane review *neither* met the criteria required at Westmead *nor* failed to be accepted for publication by reputable journals.

Passing from objections based on absence of randomisation and possible risks of a non-randomised trial without a simultaneous ‘control’ group, further objections were raised to the involvement of families in programs. The basis for these was that it would not be feasible to certify that all families were providing identical input. Resistance by some hospital doctors to family participation indicates a failure to recognise that Freeman’s successes would have usually been unachievable without family insights, as shown in Roger’s case in Chapter 2. Professional therapists complying with a generic protocol of stimulation would be unaware of such insights. It is similarly clear that their likely stimulatory impact, *as persons*, on the patients would be less than that of family members.

The notions of some hospital personnel about assessment of outcomes (namely, measurement of these after 10 weeks of a program) not only finally convinced the GIO to withdraw funding, but also indicated an ignorance of Freeman’s earlier observations that led to the awarding of that grant. The outcomes of coma arousal programs clearly did not lend themselves to a school examination-type measurement indicating either ‘pass’ or ‘fail’. Description in an earlier chapter of the ‘soft signs’ that were initially present intermittently and might only then be amenable to elicitation in familiar/familial surroundings should have alerted everyone to the need to tailor assessments individually and to repeat them. A school examination cannot be repeatedly undertaken in order to ensure that a true assessment of a candidate’s ability is obtained: examination of a putatively comatose patient *must* be repeated to ensure its validity.

If the commitment of a group of comatose patients to a ‘control’/non-treatment group is not acceptable, how could some assessment of the value of arousal programs have been achieved? One very practical suggestion, noted in Chapter 3, from an individual who had himself made a recovery from brain injury was that of a comparison with patients who had been ‘warehoused’ in terminal-care facilities following a brain injury. Such a comparison would, almost certainly, be politically unacceptable to any health minister.

An alternative, more politically palatable response could be to undertake a comparison of outcomes between two groups of patients, as closely matched as possible. One group would be people entered into active ‘arousal’ programs. Comparison could be with historical groups or with other contemporary groups receiving more conventional treatment. The discontinuation of the International Coma Data Bank removed one possibility for doing this.

A potentially viable alternative, suggested in 1995 by a medical practitioner who was a member of the NSW Parliament, was based on comparison of 'Freeman' patients with others entered into the State-wide system of Brain Injury Rehabilitation Program (BIRP) units, which operated in compliance with the accepted 'best practice' rehabilitation strategies.

The BIRP units dated from the late 1980s and were funded by the NSW Government through the Motor Accident Authority. Of 11 BIRP units established at that time, three were in the Sydney region and eight were located in country districts. In the mid 1990s, some academic rehabilitation specialists, in the course of developing an application for funding of a trial of coma arousal, considered the possibility of using outcome data from the BIRP system. At this time, it was discovered that this very well-funded system had not undertaken any study of the outcomes of its procedures. Furthermore, as will be mentioned in Chapter 7, there was trenchant opposition from BIRP practitioners to any involvement in such a comparative exercise. Their resistance to participation may have had a basis similar to their refusal to attend any meeting at which Freeman was present.

Another theoretically possible control group could have been derived from a coma register, had one existed. Freeman obtained agreement, in principle, to establish a register from a NSW health minister in the early 2000s but nothing eventuated.

The dispute between the GIO and the hospital, at the time when agreement was breaking down, over the duration of inclusion of any patient in the trial has been described above. It serves to highlight something that is a feature of any trial—namely, the nature of the assessment process that is to be utilised to generate the trial outcome data. This can vary considerably depending on what is being trialled.

Endpoints to a trial may be very clear—for example, death or survival. In the case of the Westmead trial, measurement of outcomes could, predictably, be seen not to be clear-cut. Neither the outcome for an individual patient nor the outcome of the aggregated patient group could be simply marked as pass or fail. The reasons for this difference relate to the gradual and often inconsistent course of emergence from coma, as discussed in Chapter 4.

Freeman's 'soft signs' might only be detectable intermittently at an early stage. They might only be observed separated in timing from the observer's attempt to elicit them by an interval sufficient to lead to a failure to recognise them as a response. Most importantly, they might, at least initially, only be demonstrable in the presence of family members. All of these requirements and limitations could easily be taken to invalidate observations made when adjusting for them.

