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Blinding authority

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Abstract:	In this paper we present an ethnography of biomedical knowledge production and science collaboration when they take place in developing country contexts. We focus on the arrival of international clinical trials to Sri Lanka and provide analysis of what was described as the first multi-sited trial in the country, a pharmaceutical company sponsored, phase 2, randomised, double-blind, placebo controlled trial carried out between 2009-10. Using interviews with those who conducted the trial and 6 months of participant observation at the trial hospital, we describe the work that goes on to perform trials according to international standards. The paper describes what happens when RCTs encounter existing epistemic virtues, and documents the impacts on ideas of authority, expertise and doctor-patient relationship found in Sri Lankan medicine.

Introduction

Biomedical science derives much of its analytical and empirical power from the claims that are made regarding its universality. Irrespective of where the techniques and procedures for scientific experimentation are enacted, the facts that it yields are believed to be essentially the same. In order for this to be the case, much effort has to go into the work of homogenisation, standardisation and stabilisation. Statistical variables, terminologies, languages, scales, measures, standards and properties, all have to be calibrated, demonstrated and put into practice in order that trials might become 'immutable mobiles' of the kind that Bruno Latour has elaborated upon – things that might bring change but without being changed in themselves (Latour 1987). Without this work, the experimentation upon which progress in biomedical science depends will not travel and, even if it did, it would produce results that were neither valid nor transferable. So, 'when experiments travel', to use Adryana Petryna's phrase, a good deal of preparation must be done to locate biomedical research within the global scientific episteme (Petryna 2007a, 2007b & 2009, also cf Fisher 2009; Lakoff 2005, Molyneux and Geissler 2008, Sunder Rajan 2007).

One of the ways in which experiments are currently travelling, and at some considerable velocity towards developing countries, is in the form of clinical trials carried out to ascertain the effectiveness of drugs, medical appliances and procedures. Such experiments have evolved in a matter of decades from relatively small-scale localised testing into vast and complex multi-sited trials involving thousands of people who may be located in many different countries (Glickman *et al.* 2009). Typically, a large scale clinical trial funnels standardised data from diverse settings into analyses that produce results that are methodologically plausible and statistically robust. Findings take on the character and currency of aggregated evidence on the basis of which generalisations might be made.

The 'gold standard' for such trials is the randomised, controlled trial (RCT), in which subjects are allocated different treatment groups under carefully monitored conditions in order that effects and efficacy might be evaluated (Marks 1997, Timmermans & Berg 2003). Immutability and increasing mobility are guaranteed through ever more scrupulous adherence to the rules and procedures for clinical trials laid out in documents such as the International Conference on Harmonization Good Clinical Practice Guidelines (ICH GCP). Although, as Abraham has argued, these standards are not in themselves evidence-based but rather reflect a corporate bias in favour of the pharmaceutical companies as against the interests of research subjects themselves (Abraham 2007). Nonetheless, evidence that these guidelines have been faithfully followed guarantees recognition and acceptance of results by wider scientific publics – drug regulatory bodies, academic peers, and journal audiences. Demonstrable capacity to index local practice to 'global standards' is essential if new pharmaceutical products are to gain acceptance by licensing organisations such as the American Food and Drug Administration, without which products will not be able to enter lucrative international markets.

The neatness of the RCT model and its claims to epistemic authority have been brought into question by a number of researchers interested in the processes rather than in the products of human experimentation (Cambrioso *et al.* 2006; Helgasson 2010; Moreira & Will 2010; Sismondo 2008). Here, the interest is in the mutability and manipulability of mobiles rather than their apparent immutability. Paying attention to the process reveals the modifications, negotiations, creative acts, and interpretations that underpin the successful accomplishment of a trial, and how the 'universalising rhetoric' of science operates in practice (Jasanoff 2005: 15). To borrow an analogy from Latour, those who are conducting clinical trials are not mere 'placeholders' in the mobile (Latour 2005); they are actors who follow scripts but they also interpret and improvise their parts, drawing on a multiplicity of experience, objects and persons that are then presented as consistent with unified comprehensive experimental paradigms (Knorr-Cetina 1999).

