Ethical Malpractice in Randomised Controlled Trials in India: An Appraisal and Improvement Proposal

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Abstract

Over the past two decades, numerous randomised trials exploring the efficacy of cervical cancer screening in intervention and control groups have been conducted across India. The trials have attracted both scrutiny and regulatory action for their failure to adhere to the ethical standards expected of the clinical research community (Baggchi, 2014). Exploration of the ethical malpractice in the Tamil Nadu cervical cancer trial, and examination of the context in which the trial was conducted form a basis for consideration of how research practitioners can act as exemplars and enablers of ethical research. An improvement plan is proposed for individual research practitioners working on clinical trials; incorporating educational and professional development requirements, evidencing of key research skills with the aim of issuing a standardised framework for the job role to contribute to quality assurance processes and ensure safe and ethical research practice.

Keywords: Ethics; Randomised control trials; ethical standards

Pierce, N. (2015) Ethical Malpractice in Randomised Controlled Trials in India: An Appraisal and Improvement Proposal. *Journal of Applied Psychology and Social Sciences, 1* (1), 49-62

Introduction

Cervical cancer is one of the most common cancers to present within developing countries (Sankaranarayanan, 2013), with a number of recent cervical cancer trials taking place in India. Three of these trials, beginning in Mumbai in 1998 (Srinivasan, 2013), with data collection continuing in Osmanabad and Tamil Nadu until 2003 (Sankaranarayanan et al, 2007) were funded by foundations within the US and have drawn criticism in a recent report published by The Indian Journal of Medical Ethics (Srinivasan, 2013). The context to which these studies belong is particularly relevant in highlighting the ethical misconduct of the trials. Ethical permission was received for the studies during the same time period in which pressure groups (Herson, 1998) were active in their objection to the use of Randomised Control Trials in maternal HIV transmission research (Srinivasan, 2013). These criticisms led to amendments to the Declaration of Helsinki's ethical guidelines on medical research. The Declaration changes detail the acceptability of placebo or no treatment, only when a null hypothesis exists (Srinivasan 2013). The trials conducted in India were not designed to test a null hypothesis, rather a known intervention was denied to the control groups of each of the three studies. These events suggest that clinical equipoise, the foundation for ethical justification of RCTs, was not present; both an ethical and institutional breach of clinical research practice.

What is perhaps most disturbing about the ethical failings of these trials is that such a design would not have been approved by the regulatory bodies within the nations providing monetary funding for the trials, namely the United States (US). Indeed, the US Office for Human Research Protections ruled that mechanisms for providing relevant information about the trial to participants to allow them to give informed consent were not in place (Bagcchi 2014). Instead, the trials were outsourced to India where healthcare infrastructure and medical regulation standards differ from the US, thus enabling clinical trials of poor ethical standards to be conducted. Whilst there are clear and definite disparities in healthcare services between India and the US, this is more related to equity of access rather than a marked difference in cervical screening practices. The Indian government (and private practices) offer cytology-based services, much like the US, (Sankaranarayanan 2013) which additionally makes use of the Papanicolaou test as a screening method for cervical cancer through extraction and testing of cervical cells for abnormality (Storck, 2014). As the services offered by both nations (trial host and trial funder) are comparable to a significant extent, ethical malpractice can be identified in that a) a known to be effective intervention was withheld from the control groups of the Indian trials; and b) the intervention is one that is routinely provided and practiced by the healthcare services of the trial hosting country.

These cervical cancer trials, like many others are representative of the globalisation of clinical research. Within a liberal economy, work is allocated to bidder offering the lowest price and developing countries such as India are able to offer lower operational costs, less bureaucracy and quicker clinical testing timelines than their Western counterparts (Glickman et al., 2009), making them a more attractive hosting location for pharmaceutical companies. The ethical implications of globalisation are numerous and include, as highlighted by London (2002) discrepancies in educational levels and social structures may disadvantage research participants and jeopardise their ability to provide informed consent. A resulting report from The US Office for Human Research Protections has deemed that the trial participants in two (Mumbai and Osmanabad) of the studies were not given appropriate levels of information to enable them to give full informed consent to the study, and that the design of the trials investigated were unethical in their withholding of established healthcare interventions (Baggchi, 2014). Pandiya (2011) cites the regulatory concern around the ethical oversight in Indian clinical trials; the quality of ethics committees including operational procedures, administrative functions and regularity of meetings were recognised as both problematic and detrimental to the quality of the committee function.

