ETHICS IN CLINICAL DRUG TRIALS OR CLINICAL RESEARCH IN PRIVATE PRACTICE

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Introduction:

Drug trials and clinical research have long been seen as the domain of tertiary medical institutions, rather than being conducted within the setting of private practice medicine (1). While this should not impact upon the ethics that are applicable to the conduct of such projects, it is in inevitable that there will be differences in the standard operating procedures which prevail within the different environments that influence the delivery of services within the public or private medical settings (2).

Large tertiary institutions have a much wider referral base than exists in private practice and hence self-referral of patients is much more prevalent within the public sector, as compare to private practice (3). By definition this implies greater access to a wider population base when recruiting subjects for clinical research or to be included within clinical drug trials (3). Such wide based referral is further enhanced by the in-house cross-referral of patients from Accident and Emergency Departments, within the hospital, to the hospital-based Outpatients services that prevailed within tertiary institutions. Unlike private practice, there is a range of subordinate doctors who supplement the medical team which functions within the Outpatients Clinics and hence there exists a multiplier factor to assist with recruitment for research purposes (4). Often private practice clinicians work as sole practitioners and rely completely on their existing referral base to attract suitable candidates for inclusion within research projects.

There has been condemnation of the practice of recruiting one's own patients into clinical trials and clinical research (5) but to exclude such subjects would result in the effective exclusion of private practice as a viable environment in which to conduct such research. The paper to follow will explore this issue together with a range of other circumstances in which research, conducted in private practice, differs from that undertaken within the public sector and will examine some of the ethical considerations that are relevant. The paper will draw heavily upon personal experiences of the author to provide examples of how some of these ethical dilemmas have been addressed while still preserving both the autonomy of patients and at the same time not denying these patients access to new treatment modalities which may have the potential to dramatically improve their quality of life.

Involvement of private practice:

Delivery of medicine within private practice, in the Australian context and specifically within specialist practice, relies exclusively upon referral of patients from primary care physicians, known as General Practitioners (GP's) (6). These GPs will often refer patients to a number of specialists while at the same time also referring patients to hospital clinics and Accident and Emergency departments within those hospitals. It follows that the patient pool available to clinicians in private practice is considerably reduced as compared with

colleagues who practice within the same discipline but within the tertiary referral medical centre in the public sector.

Often the waiting time to see clinicians in private practice is shorter than is the waiting time to see the doctors who operated within hospital Outpatient services. This may result in private practice clinicians seeing a different patient population than that which attends Outpatient Clinics, such as seeing patients at an earlier stage in their illness, more anxious patients or those patients who are unwilling to wait for Clinic availability or insist upon seeing the doctor of their choice (7). While the public sector may have a greater patient population pool, these patients may fall outside of these parameters and the exclusion of private practice from clinical research could result in the exclusion of this type of patient from research projects and that, of itself, might be unethical within the broader picture of clinical research or drug trialling.

This may explain why sponsors of clinical trials choose to include private clinicians amongst their investigators but it does not address the issues of why these investigators should agree to become part of the investigative team nor does it explain why their patients consent to be subjects within such research projects. Sceptics may argue that the reason for both sponsors and clinicians to undertake clinical trials is simply a question of momentary gain and financial inducement (8) but the undertaking of clinical trials and research is quite expensive, even to the clinician, as it entails real changes to practice procedures and places quite heavy burdens on all those involved within the practice. While logic dictates that there must be compensation for these costs, the real reason for undertaking such research, be it as a sponsor or investigator, is to find new treatments or answers to questions which ultimately will improve the delivery of medicine to the target population of patients (9). The conduct of clinical research that does not seek to address such issues is of itself of questionable ethical statement (10).

It follows that clinicians in private practice, who agreed to be part of a research team, should be motivated by the wish to either find the answers to the questions raised or alternatively to offer their patients more appropriate or more effective or less intrusive treatments for conditions which thus far have not been offered optimal solutions (11). This is of fundamental ethical importance when such clinicians agree to partake or contribute to research projects.