When clinical trials land in new contexts, many of the problems encountered by those attempting to make them work are likely to be of the kind found anywhere. However,

what we are keen to highlight here are the particular tensions that surround the introduction of new rules and practices which must be diligently followed on the one hand and the displacement of local and familiar routines on the other. The resulting perturbations are not only about technique and competence, but, as we go on to demonstrate here, involve an important but rarely broached aspect of global RCTs, namely, the way they stimulate different ways of thinking about how to read information from bodies and act upon that information (cf Adams *et al.* 2005).

Comment [d1]: Redrafted to emphasise what is commonality + what is new in what we are doing

New regimes of biomedical experimentation bring shifts in ideas about knowledge, causality, induction, inference and evidence. We show here that there is not one 'specific tradition of thought', nor one 'group of authoritative specialists', but a kaleidoscope of hybrid forms each with its distinctive character, these represent significant points of negotiation and accommodation in the otherwise clearly scripted accomplishment of multi-sited clinical trials. In drawing attention to 'epistemic virtues', Daston & Galison (2007) highlight how persons who take on the role of knowers in scientific research are connected to the knowledge they produce, not only as its practical orchestrators but also as its moral authors. Yet, they must also strive to create knowledge in which the marks of the knower have been erased, that is, aspire to 'knowledge unmarked by prejudice or skill, fantasy or judgement, wishing or striving' (ibid: 17; also see Zabusky 2000). Considering this apparent contradiction – between presence and non-presence, seeing and not seeing, intervening and not-intervening - requires us to engage not only with the products of science but with the social fields and cultural repertoires which inform the practices of scientists.

In this paper, we analyse how the arrival of the RCT model into a developing world setting is blended into existing practices but also rubs up against them. The bringing together of scientific endeavour across the North-South divide, between countries with established traditions of biomedical science and those that are 'scientifically lagging' (Watson *et al*. 2003), suggests a number of warm themes: networks might be extended, knowledge passed on, good scientific practice disseminated, innovative synergies

improved, a culture of technological dependence mitigated, subject protection improved, exploitation challenged and so forth. With the arrival of RCTs, however, cool themes also arise and notably the ease with which collaboration and bioethics might help mask exploitation in settings that are resource poor and inadequately regulated. We show that there is not merely a mode 2 science of the kind mapped out by Gibbons, Nowotny and others to demonstrate the socialisation of science (Gibbons *et al*. 1994; Nowotny *et al.* 2001; in developing country contexts see Holland 2009) but a more complex engagement between experimental practice and culture which might be better characterised as science practiced in mode 2^n where the *n* counts for the multiplicity of cultural factors that need to be recognised, negotiated and accommodated in order that in any particular country a trial might be accomplished in line with the norms and standards of clinical good practice .

Methodology and analytical focus

The setting for this work is the conduct of an RCT in Sri Lanka, a country in which the history of large international multi-sited RCTs is very recent. It is also a country where there is currently an ardent desire to become part of the global laboratory that RCTs have ushered in.[1] To figure in this laboratory it is essential that local practices meet 'global standards' and that this can be demonstrated, supported and, most importantly, evidenced and audited. Like some landing strip for a latter day cargo cult, the conditions for this new form of wealth creation must be built as a necessary precursor to future prosperity. Glossed as 'capacity-building', these activities include recruitment of personnel (clinical research assistants, trial managers, statisticians and data managers); the formation of ethical review committees; setting up hospital sites; the establishment of monitoring procedures; and the assembly of rooms, computers, and other technology; the creation of virtual networks, and other paraphernalia of the multi-

[1] Whilst participation in international licensing multi-sited RCTs has a very recent history, single-site clinical trials go back a long way. Pieris (2001: 132) refers to a report in the Journal of the Ceylon Branch of the British Medical Association from 1917 describing a trial carried out at the General Hospital using Morphine and Hyoscine as anaesthetic during labour.

centred trial. Without this capacity, the benefits of future economic, intellectual and social capital will not flow.

Specifically, ethnographic research was carried out into the ways a pharmaceutical company sponsored, phase two, randomised, placebo-controlled trial was set up and implemented, and Sariola also interviewed the doctors and researchers who were involved in the trials. Themes covered in these interviews included: the trial process, ethics of clinical trials, relationships within the team, responsibilities of the different team members, consenting process, doctor-patient relationship, and doctors' roles in the Sri Lankan society.

