

Bioethics

ETHICS IN CLINICAL DRUG TRIAL RESEARCH IN PRIVATE PRACTICE

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Abstract: **Introduction:** Private clinics and clinicians have been involved in clinical drug trials for approximately two decades. This paper reviews the ethical consideration inherent in this process. **Methods:** Involvement of a single community based, private, Australian neurological clinic in the conduct of trials was audited. Changes in ethical considerations were analysed. **Results:** The clinic previously audited its clinical trial involvement, starting with pharmaceutical company orchestrated trials. These were vetted by hospital based ethics committees (ECs) which then refused to review private research. A private EC accommodating NH & MRC standards was formed to assess private research. Indemnity concerns forced return to institutional ECs with government guaranteed indemnification.

Trials evolved to investigator initiated, company sponsored studies thence a company asking the clinic to devise, sponsor and manage a trial. The latter relegated trial co-ordination to the clinic which would control publication thereby creating new ethical standards. **Discussion:** Private practice trial involvement evolved from reluctant inclusion to a pivotal role in privately sponsored studies. Access to ECs is government endorsed and publication is independent for investigator-sponsored trials. There has been modification of standard operating procedures and enhanced ethical standards.

Keywords: Drug trial research; ethics committees; research codes of conduct; private practice

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INTRODUCTION

Private clinics and clinicians have been involved in clinical drug trials for approximately two decades^{1,2}. The inclusion of private practice into mainstream clinical research meant that community based doctors, who were so involved, could offer their patients additional treatment options which were not yet available to the wider community. It also meant that pharmaceutical companies could increase the denominator population from which the trial sample may be selected. This appeared to benefit everyone involved but it also generated questions of ethics which needed to be addressed and for which answers needed to be found^{3,4}.

The Royal Australasian College of Physicians (RACP) has developed ethical guidelines to cover the relationship between medical practitioners, researchers and industry^(5,6). These guidelines reflect upon potential 'conflict of interest' and advocate adherence to voluntary codes of conduct with individuals being responsible for their actions after giving due consideration to the evidence, the arguments and the issues relevant to each individual circumstance. With regards to research, the RACP advocated that dualities that emerge should be addressed on a case by case basis⁵. Publication of result findings should be the responsibility of the investigators and not the sole priority of the sponsoring company with both positive and negative results being published. It was recognised that "...industry...decides if, where and when a study is going to be published, All too often , a physician involved in such industry-funded studies does not have much say in the design of the study..."⁶.

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1. Beran, R. G. & Tilley, M. I., "Clinical drug trials of anti-epileptic drugs performed in private practice setting". *Epilepsia* 35 : 103-106, 1994
 2. Beran, R. G. & Beran, M. E., "Conduct of trials in private clinical practice". *Epilepsia* 4(7) :875-879, 2000
 3. Beran, R. G., "The ethics of clinical research and the conduct of clinical drug trials : International comparisons and codes of conduct"
Med Law 19(3) : 501-21, 2000
 4. Beran, R. G. (Ed), *Epilepsy : A question of ethics*. Yotzmot, Haifa 2002
 5. Royal Australasian College of Physicians (Komesaroff P. Chair), *Ethical guidelines for relationships involving medical practitioners, researchers and industry*. 3rd Edition, RACP, Sydney 2005 (www.racp.edu.au/public/news/ethics.htm)
 6. Bruce A. "Preventing another Vioxx: physicians, clinical trials and pharmaceutical industry". *RACP News* 24 (5):8-10, 2005

The RACP acknowledged the importance of physician involvement in clinical research recognising that it is these same physicians who "...are going to be using the medicine and using them first..."⁶. Concurrent with this philosophy was the need to ensure "...that clinical trials are worthwhile, well designed and managed and of the highest ethical standard ..."⁶.

The pharmaceutical industry has also established its own codes of conduct^{7, 8} which supplement those of the RACP and which argue strongly against imposing undue influence on the conduct and payment for clinical trials, in accordance with Good Clinical Research Practice as published by the Therapeutic Goods Administration of Australia.

What follows in this paper is an overview and review of these ethical considerations as they have emerged during the evolutionary process as is relevant to a single community based private neurological practice based in Sydney, Australia.

METHODS

The involvement of a single community based, private, Australian neurological clinic which has a long experience in the conduct of clinical trials, was audited and reviewed. The evolution of standard operating procedures were analysed from the inception of its involvement in clinical trials up until the present when the practice was invited to become the sponsor of one such trial which was a multi-centred, randomised, placebo-controlled study that was classed as investigator initiated.