Due to the amount of criticism the trials have drawn, the purpose of this appraisal is to assess the ethical failings of one of the three studies targeted for its poor conduct, and to propose a framework to provide assurance that such practice would avoid being repeated. The Tamil Nadu screening trial was chosen as, to date it has escaped the level of scrutiny afforded to the two trials to which it is related (Srinivasan, 2013), although its design and quality of conduct was largely similar. The primary outcome of the study measured the incidence and mortality rates of cervical cancer in the Tamil Nadu district of India. One hundred and fourteen clusters of women, 57 in both the interventions and control groups, made up the study cohort. Depending on allocation, women were given either existing care or visual inspection with 4% acetic acid (VIA; Sankaranarayanan, 2013). The results of the study showed that the intervention group benefitted from “a significant 25% reduction in cervical cancer incidence and a 35% reduction in cervical cancer mortality compared with the control group” (Sankaranarayanan, 2013, p. 221). In designing a trial that produces results such as these, based on the withholding of an established and recognised preventative procedure, immediately the issue of clinical conflict presents itself.

To address this, Western cervical cancer screening practices were examined. Within the UK, the National Institute for Health Care Excellence recommends that all women between 25 and 64 years old are eligible for cervical screening (NICE, 2010). Similarly, US standards recommend that

screening should take place from the age 21, but does not specify the frequency of screening (Centre for Disease Control, CDC, 2014) or any further specific details. Both organisations practice systems to appraise research evidence and develop health guidance and recommendations for national healthcare providers. Research evidence used to form the NICE guidance dates as far back as 1980 (CDC, 2014), which suggests that when the 2007 Tamil Nadu study was designed and implemented, a null hypothesis (needed to justify actively offering screening to only one group within the trial) was not present. To elaborate, evidence already existed that recommended screening for cervical cancer as a preventative service, making the design of the 2007 trial unethical.

To specify the care given to each group within the study: 1) the control group were not actively screened; they were given advice on how to access screening, signs and symptoms of cervical cancer, early diagnosis and treatment; 2) the intervention group were invited for visual inspection with 4% acetic acid (VIA) screening, and given details of where the screening would take place. Participants were randomly assigned to each grouping (CDC, 2014). It was argued that, although the control group were not invited to a screening appointment, they were educated on the benefits of screening and given the appropriate information to pursue access to such services. No information was withheld from the group. It may be reasonable to assume that if control participants wished to be screened, then they easily could have done so, and therefore the design (independent of the null hypothesis issue discussed above) of the study is in fact ethical. However the issue with this approach is its failure to take account for equity of access to screening: participants in the intervention group were privileged in their access to screening, there were no logistical issues as in the control group, who had to organise their own access. It is reasonable to suggest that this inequity may be more acceptable if the study were taking place within a country with a more developed healthcare infrastructure that was able to offer cervical screening as a routine practice; the US and UK guidance documents previously discussed are examples of such infrastructure that could enable participants within the control group of the Tamil Nadu study to access the screening that had been given information on, more easily[1]. Furthermore, it has been proposed that this aspect of the trial does not enable participants to give informed consent to involvement within the study, as the information given to the control group could mislead participants into believing that what they are receiving is in fact "standard care" (whilst the

[1] Randomised controlled trials by virtue of design will provide differing treatments to participants groups in order to test a hypothesis and elicit data, thus adhering to the overarching goal of clinical research in developing generalisable knowledge. Differences in treatments are not always concomitant to a difference in standards of risk safety, particularly when established and accepted treatments are readily accessible. As such, organisations designing clinical research should embody this basic standard of limiting harm to research participants.

intervention group receive a special "non standard" treatment). This is not the case, as the interventional screening method used, is in fact available in India (Baggchi, 2014). Participants, therefore are consenting to potentially belonging to a group within the trial that not only has been misinformed on the standard of care available to them, but also one that has been denied the opportunity to access a routine care practice, itself an unethical practice.

It is not within the scope of this analysis to examine every contributing factor that enabled the study to gain ethical clearance and approval, however Baggchi (2014) provides an overview of the reaction to the Tamil Nadu trial, and two other similar studies, including the results of a report from The US Office for Human Research Protection which states that withholding healthcare that is known to be effective from control groups is seen as unethical, and has caused much controversy over the application of this standard within deprived geographic areas (Baggchi, 2014).