We investigated how the RCT provides just one regime of knowledge making, albeit a very powerful one. The rigorous objectivity and detachment needed for the conduct of a large multi-sited RCT, is capable of prising apart other modes of connection which must be set aside in the collection of credible scientific evidence. The fieldwork presented here documents the reconfigurations involved in these new processes of knowledge production: breaking connections, rupturing relationships and instilling a sense of detachment. '*Why the interest in the messy stuff?*' asked one of the trial researchers at Sariola's fieldsite. He was bemused at her interest in anything other than the outcome of the trial, nothing else could possibly be of relevance. But, we contend that in the 'messy stuff' lies a complex biopolitical operation in which existing practices, and assumptions are transfigured in favour of new modes of detachment in order to render the body an object of pure quantification.

The crux of the argument we develop here is thus essentially a cultural one, which draws attention to the fact that in the acceptance of new forms of authority, aspects of existing medical and scientific practices must necessarily be disciplined and displaced. Erasing the knower from what it is that is eventually known is premised on the existence of certain kinds of knowers who must be trained and instructed, not just in

what to know, but how to know it; detachment of the social is necessarily preceded by the socialisation of detachment. But what exactly are the practices that these novel forms of rationality discipline and displace?

'Modern science' in developing world contexts

In numerous essays and talks published over the two decades, the eminent Sri Lankan microbiologist Professor S.N. Arseculeratne has sustained a scathing critique of the state of science education and awareness in his native Sri Lanka (Arseculeratne 1997; 1999; 2008). In his view, there is a widespread deficiency in the way that science is promoted and understood in Sri Lanka, a kind of scientific malaise that runs through the major teaching and research institutes and which is particularly evident in the way that medical education is delivered. His pessimistic view on the state of Sri Lankan research culture is endorsed by statistics which suggest that science capacity (based on numbers of international collaboration, publication, and funding) in Sri Lanka is fourth lowest in the world (Wagner 2008).

One of Professor Arsecularatne's main criticisms of the state of research in Sri Lanka is that medical education is largely based on factual recall and rarely encourages analytical, experimental or creative approaches. In one of his most recent talks he urges that medicine needs to be seen 'not merely as a craft with utilitarian ends, but as an important component of science with an intellectual background that includes the history and philosophy of modern science' (Arseculeratne 2010). One corollary of this utilitarian orientation is that medical research is not strong in Sri Lanka. Underdevelopment in biomedical research can also be attributed to the 30 year civil war and other violent uprisings in the past 20 years which have had an impact on the amounts of research funding available and have also contributed to a significant drain of expertise out of the country.

In contrast to this view of the rote-learning medic practicing in an enfeebled research environment, Sri Lankan medical students are also pointed towards a venerable tradition in which local doctors working in resource poor settings have overcome tremendous odds using their ingenuity and skills of improvisation. As Pieris puts it in her history of the Sri Lankan medical profession: 'the dedicated government doctor could be described as possessed of a perpetual pioneering spirit in that the government service invariably held shortcomings which the doctors had to somehow overcome if they were to deliver a satisfactory service' (Pieris 2001: 139). In contemporary settings, doctors still have to be able to perform with limited diagnostic testing facilities and make decisions drawing on basic clinical expertise, judgement and experience.[2] The heroic image of the doctor that medical students are taught to emulate is that of the healer, the one who, in the service of others and without thought of material gain, brings relief from suffering – a benevolent and paternalistic role which has particularly powerful resonances within Sri Lankan culture.[3]

The system into which junior doctors were being inculcated at the time of our research could thus be described as 'craft'-oriented and one in which the full impact of an evidence-based medicine paradigm had not yet fully penetrated. As Timmermans and Berg would have it, this is a system characterised by a 'disciplinary' rather than a 'mechanical' objectivity (Timmermans & Berg 2003). Students encounter an authoritative approach in medical education and practice where relationships are marked by strong vertical hierarchies based on status, knowledge, charisma and reputation. Relationships are marked by intellectual and professional patronage; they often follow lines of kinship, religion, class and, occasionally, caste. They are also likely to be based on membership of a particular medical cohort or what are referred to

[2] While in earlier times, this tradition of independent experimentation placed Sri Lanka on the map as a place where some significant medical advances were first pioneered, particularly in the field of surgery and the management of tropical diseases, and Pieris refers to the mid-19th century surgeon P.D Antonisz being lauded for carrying out the first successful oesophogotomy and ovariotomy (Pieris 2001: 129).