The ethical concept of beneficence should be the motivating factor for all those involved in the conduct of clinical research (12) for without respect for this concept there cannot be adherence to the underlining dictate of, " do no harm" (13). Beneficence dictates that the clinician should respect the patient's needs and thus the prospective study should have the potential to benefit the patient in some way. Because the research project, or clinical trial, will often be testing new ground, there is always the potential that the subject may suffer as a consequence of inclusion within a trial and this must be made abundantly apparent to any prospective research subject, as to do otherwise would disregarded patient autonomy and informed consent (14). As a corollary of these concepts, both patients and clinicians should expect that the research, in which they have agreed to participate, has a very real potential to offer benefit and it is on this basis that they have agreed to become involved.

The external review process:

Before a trial or clinical research can proceed it must be subjected to an external review process which must meet predetermined standards (15). This may dictate that the protocol for the study is first assessed by an expert within the field of research who can critically appraise the scientific merits of the proposed investigations (16). There is also need for there to be a Review Board which in Australia takes the form of the Human Research Ethics Committee (HREC) which is constituted in accordance with stipulated standards (17) and functions as a gatekeeper to protect the interests of patients while at the same time not wishing to obstruct worthwhile research (17, 18).

Proposed research must be submitted to the HREC for its scrutiny and must be approved before the investigator can initiate the research. The HREC will expect access to the research protocol, any relevant information that may pertain to the project and will review both the patient information documents as well as the form and content of the 'informed consent' document. This will ensure that these documents are couched in language that is of a standard that can be understood by the average patient, devoid of unnecessary jargon and sufficiently inclusive to advise prospective research subjects of any potential risks that may be encountered as a consequence of agreeing to partake within the project (19).

This goes some way to ensure that patient rights are protected and that patients are given sufficient information to make an informed decision prior to consenting to be part of any research project. The relationship between doctor and patient is not one of equality and hence there is a potential for the doctor to either overtly, or covertly, coerce patients to agree to be part of such research and this must be stringently resisted (20). It is for this reason that there is criticism of doctors recruiting their own patients to agree to be part of any research project and consideration of this real concern must be addressed when undertaking the process of accepting informed consent (20).

A serious consideration that may impact upon the conduct, and hence approval to conduct, a trial that involves humans is the real potential to do harm to trial subjects. This may result in litigation of both the investigators and the HREC and hence it is common practice for the HREC to seek confirmation that the trial is covered by appropriate indemnity insurance (21) and that this insurance also protects the members of the HREC for their role in approving the conduct of the trial (22). It can be seen that the rights of everyone who was involved in such a study need to be protected and it is often suggested that investigators, particularly those in private practice, contact their medical indemnity organisation to ensure that they are adequately protected should there be an unforeseen consequence of conducting the trial with litigation initiated under the tort of negligence, should there be a trial violation, even by an employee of the investigator for whom the investigator may hold vicarious liability (23).

Informed consent:

Lack of equipoise, between doctor and patient, in the consenting process requires even greater attention within the concept of conducting research in the private practice setting as it may be perceived that the doctor-patient relationship could be more intimate within a smaller facility rather than a large tertiary referral teaching institution (24). There are a number of ways in which to protect the patient's rights, above and beyond the requirement

for external HREC review and approval of both the study and information documents which must be discussed with the patient.

A necessary inclusion within the patient-provided material is a statement that reassures the patient that should he/she declined inclusion within the study there will be no repercussions to ongoing level of care and it will not impede future doctor-patient relationship (19). This is a mandatory requirement of the most HRECs for without such a clause the potential for intimidation in patient management is unacceptable (15). This clause goes some way to protect patient rights but does not address the lack of equipoise in the doctor-patient relationship.

One way to overcome this potential for coercion is to relegate the consent process to someone other than the clinician and this has been the process adopted by the author (25). An alternative to consenting process which has proven successful has been to introduce the patient to the basic concepts of the research project and if the patient expresses an interest to learn more then to refer the patient to someone else who will initiate more detailed discussion and informed consent.