It has been emphasised repeatedly that Freeman's success in assisting people was attributable to his recognition that communication was frequently dependent on the intermediation of family members. This applied equally whether the task was determining if a new patient was genuinely uncommunicative, deciding on the implementation of a stimulatory program or assessing whether a patient was emerging from coma after participating in a trial.

Conclusion

As with many of the events involving the management of people who remain unconscious for prolonged periods after brain injury, the history of this attempt to conduct a trial raises some general but crucial issues unrelated to brain injury.

It is axiomatic that, before its endorsement as an acceptable therapeutic response, any new treatment option should be trialled and shown to be at least as safe and effective as the forms of therapy already available. This entails the comparison of the new, 'experimental' therapy with the best existing 'control' therapy. That said, the specific form of trial to be adopted in any instance should be determined by the nature of that treatment. The epidemiological input to trial Freeman's approach to coma arousal recommended a double-blind randomised control format.

One feature of this format is that neither the practitioners responsible for the administration of the two types of therapy nor those undertaking the assessment of outcomes is aware of whether any participating subject is receiving the new therapy or the control one. The nature of the control will be determined by the types of therapies that already exist, but the control group is entitled to receive the best that is available. The randomisation referred to in the description of the trial refers to the allocation of entering subjects to either experimental or control groups. It is essential that entering subjects, or their representatives, consent to their random allocation to one of the groups.

It should have been evident from the outset of planning for the trial that this format was not compatible with the new form of therapy to be examined. There were both practical and ethical reasons for this. At a practical level, it would be impossible for either the supervising or the assessing medical practitioner to remain 'blinded' about which group of patients is receiving intensive stimulation from family members and which is receiving none. In view of the implicit wish of families requesting assistance from Freeman to receive this, it is not reasonable that any family, when adequately informed about the randomisation process, would be willing to risk being allocated to the control group. Most of the patients who were candidates for the trial had already experienced the 'control' process and found it to be inadequate. If genuinely informed consent—an ethical essential—had been required, there would have been no starters.

Passing from the issues of 'blinding' and informed consent that are applicable to any trial, there were some features peculiar to the proposed trial that would be incompatible with administration of therapy to the experimental group and measurement of outcomes in either group. An essential feature of Freeman's approach was the recruitment of people previously known to a patient to provide stimulation; however, if uniform stimulation was to be administered to all patients in the experimental group, the trial plan required that it be administered by paramedical personnel, an arrangement that would eliminate the availability of stimuli with personal relevance to the patient. In relation to measurement of outcomes, it was clear that early signs of awakening were commonly inconsistent ('soft signs'), and this would not readily slot into any reproducible scheme of recording.

All in all, the double-blind, randomised control trial format, whilst legitimately the backbone of any trial of a new drug, should have been seen to be quite inapplicable to a trial of coma arousal. One size, clearly, does not fit all. This incompatibility has been demonstrated by the absence of any trial that has fully met the criteria of the Cochrane study for this trial format.

Additional impediments, if any were needed, to the trial being accomplished were the scepticism of some of the personnel involved, the collision between determination of when a patient exited the trial to enter the hospital's rehabilitation program and the lure of the relatively large budget of the trial.

Leaving aside consideration of the format of the trial, some of its features would have been difficult to accommodate within the general aims of trials. Any trial is required to determine that the new therapy under test is both at least as safe as established alternatives and at least as effective as the alternatives (but, preferably, better). In practice, the first of these requirements would usually imply that the 'experimental' group could be at a disadvantage, but, in the proposed trial, it was much more likely that the control group who were receiving the established therapy would be disadvantaged by deprivation of access to the new therapy. The reason for this was that the established form of therapy was acknowledged by hospital personnel to be effectively 'no treatment'.

Apart from the impediments considered above, the events during the lead-up to implementation of the trial raised some disturbing questions about potential conflicts of interest between the dual role of participating doctors as clinicians and as researchers. On some occasions, it appeared that, when dealing with experimental subjects, the research aspirations of the clinicians with this dual responsibility could be trumping their responsibilities to the same individuals as patients.