[3] For example, Buddha is often compared to a physician diagnosing an illness and prescribing its cure. As the influential scholar-priest Walpola Rahula points out: 'He is the wise and scientific doctor of the world (Bhisakka or Bhaiṣajya-guru)' (Rahula 1978 [1959]:17).

locally as 'batchmates'. The steep power gradients that separate junior medical staff from their superiors manifests in a good deal of fear, concern to avoid offence and a tendency to replicate rather than challenge received wisdom among the former. To fall foul of a powerful senior is to risk long-lasting damage to reputation and future prospects. The teacher's position in this hierarchy is in part based on managed ignorance – he or she keeps people in their place by determining what it is they get to know or are prevented from knowing (Dilley 2010).

Introducing RCTs into hospitals and clinics must engage with this existing 'field of practice', to use Ingold's term (Ingold 2001: 114). This is one that is marked by poorly developed research culture, where there is emphasis on medicine as healing, where relationships are highly stratified and power differentials are vertical. In this encounter, a series of tensions emerge. These concern issues such as the place of experience in epistemology, the hierarchical distribution of knowledge, the nature of expert authority, the management of ignorance, the place of evidence-based medicine in a craft tradition and ultimately between care and research in biomedical encounters (Davis *et al.* 2002; Easter et al 2006; Fisher 2006). In the sections that follow, we describe how in the conduct of the trial, the cultivation of detachment becomes central. First, we discuss how randomisation, blinding, and responsibility for clinical decision-making land in a context where seeing, caring and healing by the doctors prevail, and second, we discuss what kinds of changes to existing ideas of authority and expertise the RCT brings.

On blindness and vision in biomedical research in Sri Lanka

We begin this reflection with a vignette that illuminates the changes that RCTs usher into the social life of biomedical research in Sri Lanka. The main *dramatis personae* are five trial assistants who were also junior doctors, two pharmacists, four senior doctors, an Indian CRO monitor and two representatives of the sponsoring pharmaceutical company – one Sri Lankan and one English. The trial was located in a university faculty and conducted in a clinic in a near-by government hospital. As one of the first trials of this kind in Sri Lanka, the team involved were extremely committed to getting it 'right'.

The junior doctors/research assistants were in charge of data collection from the patients and observed the giving of trial drugs while the senior doctors gained consent from patients and handled the investigations. Pharmacists handled the drug regimens. The Indian CRO monitor audited the data collection and the resulting data which was sent abroad for analysis. The story takes place on the day before the first patients were to be given the experimental compound or the placebo. The experimental compounds were supplied by the overseas trial sponsor in white boxes that had randomised number codes on them.

In preparing the delivery of the experimental drugs to the research subjects, one of the research assistants noticed that something was wrong. The team of research assistants huddled together and studied the envelopes and the fridge where the drugs had been kept in an attempt to figure out what was amiss. They read over and over the randomisation instructions that told them to match each kit number to the numbers found in the envelopes. However, they began to realise that they did not have the kit number to match the randomisation numbers, but rather had been given information about which dose, active or placebo, each patient would be given. In effect, they had been 'unblinded', and this was a code break and therefore a protocol violation. They went to talk to the senior researcher managing the trial. Lots of phone calling ensued, documents were written, forms signed and anxious shifting of weight from one foot to another as the assembled team considered what to do. They concluded that they knew which doses that patients 9 and 15 were going to get and reasoned that even if the remaining patients were blinded according to plan, they could not unknow what it was that these two patients were going to receive. As this extract from Sariola's notes reveals, the senior researcher took charge of the crisis. He addressed the group thus:

> '*They will have to randomise the whole thing again. Call the patients and give them some lame excuse not to come tomorrow'.*

But then he changed to Sinhala to give instructions.

> *'We have to inform the patients, we have to contact these patients before tomorrow'.*

Switching back to English he continued:

'At least now we know, we have got the experience.'

He picked up the phone to call to [overseas sponsor] and, as he waited for an answer, he spoke to the group, as if to reassure them:

'It was not our fault. Not our fault, we were sent the wrong envelopes'.

Someone in the overseas headquarters picked up the phone:

'Hi, XX here. Listen, a small issue. You sent us the wrong envelopes. We have been unblinded, need to re-randomise everything ... Right, okay ... I'll talk to you again in the evening'.

