CONDUCTING CLINICAL

TRIALS

IN PRIVATE PRACTICE

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ABSTRACT

INTRODUCTION

Clinical trials of new agents enhance treatment options. Such trials are usually conducted in large tertiary referral centres, rather than the private practice setting. This paper reports the experiences of a private outpatient neurological clinic, which conducts such trials as part of its commitment to improve patient care and offers suggestions, which may be used to review the approaches of others involved in such trials.

METHODS

Strategic Health Evaluators P/L (SHE) is the research arm attached to the clinic and at any one time would have 5 - 6 trials running concurrently.

Conducting such trials has necessitated the development of new approaches to: patient recruitment; achieving informed consent; interactions with various players, including sponsors, monitors and ethics committees; staffing and equipment; dispensing; and sequestrated financial records.

RESULTS

Acknowledging lack of equipoise between patient and doctor, the clinic developed a novel approach to informed consent. The clinician introduces the study, the trial coordinator performs most of the duties of obtaining informed consent and, only if entry is accepted, does the doctor complete the exercise, countersigning and thereby taking ultimate responsibility for the process, which enhances patient autonomy.

The trial co-ordinator ensures: all trial-related activities are properly supervised with adequate checks and balances: ensures patients get proper supervision; that trial requirements are properly administered; and that contact is maintained with all those involved with study-related activities, including supervisors, monitors, ethics committees, office staff and the clinician and correspondence and source data are verified and countersigned and dated.

All financial transactions, relevant to the conduct of trials, are sequestrated from standard practice finances. No trial-related visits or activities are charged to the universal health insurer and records are maintained in separate spreadsheets, individually referable to each trial.

DISCUSSION

Trials conducted in private practice allow patients access to novel treatments without referral to a tertiary institution, thereby maintaining continuity of care. The recruitment base is broader and may better reflect 'real world' practice.

The private practice setting generates different pressures and ethical expectations. This paper discusses these demands and how they are addressed and offers concepts that could be transposed throughout the wider scientific community. The novel approach to informed consent provides additional scope for patient's autonomy. Having all material reviewed by the trial co-ordinator and initialled and dated by the principal investigator, adds an additional dimension to confirming source data and complement validity. The system applied additional checks and balances which could be used by others involved in such research.

INTRODUCTION

To enhance treatment options, it is imperative to continue to develop new therapies for those illnesses for which the current remedies are suboptimal [1]. To achieve this goal, newly developed treatments, once ready for human experimentation, must be trialled in accordance with ethical and legal expectations [2]. These include: consideration of risk/benefit ratios [3]; informed consent [4]; compliance with good clinical practice (GCP) [5]; logical and systematic progression through phases I - III of the trialling procedures [6]; and ongoing post-marketing surveillance plus potential phase IV trials [7].

Such trials are usually conducted in large, tertiary referral centres rather than in the private practice setting [8-10]. This is not dictated by scientific expectation but, rather, as a matter of: convenience [13], the availability of adequate infrastructure, [10] and a greater willingness to participate in trials by academically affiliated practitioners in comparison to the non-affiliated, for a variety of both personal and departmental/institutional considerations [17, 18].

This paper reports the experience of a private, community-based, outpatient neurological clinic, which conducts such trials as part of its commitment to improve patient care. It explores the reasons why private practice should consider being involved in such trials and why sponsors of such research should involve the private sector. It examines the ethics involved in extending such research into the private sector. It also addresses and investigates how the involvement of both the private and public sectors can be complementary, insofar as to realise optimal clinical and ethical outcomes, and to achieve additional scientific yield and enhanced healthcare delivery.

METHODS

Strategic Health Evaluators Pty Ltd (SHE) is a registered company that conducts research as a separate entity, as well as being an integral component of the index outpatient clinic.

Members of the clinic co-operate with personnel involved in SHE. These include: the physician, who is both a Director of SHE and serves as the Principal Investigator within approved trials; the Practice Manager, who ensures differentiation between SHE and the clinic activities on an administrative basis; and clinic staff with responsibility to ensure that the clinic, as well as its research activities, run smoothly. At any time, SHE is responsible for undertaking 5 - 6 concurrent clinical trials, either as a contributing site, within larger multicentre studies, which may include tertiary referral centres, or as unique site-specific investigations, idiosyncratic to the clinic.