The author uses the approach of referring the patient to a research assistant (RA) who is usually a young scientist with less capacity to influence the patient and who clearly understands the obligation to maintain patient autonomy to either accept or decline participation within the trial. By this approach the patient is placed in a more equal position with the person seeking informed consent and it avoids the potential for the doctor to impose undue influence. The consent document is then signed and countersign by both the subject and the RA while witnessed by an adult who was not part of the consenting process to ensure that such signature was of voluntary nature. Once the consent process has concluded with the RA the patient is offered the option of seeking further clarification with the clinician to ensure that all unanswered questions have been addressed and the clinician then also countersigns the informed consent document to indicate that the process has respected all these considerations (25). The patient is then given copies of both the patient information and signed informed consent documents as a personal record of their voluntary inclusion within the process and a second set of both documents (including signatures) is retained within the patient's clinical records to act the source data for any future audit (15). Once this process has been concluded the patient becomes part of the subject pool within the research project and research related activities can be undertaken with the clear and demonstrable consent and approval of the patient with full respect of their autonomy and hence appropriate ethical standards.

Trial conduct:

The actual execution of any trial is no different whether that trial be conducted in a major public institution or within the private practice setting. The HREC has agreed to the conduct of the trial in accordance with the trial protocol and the investigator has also agreed to be bound by the dictates of the protocol. Should there be any deviation from the protocol this will be subject to scrutiny and may result in the exclusion of that investigator from further involvement within the project. A minor infringement of protocol might be ratified by both the sponsor and the HREC and an anticipated protocol violation may be addressed by seeking suitable waiver prior to same.

A waiver will only be granted if its application does not impact upon the study with sufficient force to negate any subsequent activity within the trial or research project (25). It is inevitable that any study which involves human subjects will result in deviations from protocol dictates, either as a consequence of problems with communication or a lack of compliance on the part of the patient or the investigative team which usually occur without any desire to compromise the research (26). Research that involves humans ultimately relies on an understanding by all concerned and there can never be a guarantee that such understanding is unequivocally correct although every effort should be made to try to minimise misunderstandings.

As research and clinical trials are designed to chart new ground there is always the potential for there to be unforeseen adverse events, some of which may be serious and hence life-threatening or resulting in hospitalisation. Such serious adverse events (SAEs) must be reported to the both of the sponsor, or their surrogate (usually a clinical/contracted research organisation (CRO)), and the HREC as soon as they become apparent so that both the sponsor and the HREC can deliberate upon the facts of the SAE to decide continuation of the study and any potential need to revise the consenting process in the light of the SAE (27). This represents an ethical imperative to protect the rights of the patient to ensure that the consent that was provided remains valid within the scope of any new information that may emerge as a consequence of the SAE.

The sponsor also has the obligation to advise all other investigators, involved in trials of the same product, of SAEs which may have occurred within the context of other trials in which the investigator was not involved (15). These SAEs will also impact upon future decisions for the continuation of the conduct of trials or related research as their existence cannot, and should not, be ignored (15). At all times, within the conduct of a trial, patient protection and autonomy must be paramount and the ethical obligation to respect patient rights surpasses all other considerations.

Within the context of 'blinded' studies, in which either the subject, or the investigator or both are not informed which treatment modalities, if any (in the case of a placebo-controlled trial), the subject is taking, there must be an approved process to allow the unblinding of the patient's status within the trial. This will allow the investigator to make an informed decision regarding the subject's continued involvement within the trial in the light of either a reported SAE or an adverse event which the patient has experienced and its relevant to the study medication (27).

Post-trial conduct:

As with research conducted in the public sector, researchers in the private sector continue to have ethical obligations to the trial subjects after the trial has concluded (28). There is an obligation to ensure that all materials collected within the trial are retained for a mandatory period (15) to allow post-trial audit which demands that there exist sufficient source documents to justify all data relevant to the trial (15). From the very outset of the study, patients must be informed that access to their clinical notes will be provided to a variety of bodies and organisations, a fact that the HREC will have insisted to be included in the patient information material, and this potential intrusion into patient privacy does not stop at the conclusion of the study and may continue for a further 15 years (29, 30).

There is also an obligation for all relevant material that has been discovered as a consequence of the trial, or research, to find its way into the public domain so that its impact can realise the widest good for the greatest community (31). There has been considerable debate about biased reporting of research findings particularly if those findings are counter-productive to a study medication which the sponsor, usually a pharmaceutical company, wishes to market (32, 33). Investigators, irrespective of whether they operate with in the private or public sector, have an obligation to both their patients and to the wider community to try to make public the findings of any research project and to do so with all vigour (32, 33, 34).