The evolution of operating performance and mandated behaviour, adhering to

7. Pharmaceutical Society of Australia – *Policy – Code of Conduct*

(adapted from the Royal Pharmaceutical Society of Great Britain Code of Ethics) 22/12/05 (www.psa.org.au)

8. Medicines Australia – previously Australian Pharmaceutical Manufacturers Association Incorporated – *Code of Conduct*, 12th Ed. Sydney 1999 (with electronic updates Code of Conduct 14th Ed, 2002 at www.medicinesaustralia.com.au)

good clinical practice (GCP)⁹⁻¹¹ were analysed to determine how these affected the overall provision of healthcare, while at the same time accommodating the rigorous dictates of clinical research.

RESULTS

Initially the practice was invited to be a subordinate co-investigator with an interstate, tertiary referral, hospital-based clinic in the Queen Elizabeth Hospital, in Adelaide, South Australia. The Sydney clinic had to agree to be bound by the dictates of the Institutional Review Board (IRB) of that hospital. The chief investigator, in the Sydney clinic, was well-known to that IRB and his good fame and character had to be corroborated to the IRB by the senior clinical pharmacologist at the South Australian Hospital.

Similar assurances had to be provided to the pharmaceutical company which was the sponsor of the trial. At this time, in the evolution of multi-centre trials, particularly in Australia, the pharmaceutical company had never operated outside the boundaries of a tertiary research institution.

In the initial period of involvement in clinical trials, the supervision and co-ordination of trial procedures was an additional job description which was attached to a member of the existing clinic staff. One staff member was designated to co-ordinate trial activities with the bulk of trial responsibilities being acknowledged and accepted by the clinician involved. At this time, the sponsor had in-house research personnel who monitored trial conduct and

9. Committee for Proprietary Medicinal Products. *Guideline for good clinical practice*, ICH Harmonised tripartite guideline (originally approved 17 July 1996)

10. National Health & Medical Research Council, *National Statement on Ethical Conduct in Research Involving Humans*, Commonwealth of Australia, June 1999

11. World Medical Association Declaration of Health – *Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects*, Adopted by the 18th World Medical Assembly (WMA)

Helsinki, Finland, June 1964 and amended by the 29th WMA Tokyo, Japan, Oct 1975; 35th WMA, Venice, Italy, Oct 1983; 41st WMA, Hong Kong, Sept, 1989; 48th WMA, Somerset West, Republic of South Africa, Oct 1996; 52nd WMA, Edinburgh, Scotland, Oct 2000; Note: Clarification Para 29, Added by WMA, Washington, USA, 2002

source data were taken to be a combination of trial folders together with routine patient records.

As the procedures expanded there were trials being conducted in parallel with some blinded studies becoming open-label, long-term, safety and efficacy trials while other new trials were commencing. The practice could no longer rely on staff 'good will' and there was need to employ a dedicated trial co-ordinator who assumed greater responsibility for the day-to-day running of trials.

There was also a need to sequester trial conduct from routine clinical practice. A new identity, Epilepsy Research and Services, was formed which later evolved into Strategic Health Evaluators Pty Ltd. This new entity adopted independent staffing and accounting procedures to ensure that there would be no opportunity to confuse routine clinical conduct with trial dictated activities. This independence protected against charging the State Health Insurance Commission for visits mandated by trial protocol and for which trial sponsors provided recompense. All trial accounting became quarantined from other practice accounting.

Based upon conduct in earlier trials, the clinic was acknowledged in its own right which meant that it had to function independently of other sites which were also involved within any multi-centre trials in which the clinic participated. This meant that the clinic had to develop a rapport with its own IRB. Initially this was provided by one of the hospitals to which the chief investigator was attached. As the workload expanded and the sophistication for trial approval increased, the hospital based IRB Ethics Committee (EC) declined to assess further projects conducted within private practice, thereby necessitating the clinic to develop an alternative strategy.

Initially it was difficult to establish an alternative EC until the Epilepsy Association of New South Wales (EANSW) created a National Health and Medical Research Council (NH & MRC) approved and registered EC, which was prepared to evaluate research conducted within private practice. The constitution of the EC conformed and surpassed NH & MRC guidelines, including two members of the clergy, two lawyers, two researchers, two doctors and both male and female lay people under a chairperson who managed the administration of the EC but who did not vote so as to ensure the impartiality of the chair. When Disability Resources Incorporated (DRI) was separated from EANSW, the EC was transferred to DRI but its modus operandi was maintained as were the personnel involved. The independence of the EC was

managed by its chairperson, who maintained strict records.