Addressing the group after the phone call is over, he announced:

'We will start next Monday instead.'

At one level, the vignette describes an everyday episode in the course of a collective technical endeavour: a problem arises and is solved; the unintended deviation from what was planned is diagnosed, hierarchies are activated, solutions are formulated, judgements are made, and actions are taken – the crisis passes. Likewise, the response to the crisis would not be much different in a laboratory or hospital ward anywhere in the world. At another level, however, the vignette gives an important insight into the distinctive work that goes into stabilising the process of knowledge production in the Sri Lankan context.

The notion of blinding is central to the methodology of the clinical trial and is intended to confound the possibility that those who are conducting the trial might have any knowledge of which patient is getting what treatment. The purpose is to eliminate the possibility of bias, technical, regulatory or otherwise, on the part of the researchers. In keeping with the requirements of the Good Clinical Practice Guidelines, documentation, including the patient information sheets for the trial, must be translated into local languages. In this case the languages are Sinhala and Tamil, 'Double-blinding' along with other words in the technical vocabulary of RCTs are not ones in common parlance in Sinhala and Tamil. For example, put before a native Sinhala speaker with experience of translating documents from English into Sinhala, it was clear that many words in the vocabulary used were either complex neologisms, hybrid terms or straight borrowings

from English that would not be easily grasped by non-specialists. However, it is not our intention here to revisit a well-documented challenge in rendering science accessible across chasms of 'literacy' of one kind or another. What is of note at this point is the glimpse that the act of translation gives us into some deeper epistemological issues surrounding the ways in which knowledge and its creation is perceived in different language worlds and how these worlds reflect the standardisation performed in introducing RCTs into Sri Lanka.

In Sinhala, the term for blinding that was used in the patient information sheets and consent form was *ubhayā dṛśya næhæsumeṇ* – double (both) vision negated. Interestingly, the translation produced by medical translators locally did not elect to use a word which refers to blinding as the removal of sight (*andha karanava*). The usage here refers to negated vision. Whilst there are connections between ideas of vision and the status of evidence to be found in many different cultural contexts (Bloch 2008), consideration of the idea of vision negated, as distinct from the state of blindness, is subtle but important in a society in which vision and eyes carry a distinctive symbolic and metaphorical load. Vision links to knowledge, realisation, enlightenment and indeed to animation and life itself (the Sanskrit root *drs* means not only to see but to behold; to visit; to learn; to investigate). 'Blindness', on the other hand, can be a derogatory term wh carries connotations of ignorance, darkness and even stupidity. It is an intrinsically disabled state and therefore an undesirable one. The idea that doctors should be placed in this position is thus somewhat incongruous. Vision leads to knowledge and is integral to experimental and investigative procedures. Doctors might be presumed to cultivate this kind of seeing as part of their skill as healers. Yet, in this context, it appears to meet an intention to prevent or impair it; the vision that is otherwise intrinsic to human experience in general and a doctor's role in particular, is being uncoupled from its groundings in curiosity, empirical understanding and inference. The intended rhetorical and metaphorical force of the notion of blinding in RCT methodology is to render trialists anywhere subordinate to scientific rigour and procedure. Whilst, the move into Sinhala carries much of the same force it also activates a particular semantic and epistemic universe in which negating vision implies the

impairment of a faculty which is otherwise seen as critical to medical procedures and experientially based knowledge.

Comment [d2]: Redrafted para

The practice of 'blinding' and randomisation reveals a new kind of intentional unknowing; a 'mechanical' or 'regulatory' objectivity that had to be inculcated among the junior doctors dealing with the trial patients (Cambrioso *et al*. 2006; Timmermans & Berg 2003). Indeed, objectivity and the guarantee of scientific validity are achieved by eliminating certain kinds of relationships between the junior doctors and their patients. In ways that they find discomfiting, they are cut off from the knowledge of which patients get the active dose or the placebo and those who conduct the analysis of the data have no contact with the patients, they just compile the data. As far as this methodology goes, the researchers are ciphers in the conduct of the trial. Doctors, who might otherwise follow their disposition as healers, that is, imitate the resourceful ingenuity of their teachers and invest emotional energy in the outcome of their interventions, must now practice a new kind of detachment. They are no longer operating in craft-mode but are recast as mechanical and meticulous monitors of the body and its functions.