While conduct of site specific studies may be as simple as recognising unusual phenomena, examining these in a critical fashion and identifying the underlying pathophysiology [19 - 25], involvement in multicentre studies is more complex and demanding. The latter requires completion of feasibility surveys, to confirm suitability and capacity to undertake the trial, followed by a selection process to be accepted for inclusion by the combined consideration of the trial sponsor and its relevant Clinical Research Organisation (CRO), which is a hired company contracted to oversee the conduct of the study [26, 27]. Each of these considerations evokes inherent practical and ethical issues, which demand respect for GCP [5].

Irrespective of the nature of the trial, its conduct has necessitated the development of new approaches to the recruitment of participants to ensure the highest standards of ethical respect [28]. Acknowledging that these patients are generally selected from the clinic's outpatient population, referred directly by their family physician, without any preconception of involvement within any given trial, the inclusion within studies must accommodate additional safeguards [29]. There has been a need to modify the approach to obtaining informed consent that respects these ethical demands while still offering these patients potential access to new remedies being trialled [30].

This modification of obtaining informed consent has evolved to overcome the appearance of potentially conflicting aspirations for all those involved within the trial [30]. This includes the sponsors, monitors, CROs, Human Research Ethics Committee (HREC) directives plus the aspirations and expectations of staff, the clinician and the patients. It has necessitated a review of staffing and available equipment [28] to ensure

that the clinic is capable of satisfying the dictates of specific trial protocol without placing an undue burden on the normal clinic activities. There was need to reappraise the approach to dispensing trial specific medications, to recognise the possible need to be stored in a controlled, temperature specific environment, within defined temperature ranges, in a secured environment.

The clinic evolved as the provider of health care services, rather than as a committed research facility. It continues to operate as an outpatient consultative neurological clinic and hence all trial-related financial matters needed to be sequestrated from routine clinic accounts. Being located in Australia, with a universal health care insurance, known as Medicare, [31] it was necessary to ensure separation of economic management for trial-related services and those appropriately covered by Medicare [31].

Respect for these issues necessitated a critical review of both the activities of SHE and those of the clinic, beyond the conduct of clinical trials. This review focused specifically on the ethical considerations and involved all members of the team to ensure that it was as comprehensive and inclusive as is possible.

RESULTS

To facilitate the most effective and efficient identification of prospective trial candidates, for inclusion within any research project, the clinic evolved a diagnostic coding procedure, based on diagnostic labels, that was idiosyncratic to the clinic [32]. This served as a form of quality assurance, within the practice, but also enhanced the capacity for rapid recruitment within clinical trials. It meant that potential candidates could be identified and offered the option of voluntary inclusion within any proposed project.

The clinic, being a routine provider of outpatient healthcare, required additional staff to ensure trials were appropriately conducted in accordance with GCP [28]. This necessitated the employment of a Trial Co-ordinator [28] and recent science graduates were chosen to fulfil this role. Such a person was responsible for all trial-related matters and was answerable to the practice manager and the principal investigator, to

ensure that all trial-related activities were properly supervised, with adequate checks and balances, and accommodated ethical expectations. Included in these responsibilities was the development and maintenance of a Standard Operating Procedure Manual, to ensure that all trial-relevant activities were easily understood, irrespective of who was in the role. The purpose of this manual was to ensure a seamless maintenance of all trial-related procedures, with anticipation of any potential, unexpected eventualities. The co-ordinator also served as a liaison person to maintain communication between all trial-related participants, including supervisors, monitors, HREC personnel, office staff and the clinician. All trial communications were reviewed and critically appraised to ensure that these accurately reflected everything that had been done within the trial, thereby ensuring accurate source data in a most comprehensive manner.