As the sophistication of trials continued to increase it was deemed appropriate to seek a government sponsored EC to ensure that the membership of the EC was sufficiently indemnified should there be litigation following any serious adverse event (SAE). To accommodate this potential risk, overtures were made to a number of ECs and ultimately the Northern Sydney Area Human Research Ethics Committee (HREC) agreed to vet projects undertaken by the clinic. This was not without difficulty and initially the EC wanted the principal investigator of the clinic to indemnify each member of the EC for \$10 million AUD per study, a cost that would have prohibited further private practice research. Through the offices of the chairperson of the EC, the manager of the Northern Sydney Area Health Board and the chief investigator in the private clinic, representations were made to the State Minister for Health, who agreed to indemnify the EC in an identical fashion to the indemnification provided for similar research conducted within the public hospital system. Since that time, the HREC of the South Western Sydney Area Health Service has also agreed to scrutinise protocols considered by the clinic, thereby making access to ECs simple and efficient.

Part of the role of the trial co-ordinator has been to liaise with the EC to ensure that the EC is: advised of all SAEs; suggests trial protocol variations for approval; submits new trial protocols for approval (including patient information sheets and informed consent documentation to validate clarity and language); and provides investigator brochures and other materials that were made available by the trial sponsors. The co-ordinator also ensured that the EC was notified of adverse events (AE) experienced by patients within the practice and maintained on-going advice as to the status of each trial and its completion by way of annual reports.

The EC has conducted three separate site inspections to monitor for: the suitability of the practice; its facilities; adherence to trial dictates; practice environment with respect to security of medication kept at the site; maintenance of temperature charts; protection of patient chart privacy; and competence of trial personnel. Such audits have confirmed the adherence of the practice to EC instructions and advice.

Audits have also been undertaken by pharmaceutical company representative personnel, both local and international, and by representatives of clinical research organisations (CROs) employed by the pharmaceutical companies to

ensure compliance with research methods and protocol dictates. With enhanced sophistication of research study expectations the pharmaceutical industry sponsors have relegated monitoring of activities within trials to contracted CROs which function specifically to supervise such research and which have actively monitored all subsequent trials and have communicated any perceived deficiencies in writing to the research assistant (RA) and clinician in duplicate. These are archived in trial folders which are kept separately for each trial and which track the history of all communications per trial administered in the clinic.

Part of this process has seen increased effort to maintain strict source data which is used to verify all trial folder inclusions. The RA trial co-ordinator, has developed patient record inserts to be kept in each subject's clinical file in addition to the standard history notes. These pro-forma documents identify all procedures which are mandated to be necessary for each patient's scheduled trial visit at any particular time within a trial. All activities undertaken at a trial visit are also dictated for inclusion within the letter which is sent to the referring general practitioner and these letters are examined by the RA, prior to mailing of the letters, to ensure complete coverage of all necessary source data as may be required for an external audit, be it from the US Food & Drug Administration (FDA) or the Australian Therapeutic Goods Administration (TGA).

To protect patient autonomy and overcome any potential suggestion of undue influence, the clinician does not personally initiate or conduct the 'informed consent' process. It was recognised that the clinician is in a position of authority while the RA is a younger scientist who has had no previous contact with the patient. Thus, once the patient expresses interest to explore a new treatment modality, he/she is referred to the RA who explains the study, its aims and demands and assures that refusal to participate will not influence ongoing medical care by the clinician. The RA answers all questions and completes the consent process before referring the patient back to the clinician. The clinician will respond to any outstanding questions and countersign consent, if it is freely given, or alternatively continue with medical care devoid of any trial commitments.

With its increased experience in the conduct of clinical drug trials, the centre started to develop investigator initiated studies. These included Special Access Scheme use of medications made available on compassionate grounds and restricted to patients within the practice. These protocols were administered

in a fashion similar to that adopted for clinical trials^{12, 13}. The clinic was also involved in the initiation of multi-centred, clinical trials which were submitted to, and subsequently approved and sponsored by, the pharmaceutical industry¹⁴⁻¹⁷. These studies confirmed the competence of the centre and its commitment to undertake research in a peer-reviewed and publishable fashion.

More recently this concept of investigator-initiated study has been further developed. An international pharmaceutical company approached the clinician to devise and submit a protocol for a placebo-controlled, randomised, multi-centre study to determine efficacy of an established medication for an off-licence application¹⁸.