The particular kind of detachment that is advocated here is primarily in conflict with the relationship that a doctor would normally have with a patient, that is, a therapeutic one in which he or she would expect to exercise an active decision-making in the patient's interest (cf Easter *et al.* 2006; Fox 1959; Mueller 1997; Taylor 1992). A senior researcher went further in describing how the detached, blinded, conduct of clinical trials undermines the bond of trust between the patient and the doctor:

> *'What I feel is that going down this clinical trials route will generally contribute to further distancing the doctors from the patients. Our consent form generated such anxiety among the patients that I felt it was leading to distancing. There were instances where I had to talk to the patients for a few hours and then I thought to myself: what are you doing here? You've created so much doubt with the consent form in the patient. By pursuing more with the answers that they want probably to*

hear, I was contributing further to the distance. Patients are not looking at it from a philosophical viewpoint but the common propaganda. 'Western pharmaceutical company is exploiting the Sri Lankans, or people from developing countries. Am I going to be a guinea pig in this trial?' So I thought to myself: this is not the way to get through to these people, there has to be another way. Informed consent as a tool isn't appropriate but it is a standard. How do you get out of it?

SS: What's the problem with the distancing?

Medicine has become a financial transaction and there is an aspect of profiteering expense of another. The context in clinical trial would fall into that. [The patient might think] What is there for him [the doctor] to offer this for me? In the phase two trial you don't really know if it works or not. Given that, when you tell the patient that this is the situation, it raises the first doubt. 'If that is the case, why does he want to give it to me?' Then various other constructs such as exploitation come in to mind… In medical paternalism in the doctor-patient relationship the doctor knows best. And when the doctor knows what is best for me, why is he giving me this experimental drug? That's the conflict. That's why I feel that there has to be a better way of doing this. I just don't know what that is.'

In the quote, the doctor describes how the clinical trials encounter is an inversion of power and trust relations that he has come to expect in a medical context. Trust is replaced by a role in which the intervention is 'blinded', doctors are intentionally put in a position where they cannot influence who gets what drug. In the paternalistic medical relationship, doctors are expected to be dominant and the detachment that comes with blinding and consenting have the potential to undermine the mutual understandings of how a good doctor and a good patient should act towards one another. Eliminating one modality of attachment – to the patient as a person, to the idea of relief and to the role of knowing intervenor – is intended to amplify others – as a monitor of human subjects tuned to observe the precise impacts and 'adverse events' of a drug which they may or may not know they have administered. The doctor is detached, and yet the Sinhala translation of blinding maintains that they are not ignorant or incompetent, they have simply had their vision blocked.

The arrival of the RCTs has not only introduced new modes of detachment into clinical relations with patients but also into relations among medics themselves. Randomisation, blinding, and responsibility for clinical decision-making, land in a context where seeing, caring and healing is seen to be done by others whose job it is to supervise and teach. Much of this practice was tacit but nonetheless had to be challenged in order to produce the kind of data needed to meet pharmaceutical company standards. As we see in the next section, the new discipline of the RCT brings existing epistemic authorities and expertise into question.

Changing forms of authority and expertise

Conducting a trial that had been unblinded would have constituted mismanagement and could have had a wide range of professional and economic consequences for everybody involved. The episode reveals a series of dislocations which are interesting when set against the hierarchies that usually operate in medical settings. Two things are of note. First, it is the junior doctors that are pointing out the error and bringing it to the attention of the senior doctor, something that in existing, non-research, clinical settings might be tantamount to a breach in etiquette. Second, the authority that is ultimately invoked is one which lies not only outside the laboratory but outside the country. Authority is to be found in the disembodied voice of the trial sponsor on another continent and with the external monitors who instruct the team on the minutiae of data collection. Both these observations point to ways in which the novel rationalities which come with the trial unsettle existing hierarchies and roles. New forms of disconnection open up the possibility for challenge and critique which are not typically part of the relationship between juniors and seniors. The RCT challenges its familiar, rigid and carefully observed medical hierarchies and replaces them with one that is novel, diffuse and emergent.