As potential trial participants were recruited from within the routine practice population, it was important to acknowledge a lack of equipoise between the patient and principal investigator, who was also the treating clinician. To accommodate this inequality, the clinic developed a novel approach to obtaining informed consent [4, 30]. This approach recognised the lack of equipoise and aimed to restore as much patient autonomy, as is practicable, to allow patients to refuse inclusion within any given trial without fear of hindering the physician-patient relationship.
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To facilitate this procedure, the clinician would discuss the trial in very broad terms with the prospective subject. If the patient was willing to take the matter further,(s)he was then referred to the trial co-ordinator, a young scientist, employed by SHE. This person was not previously involved in the patient's care and thus was one step removed from the patient's clinical management. In accordance with GCP, [5] the scientist would explain all components of the HREC approved patient information material. This ensured that the patient was given all relevant material, pertinent to the trial, in a level of language appropriate to a layperson and approved by the HREC [5]. This went some lengths towards restoring the patient's capacity to refuse trial inclusion, without fear of offending the treating clinician. The treating doctor, in accordance with GCP [5], had already indicated a willingness to maintain ongoing therapeutic relationship with the patient, should (s)he refuse trial inclusion [30].

Only if the patient accepted involvement within the trial, did (s)he return to the clinician who would countersign and complete the process of informed consent [30]. If the patient declined trial inclusion, (s)he returned to the clinician, such that the therapeutic relationship was resumed as if there had been no consideration of trial inclusion [30].

Being a private practice clinic, there was no access to onsite pharmacy or a pharmacist and the dispensing of trial medication required additional consideration. The team needed to be cognisant of potential error to ensure medication dispensing was accurately recorded, appropriately monitored and double-checked. Some trials necessitated maintaining medication in a controlled environment, employing a temperature specific and regulated refrigerator, in a secure environment to which access was restricted to trial personnel. A temperature log was maintained to ensure that the medication was correctly stored. It was also necessary to ensure that all medication was within its defined shelf life.

All financial transactions, relevant to the conduct of trials, was sequestrated from standard practice finances. This ensured that no trial-related visits or activities were charged to Medicare [31]. Financial records were maintained in a separate spreadsheet, individually referable to each trial and cross-referenced by both the trial co-ordinator and practice manager. Invoices were numerically logged and recorded, to ensure accuracy and access for future audit.

DISCUSSION

Trials, conducted in private practice, allow patients access to novel treatments that may otherwise be unavailable [1]. Such trials, conducted within the private practice environment, necessitate the development of new approaches to satisfy additional ethical considerations, which transcend standard practices within a medical clinic.

The incorporation of these additional procedures provided incentive to address extra demands to meet ethical standards. These included: a novel approach to acquiring informed consent [30]; the addition of extra personnel [28]; the development of a practice specific manual [34]; allowing trial monitors to review all-related trial procedures [35]; maintenance of quality assurance with the adoption of diagnostic coding [32]; involvement of an external HREC to review trial-related expectations [36]; need to respect to GCP [5]; retaining trial medication in an approved environment with appropriate dispensing records [37]; and establishment of sequestrated financial records [38] .

Clinical trials, conducted within the private practice setting, also allow patients, attending the clinic, to maintain continuity of care. It avoided the need to involve tertiary referral centres, with the potential of including a variety of junior staff, thereby possibly diluting direct contact and responsibility with the treating doctor as exists within the small private clinic [28]. It also serves to strengthen the bonds between doctor and patient, if managed in an appropriate manner, with the patient appreciating that their doctor had been approved for inclusion within multicentre, academic trials [28].

The conduct of trials within the private practice environment, allows sponsors to include clinics, which operate as initial referral centres, rather than as tertiary referral centres [28]. This suggests that the clinics are more reflective of the 'real world' standard of care [28]. It translates into such trials, including a wider spectrum of patients, thereby allowing the results of such studies to have broader relevance and applicability to the management of the condition under review. It had the potential for accelerated recruitment of treatment-naïve patients, early within the disease process, who were referred to the family physician's preferred clinician rather than to an outpatient service, often provided by more junior staff under supervision [28].

The procedures and practices, outlined within this paper, were reflective of a single outpatient clinic. This does not mean that their relevance should be restricted to that clinic. The response to the different pressures and ethical expectations, outlined within this paper, should be transposable and transportable to other private clinics and clinic environments. This should allow clinicians to offer their patient's additional

therapeutic options, thereby contributing to greater satisfaction by ensuring that these doctors, involved in such research, remain at the forefront of relevant therapeutics [28]. It should add to patient confidence with the clinician and offer all those involved within the clinic the awareness that this clinic was providing additional services, above and beyond those of standard, routine care.

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