Pending approval by the company, the study would be funded by that company but sponsorship would be relegated to the investigator. This removed involvement of the pharmaceutical industry from hands on management or control of operating procedures. It implied that the pharmaceutical company relinquished its potential to influence the publishing (or not publishing) of any of the study results. This recent advance has demonstrated the acceptance by the company that the clinician, through his research company Strategic

12. Beran, R. G. & Sheehan, K., "An appraisal of the clinical use of lamotrigine". *J Clin Neurosci*: 3: 239 – 242, 1996

13. Weber S., Beran R. G., "A pilot of compassionate use of levetiracetam in patients with generalised epilepsy". *J Clin. Neurosci* 11 (7): 728 – 731, 2004

14. Beran R. G., Berkovic S. F., Dunagan F. M., Vajda F. J. E., Danta G., Black A. B., Mackenzie R., "Double-blind, placebo-controlled, crossover study of lamotrigine in treatment-resistant generalised epilepsy". *Epilepsia* 39:1329 – 1333, 1998

15. Beran R. G., Berkovic S. F., Black A., Danta G., Dunne J., Frasca J., Grainger K., Kilpatrick C., Mackenzie R., McLaughlin D., Schapel G., Somerville E., "Australian study of titration to effect profile of safety (AUS-STEPS): High-dose gabapentin (Neurontin®) in partial seizures". *Epilepsia* 42 (10): 1335 – 1339, 2001

16. Spira J. P., Beran R. G., "Gabapentin in the prophylaxis of chronic daily headache: A randomised placebo-controlled study". *Neurology* 61 (12): 1753 – 1759, 2003

17. Beran R. G., Berkovic S. F., Black A. B., Danta G., Schapel G. J., Vajda F. J. E., Hiersemenzel R., "Efficacy and safety of levetiracetam 1,000 to 3,000 mg/day in patients with refractory partial seizures: A multicentre open-label single arm study". *Ep. Res* 63:1-9, 2005

18. Beran R. G., Ainley L.A.E. & Beran M.E., "A novel method for the conduct of pharmaceutical company funded clinical drug trials which ensures the independence of the investigators" *Intern. J. of Pharm. Med.* (In Press)

Health Evaluators, has sufficient standing to be trusted to deal with a study of this complexity and magnitude in an appropriate fashion.

DISCUSSION

Involvement of private practice clinics in clinical drug trials has developed from a position in which they were reluctantly accepted and tolerated, as an additional source of recruitment. Initial inclusion of this practice was consequent to the generosity of an interstate pharmacologist, with whom the chief investigator previously worked, to be considered as a supplementary co-investigator. From the inauspicious beginning the practice has become an accepted and a sought after partner in the development of such trials. Its current status has evolved into being a funded sponsor of a multi-centre, randomised clinical trial with all its legal and ethical commitments which such position entails^{18, 19}.

Concurrent with this evolution has been a wider acceptance of the practice with a professional standard operating procedure which has been acknowledged by government authorities which are prepared to underwrite the indemnity insurance for the clinic with the EC. The fact that the practice has now been appointed the sponsor of a multi-centre trial has afforded the investigator an unprecedented independence in the reporting of trial results and their methodology^{18, 19}, irrespective of whether the findings support or refute the basic hypotheses of the trial. Such report publication does not need to accommodate the interests of the pharmaceutical company which has funded the trial and has no obligation to satisfy economic considerations beyond those required to account for proper administration for the trial's conduct.

The above audit has demonstrated that the inclusion of private practice clinicians in clinical research has not been without its problems. The practice had to employ additional staff and modify its operating procedures which had to be transparent and available to audits both by the sponsors and monitors as well as the EC which approved the studies. The practice had to demonstrate its adherence to GCP⁹⁻¹¹ and to withstand a variety of external audits. It also undertook internal audits¹⁻² and published these in peer reviewed scientific literature, thereby demonstrating a willingness to be subjected to open scrutiny.

19. Beran R. G., "Legal and ethical obligations to conduct a clinical drug trial in Australia as an investigator initiated and sponsored study for an overseas pharmaceutical company". *Med.Law* 23 (4): 913 – 924, 2004

This evolutionary process has seen a broad accommodation of the RACP ethical guidelines^{5,6} and has largely overcome some of its concerns⁶. The clinic devised the study protocol for the pharmaceutical company and assumed full authority to publish the findings as it sees fit, recognising that it was the official sponsor of this 'investigator initiated' trial. This required international negotiations to satisfy legal, as well as ethical, constraints⁽¹⁹⁾. It demanded a steep learning curve and mutual respect and co-operation between the clinic and the pharmaceutical company providing the funds to underwrite the study.

From this current review of the ethics in clinical research in a private practice involved in clinical drug trials, it can be seen that private clinicians have been involved intimately in the maturation of the disciplines involved in such trials. Private practice has contributed to a reappraisal and evolution of standard operating procedures which attach to such clinical trials. There has been a commitment to sequester trial conduct and accounting from practice commitments in routine patient care.

This review of the development of such research, within the community based private practice setting, has demonstrated that these clinics have contributed to the ethical considerations and practices which attach to such trials.