As one of the monitors explained, his role was to report to the pharmaceutical company, but his organisation is independent from them. Independent monitoring is something that is required for trials that aim to get drugs licensed for international markets. In

effect, the mediating role of the Clinical Research Organisation – positioned between the trialists and the sponsor – is a lucrative insertion in the clinical trials assemblage. The CRO monitoring the trial in Sri Lanka had international offices in Australia, India and New Zealand, and had over 100 research sites across the world. The monitor on this occasion had a chemistry degree, and was also enrolled for a PhD funded by the CRO. He visited the Sri Lankan site about once a fortnight and went through the running of the trial in considerable detail with the staff. His role, as he saw it, was 'to make sure that sites identify the correct patients, ensure the safety of the patients, and deal with ethical issues or matters of confidentiality'. He did not have patient contact, but went through all the paperwork: the patient case records; informed consent forms to check that they were signed; that patients were given time to decide and had had the details of their involvement explained to them. As he described it he was there to cross- and double-check patient files relating to trial participation. The monitor played a fundamental role in directing and correcting the trialists in order to ensure that the protocol is implemented in the same way across sites. In carrying out this role it was clear that staff were unfamiliar with and occasionally annoyed by the attention to detail and frequency of his questions. Things that were not normally documented had to be recorded according to the dictum: 'not documented = not done'. In his view, if test results, examinations, the minutest of adverse reactions and observations were not recorded in writing, dated and signed, it would be the same as if they had never happened. As he commented: *'Monitoring is not just about creating rules for the sake of rules according to guidelines but these are real questions regarding real patients*.' Interestingly, he also pointed out that there are no guidelines for monitoring which seemed to be the only part in the standardised clinical research process that is not externally regulated and governed. It represents a loophole through which the inexorable involution of audit procedures might unfold in the quest for ever more perfect standardisation. The insertion of the CRO into the clinical trials assemblage is thus not only lucrative but carries significant power when it comes to disciplining local practices.

In going about his work, the monitor said that he was finding some minor flaws in the way that the trial had been done. He thought that the local team was generally well-qualified for this kind of work. His concerns related to minor faults in documentation and discrepancies in dates and times which were not seen as the fault of any particular coordinator but had arisen because they were doing things 'for the first time'. ICH GCP guidelines were a new experience to the team in Sri Lanka and they were surprised by the levels of stringency; higher than what they were used to in other kinds of clinical research and practice. The junior doctors involved in the trial all said that keeping pace with the paperwork was the heaviest part of their workload; there was a lot of it. As one senior researcher pointed out:

> *GCP guidelines and their conduct was a new experience for me. Expectations had to be met with great attention to detail. (There was) Tons of documentation. They want it to be adhered to so carefully. Actually it was very good. I didn't know if they were interested in something, whether it was trivial or not. Like when we were doing some blood samples after dosing, blood had to be taken every five minutes after. It is a protocol deviation if you didn't take it exactly at that time, and if you don't then you have to inform the ethics committee.*

And another senior researcher pointed out:

> *They want all information collected meticulously. So much detail! Sometimes what happens is that I work from 8 am to 10 pm [with non-trial patients] and sometimes I get tired and I cut corners and take symptoms according to what patients say rather than testing: "Doctor my shoulders hurt" and I'll just note it down. Here you can't do that. You have to test everything.*

The importance of instilling the discipline of meticulous recording was expressed by all the junior and senior doctors alike. The point here, however, is not just about the increase of rigour in clinical conduct and audit but the doctors' responses to paperwork tells us also about how the RCT changed the role of knowers in the process. A quote from the representative of the pharmaceutical company highlights the tension further:

> *My duty is to follow the process and I came here to guide these people, and this is said with all respect, these guys are great. There were a few things that needed talking over and I preferred to talk things face to face. So I came to talk about few things that were of major concern. It might feel like 'oh my god', but then you*

remind yourself that these people are doing a trial for the first time and they can be simply discussed through. Some little things that needed guidance that helping through will improve. Last time I came I went through the files and I noticed that there were hardly any adverse events reported. Reporting them is important and reporting everything that the patients are telling so that the risk-benefit ratio is met. So in order to collect safety and efficacy data, I saw that hardly any adverse events were reported. That's very unlikely. If that's the case, you have a wonder drug! So you doubt that. Like normally in a period of 4-6 weeks you would have a number of little coughs and colds, some little things, you might cut your finger, whatever. All of those have to be reported as adverse events even if they don't seem immediately to be related. It could be that all of them are cutting their fingers while cutting onions and then when you're collating the data you think, hmm, maybe this has to do with coordination. So this morning I explained that. Normally you'd see a lot more bad things happening and it's hard to explain these things by email or skype or whatever but I think it's best to talk about this face to face so I hopped on the plane to come over.'