Clearly the concern with the ethics of the trial lay firstly with the design of the study: no provision of access was planned for, or provided. Secondly, the regulatory measures in place to protect participants from unsafe research were applied in a professionally questionable manner, thus resulting in a situation where an unnecessary number of lives were lost to a disease whose presentation can be considerably reduced via screening programmes. This is a significant example of poor ethical and clinical governance conduct, evidencing three specific aspects of the research process where policy and process can be bettered to improve both medical outcomes and research quality: a) research design: as identified above, only a null hypothesis could justify actively withholding a recognised intervention from the control group (it is entirely possible that the trial could have been designed in a more ethically robust manner and still evaluated the hypothesis effectively); b) ethical consideration: the US Office For Human Research Protection has recognised that withholding recognised interventions as unethical, yet the reviewing ethical bodies of the Christian Fellowship Community Health Centre and IARC approved the project (cited in - Sankaranarayanan, 2007, p.398; and c) informed consent: the Declaration of Helsinki states that all consent to research must be informed consent, and that potential participants should understand any information about the research given to them (World Medical Association, 2013).

Scope and Content of the Developmental Framework

Much of what is identified above stems from institutional flaws and/or neglect in legislation, subsequent planning and execution of the study that would be extremely difficult to rectify on the individual level of the research practitioner (the professional whom the development framework section of the document has been developed for). Nevertheless, research practitioners are an integral

part of any clinical trial, and it is important that their data collection methods and treatment of study participants are of high professional and ethical standards. It is hoped that where this is the case, a proportion of the risks associated with participation in research, particularly regarding informed consent, could be mitigated. Within this analysis, research practitioners are defined as members of the following professions working in the clinical research field (as either Research Assistants, Clinical Studies Officers, Research Nurses or Research Practitioners) and will be referred to throughout this paper as Research Practitioners: Nurses, Allied Health Professionals (Occupational Therapists and Physiotherapists) Psychologists, Life Sciences or Social Sciences graduates.

The proposed competency framework (see Table 1) for clinical research practitioners will: Identify a set of core competencies and values that research staff working in clinical trials should embody; propose a method of evidencing these core competencies and values, with a view to assessment and appraisal of such, and stipulate essential qualifications and training that research practitioners should possess or work towards as part of their Professional Development Planning (PDP). This framework addresses problems within ethical practice and informed consent by: 1) Enabling research practitioners to be suitably trained and qualified to practice within their field in an ethical manner; 2) Ensuring research practitioners are competent to take informed consent from research participants including capacity assessment, addressing the potential risks and benefits inherent in clinical research, the design of the trial and the research lifecycle.

Table 1.

A proposed Competency Framework for Clinical Research Practitioners working in Clinical Trials

Education and Training requirements
Undergraduate training in Nursing, Allied Health Professions or Psychology. Formal clinical training will provide a robust foundation in knowledge of psychical/mental wellbeing, allow practitioners to work confidently with clients as autonomous professionals.
Postgraduate training as above is desirable, as it is at this level that professionals will begin to develop specialist knowledge in their chosen field, providing expert care services.
Completion of International Conference for Harmonisation Good Clinical Practice training and commitment to annual updates. GCP training standardises individual clinical research practice activity and ensures researchers are aware of the importance of conducting their duties in a safe and ethical manner (National Institute of Health Research, n.d)
Completion of Informed Consent training: General training, extending to Adults Lacking Capacity and Paediatric Consent where appropriate.
Completion of Information Governance Training.
Proficiency in the use of complex IT systems, including institutional databases (e.g. EMIS, PAS), bespoke data entry systems (e.g. individualised study recruitment databases) and secure data transfer methods.
A commitment to maintaining the standards required by an individual's profession for Health Care Professionals Council registration.