Clinical trials involve small numbers of patients and there remains an ethical obligation on all those who have trialled, and to continue to use, the study medication, even after it has received marketing approval, to maintain of vigilance for any unexpected repercussions (15, 35). Once marketed a successful product may be used by hundreds of thousands of patients rather than the relatively small numbers required for regulatory driven clinical trials. All clinicians, whether they work in the private or public sector, particularly those with first-hand experience of the study medication during its development, should be acutely aware of the need to continue to monitor patient progress even after the study has concluded and should be prepared to publish any unexpected sequelae caused by the medication following its wider application (36).

Other ethical considerations:

One of the main criticisms directed at clinicians, who conduct research and clinical trials in private practice, is the question of monetary gain which is often seen as the primary motivating factor for these clinicians to agree to be part of such a study (37). It must be realised that, unlike clinicians in the public sector, those in private practice only attract financial reward as a consequence of the work that they do and the patients that they see. They are generally not on salary and part of the conditions for the undertaking of a trial is that out-of-pocket expenses are covered by the trial's sponsor. There is not the potential to both attract a salary and charge the sponsor for the conduct of the trial and it is appropriate to charge the patient, or the patience medical insurance, for trial-related activities that are otherwise covered as part of the contract to undertake the trial. It follows that the perceived financial rewards that might accrue as a consequence of a public sector institution having research funds directed to trust funds, in addition to salaries being paid, does not attach to research conducted within the private sector. This may be interpreted as the private sector adopting the higher moral and ethical ground rather than being seduced by financial inducement.

Unlike the author who does hold academic standing within the University, most clinicians within private practice do not enjoy such recognition, despite their very real contributions to clinical trials, and hence there is not the same impetus to "publish or perish" (38). Clinicians in private practice do not have the opportunity for further advancement or promotion within the organisation as they are usually self-employed. Hence involvement in clinical research does not attract the same hidden rewards that might accrue to those within the public sector who are seen as having an obligation to bolster the standing of the institution and may rely upon involvement within research for future advancement of the career path (39). Again it follows that the incentive to be involved in clinical trials and

research, within the private practice setting, may be more altruistic than first imagined which might be interpreted as being of greater ethical consideration.

It would be unfair to dismiss the potential motivating factor of being involved in significant research above and beyond patient well-being and it is important for the clinician, whether he/she practices within the public or private sector, to constantly reappraise the reasons for his/her involvement in such projects (40). Research does allow the clinician to feel that he/she is part of the development of medicine and it would be untrue to say that this has no impact upon the decision to be involved but the ethical standards of benevolence and non-malevolence must assume priority when involving patients within such projects (41). As already stated, the potential to enhance patient well-being and quality of life must be the overriding consideration with other factors being of secondary importance.

In a similar vein, the ego-boosting potential of publication within the scientific literature cannot be ignored but again there is far greater benefit to be accrued for the clinician in the public sector as his/her relative standing is far greater enhanced by involvement in research and subsequent publication (42). There is no reason why the clinician in private practice should avoid publication within the scientific literature and, as has already been stated, there is an imperative to ensure publication of both positive and negative results of clinical research to protect patient well-being. There is no ethical dilemma in publishing results of such research so long as patient autonomy and privacy has not been violated and the potential for such publication (de-identified) is usually clearly stated within the HREC approved patient information documents.

Conclusions:

This paper has explored the ethics involved in clinical drug trials or clinical research conducted within the private practice setting. It has acknowledged that such research may draw from a different patient population than that which attends tertiary referral centres and hence there may be very good reasons why sponsors would wish to include private practice clinicians amongst their investigators. The factors which motivate the clinician to be involved in such projects have been examined and the ethical considerations are not vastly different for either clinicians in private or public practice. Patient well-being and the potential to offer new and exciting therapy should be the overarching consideration while at the same time doing everything possible to protect patient rights, their autonomy and, as far as possible, ensuring that no harm is done and that patients understand the risks involved.

In the final paragraphs, focus has been directed towards some issues which may suggest that the ethics of conducting research within the private practice setting might be of a higher standard, rather than compromised, when compared with the conduct of similar investigations within public practice medicine.

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