The under-reporting of adverse events led the company representative to speculate as to whether doctors were making their own on the spot interpretations of just what might constitute a significant adverse event and screening out much that might be of relevance. Junior doctors who were collecting the data, were, in effect, doing what all their training had directed them to do, that is, processing complex and diverse information into meaningful patterns – deciphering diagnoses with limited testing facilities. Yet, in the trial, the intention was to suspend diagnostic meaning making and to see all signs as potentially relevant. Significance would come later, and to someone else in another place, once all the data had been pooled. It would be arrived at by statistical rather than experiential means. For the research assistants it would therefore seem that their abilities as recently qualified doctors had been replaced with a different set of competences largely determined by the dictates of the protocol and carefully supervised by a variety of monitors who bring an authority which is not that of the senior doctor or physician to whom they usually defer.

Old epistemic virtues and expertise thus appear to be displaced as the junior doctors are made to think as researchers and the patient is reconstructed as a human research

subject capable of yielding a wealth of quantifiable evidence. The patient becomes a representation of sorts; a composite of measurements, readings, numbers, and other kinds of 'evidence'. In the quest for standardisation, other stories must necessarily be over-ridden or lost within the logic of the trial. Knowing and connecting too soon was one of the very things that could place the credibility of the trial in jeopardy.

Conclusion

In documenting the global spread of RCTs, much attention has been focused on the neo-liberal turn in their regulation, governance and financing (Abraham 2007; Fisher 2009; Lakoff 2005; Petryna 2007a, 2007b & 2009; Sunder Rajan 2007). What has received less attention is the day to day implementation of novel regimes of doing biomedical research. In documenting the implementation of an RCT in Sri Lanka we have drawn on ethnographic data to capture the fine grain of RCT conduct in this new setting. In this analysis, what is evident is the merging and clashing of new practices and existing paradigms. Hierarchy meets diffused power structures, craft-based knowledge meets evidence-based research, doctors' role as healers and providers of utilitarian and benevolent service are over-ridden by the need for rigorously mechanical observers. As such, RCTs constitute a distinct and powerful way of organising evidence and experience; a particular instance of the 'conquest of abundance' to use Feyerabend's characterisation of the scientific enterprise (Feyerabend 1999). The example we have used to illustrate this process and the tensions that underlie the accomplishment of global science is that of the implementation of 'blinding' and how this elementary metaphor links with a complex and culturally specific set of ideas about seeing, knowing and being that have important consequences for what it is to be a healer in the context of Sri Lankan biomedicine. In the local setting, these ideas further articulate with ones about causality and inference in medical examination. Blinding and randomisation dislocate authority and unsettle existing ways of managing knowledge and ignorance in professional hierarchies. What the RCT ushers in are new ways of thinking of what is real and apparent, what counts as knowledge and opinion, what passes as objective and subjective data, and who has the capacity to make these judgements. Demonstrable

induction into these ways of thinking and doing are essential if local experimentation is to have currency in the global scientific episteme of the multi-sited clinical trial.

Comment [d3]: Redrafted to highlight where our contribution fits

What we have described are the ways in which doctors are, in a Foucauldian sense, being 'disciplined' anew. They are trained in an allopathic medical tradition yet practice in a South Asian setting and must necessarily bring themselves into line with the authority evident in protocols, and guidelines. In this they are directed by the various monitors and managers who convey instructions from worlds outside the lab, the institution and, indeed, the country. In submitting to these new authorities, the team needed to begin to think itself out of familiar biomedical routines, connections and into new hierarchies marked by novel practices of disconnection and detachment. The process is one in which a great deal of negotiation, improvisation and 'bending' went on to create the appearance of the standardised trial. This we suggest might be thought of as mode 2^n knowledge production, that is, one which is not only socially robust but also culturally robust by virtue of having worked through the challenges of embedding trials in culturally diverse settings. However, this is not to imply that trials in Sri Lanka are in any sense run badly, deceptively or inappropriately but rather that in the running of any trial, the 'local' and the 'tacit' are ever-present and without their appropriate incorporation and management new biomedical knowledge could not be created and put into wider circulation.

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