It has been proposed that in order to work within the professional and ethical bounds of the health and social science professions as a researcher, specialist training to cover the ethical and legal responsibilities of the role are necessary (McDermott et al., 2014), with similar observations have made regarding the work of social sciences researchers (Drotar, 2013). Taking informed consent as an example of mandatory training for Research Practitioners in reference to the concerns reported around the quality of the consent given by trial participants, it is imperative that the definition of informed consent is understood in full. Further to this Research Practitioners must be able to communicate the need for informed consent to participants, and work in partnership with them to provide appropriate levels of information on the scope and objectives of the study, the roles

of all involved, how data will be collected and analysed and how confidentiality will be assured (this list is not exhaustive). Research Practitioners must also be sure to document the consent process, and seek consent at each additional phase of the study, for example at the start of a new treatment or intervention regimen. An overarching concern within the consent process is that of capacity; the practitioner as an individual must be sensitive to judging the capacity of the participant to consent to involvement in research. UK legislation such as the Mental Capacity Act (2005) is an example of guidance that is available for researchers to reference; however policies such as these would clearly have no claim to enforcement in the Tamil Nadu case study. Informed consent enables individuals to be treated in a dignified and respectful manner, acknowledging their autonomous personhood; to circumvent this process, from a Kantian perspective would not only violate this personhood, but use individuals, itself a disingenuous act (Gregory, 2003).

As demonstrated here, the vast array of both clinical and legislative literature surrounding clinical research requires its own commitment from the Research Practitioner, to ensure that a comprehensive working knowledge of both current and established professional education is maintained. Commonly referred to as Continuous Professional Development (CPD), it is an important aspect of the Research Practitioner's role, and therefore the education and training requirements detailed here are representative of the minimum standards that individuals should possess upon entry to the role. Tools such as the Researcher Development Framework (RDF; a tool intended for international use and developed in 2009 by the Careers Research and Advisory Centre) clarify the expected standards for researchers to meet, including the academic and person-centred skills needed to promote and advance research (Vitae, 2014). Research Practitioners using such resources are able to identify their strengths, areas of work that possess scope for improvement and search for appropriate opportunities to enable them to develop within their role (Vitae, 2014). It is usually expected that tools such as the RDF will also be utilised by Research Practitioners to assist in development of a CPD portfolio, used to exhibit commitment to learning and development of practice; the appropriateness and feasibility of such a system being utilised in India, is debatable. General standards of healthcare vary across both India and its public and private healthcare systems, with maternal and women's health a priority within Indian healthcare reform (Srivastava et al., 2014). However, in an economy where economic growth has not resulted in improved health for all (Subramanian & Subramanyam, 2011), the use of public funds to develop all but the most critical healthcare infrastructure is an ethically dubious notion.

Development opportunities available to Research Practitioners can vary and can include providing training to junior colleagues, coordinating promotional and outreach programmes to

wider staff groups and the general public, and supervision or line management of other research staff. It is generally expected that Research Practitioners in all but the most junior levels will possess a postgraduate qualification in a healthcare science or clinical research subject (NHS, 2014). It is recognised that researchers within the NHS may be encouraged to use a localised edition of the recently simplified NHS Appraisals Toolkit (NHS Employers, 2010). Both materials are useful, however it should be noted that the RDF is developed specifically with researchers in mind; the NHS Appraisals Toolkit is generic and adaptable to each job role, the limitations of which should be acknowledged. For example, an appraisal tool that is unable to recognise and account for the specific professional duties and career paths of clinical researchers will be less effective than one that is able to provide comprehensive and holistic guidance. Research Practitioners should therefore, (dependent on their employment sector) assess the range of CPD resources available to them and select based on which material they feel will best enable them to plan and fulfill their CPD requirements (Health and Care Professions Council, 2009). Again, these are Western frameworks and initiatives and intended as only as an example of how clinical research can compliment and be integrated into healthcare systems.

Essential Skills for Research Practitioners

The skills necessary for Research Practitioners may be identified and discussed as part of the educational and training activities detailed above. However, the development of such skills in isolation and without acknowledgement of the context within which they sit will not be conducive to the development of a competent and effective Research Practitioner. Instead, it may be helpful to think of skills needed for a role as the components of competence, defined as performance and behaviour standards required for successful performance at work (Chartered Institute of Professional Development, 2014). Harvard University's Joint Task Force for Clinical Trial Competency, a partnership between Harvard and leading pharmaceutical companies that amalgamates education and training for professionals working within clinical research (Li, 2014), identified a set of Competency Domains for best practice in clinical research. These competencies span across the entirety of the professional researcher's job role and provide a framework for skills development, in that researchers are able to attribute their skill sets to particular domains, thus identifying both strengths and areas for development.

Evidencing Key Competencies: Skills Frameworks

The Royal College of Nursing (RCN) provides a framework for Clinical Research Nurses to assess and document their level of competency in each area of practice deemed relevant to Clinical

Research (RCN 2011). Although designed for research nurses, much of the framework is adaptable for those without a nursing background (instead possessing Psychology, Occupational Therapy or other AHP training). It is accepted that not all Research Practitioners work within the NHS; however until a more general framework for practitioners of varying backgrounds is developed to map key generic research skills, it is useful to draw upon existing resources. Each competency detail provides an assessment space, in which practitioners are able to document evidencing of relevant key skills at the appropriate level of complexity. Whilst this tool could be used as personal mapping and records of achievements, it is advised by the RCN that guidance from mentors will aid the assessment cycle (RCN 2011).

Clinical Supervision

The process of clinical supervision is defined as the acting of supervisors and practitioners formally coming together to reflectively evaluate supervisee practice, and working in unison to more fully understand professional issues through problem solving and critical appraisal (Fowler, 1998). Clinical supervision is defined by Fowler as an evolving definition that applies differently to each clinical setting and level of competence. This is especially relevant to the role of the Research Practitioner, whom not only works clinically, but is also expected to develop an intimate knowledge of research policy, and the ever advancing pharmaceutical industry. Indeed, the expansive role of the Research Practitioner as an academically educated professional is used by Severinnson (2014) to illustrate the supervision process as pedagogical within a professional context. It is expected then, that clinical supervision will function as a beneficial process for the Research Practitioner to enable self-reflection and development, as well as providing a forum to evidence mastery of relevant competencies (in line with the aforementioned skills frameworks). In addition, clinical supervision should be considered for its benefits to employers, in acting as a "quality control" process to identify and evaluate skills and areas of concern within individual employee practice.

Conclusion

The aim of this paper has been to consider the role of the research practitioner in relation to the clinical governance of clinical research trials. Whilst it is accepted that the failings and malpractice involved in the Tamil Nadu trial are complex and involve multiple agencies, there is also much that can be done by the individual research practitioner to safeguard the rights and safety of research participants. As the individuals who are at the "front line" of research, and whom typically have the most contact with study participants, often developing meaningful relationships over the course of the study, the research practitioner has a pivotal role in safeguarding the dignity

and safety of study participants. It is hoped that the detail of necessary skills and formats of evidencing such will highlight the role of the research practitioner as instrumental in the ethical and safe delivery of clinical trials, particularly regarding the facilitation of informed consent within the participant's decision making process (Pick et al., 2013). The framework provided is comprehensive in its scope of the standards to which Research Practitioners should adhere, without the burden of geographical and regional limitations. By specifying only the discipline and level of qualifications required for the profession, the framework may be implemented on a global scale, allowing sensitivity to cultural and geographical practices whilst also providing a pragmatic solution to standardisation of skill mix within the profession. Furthermore, completion of courses such as the ICH GCP training can be achieved via a variety of formats, including web based learning and trainer facilitated classes, making learning both accessible and cost effective.

It is apparent that the Tamil Nadu randomised controlled trial was neither designed nor regulated in a manner that acknowledged the duty of care owed to the study participants by way of their involvement in the project. Both the Declaration of Helsinki and the widely recognised ethical precedent of clinical conflict were circumvented, with the outcomes of significant mortality rates and damage to the reputation of clinical research. Whilst it remains to be seen what the long term effects of the misconduct of the Tamil Nadu and other two Indian cervical cancer trials will be for the clinical research community, the loss of life and international attention garnered should be of considerable concern to the regulatory bodies, funders and central study team involved. It is hoped that the resulting scrutiny will enable a reflexive approach to the problems and failings, and provide a foundation for the appraisal and improvement of the clinical trials outsourcing process. Discouragingly there is already a substantive body of writing on the implications of outsourcing clinical trials, many of which justify outsourcing as a method for bringing treatment to market more rapidly (Bansal, 2012). However to make this the primary objective in outsourcing would be a mistake; this aim would fail to acknowledge that the foundation of professional clinical research lies in ethical practice and just treatment of participants. Only by adopting this philosophy as an overarching objective can clinical research justifiably develop clinical knowledge.

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