

## Meeting Pragmatism Halfway: Constructing a Pragmatic Clinical Trial Protocol

Alexander Rushforth (CWTS, Leiden University)

This is a pre-print of an article accepted for publication in *Sociology of Health and Illness* copyright ©2015 (Wiley)

### Abstract

Pragmatic clinical trials (PCTs) are today an increasingly prominent means of measuring the 'effectiveness' of healthcare interventions in 'real world' clinical settings, in order to produce evidence on which to base regulatory and clinical decision-making. Although several sociological studies have shown persuasively how PCTs are co-constructed within the particular healthcare systems in which they are based, they have tended to focus on relatively later stages in careers of trials. The paper contributes to literature by considering how the 'real world' of the UK National Health Service (NHS) is incorporated into the design of a research protocol. Drawing on a meeting held just prior to patient recruitment for a PCT in maternal health, the paper analyses a trial collective's efforts to purify the messy domain of NHS clinical care into the orderly confines of the protocol (Law, 2004), which meant satisfying demands for both scientific *and* social robustness (c.f. Nowotny et al., 2001). The findings show how these efforts to inscribe robustness into the PCT protocol were themselves mediated through epistemic and regulatory conventions surrounding protocols as devices in healthcare research. Finally it is argued that meetings constitute an important epistemic instrument through which to settle various emerging tensions in PCT protocol design.

**Word Count:** 7933

## Introduction

Medical sociologists have for some time been critical towards assumptions that the tools of evidence based medicine (EBM) necessarily provide the privileged epistemic stance from which decision-making in health care ought to be derived (Mykhalovskiy and Weir, 2004, Timmermans and Mauck, 2005, May, 2006). Within this corpus of works, less attention has been given to so-called pragmatic clinical trials (PCTs), which test new or existing medical interventions in 'real-world' settings, that is, on relevant patient populations in the course of their medical treatment (Macpherson, 2004). This lack of emphasis is perhaps surprising given that such trials are today a staple feature of Health Technology Assessment (HTA), the regulatory science movement institutionalised in many national healthcare systems. In the UK National Health Service (NHS) for instance, such trials enjoy large amounts of sponsorship through the National Institute of Health (NIHR) HTA program. As a 'social technology' for producing standards in healthcare, advocates argue PCTs embody a more 'pragmatic attitude' towards measuring interventions than is typical of traditional pharmacological trials which measure efficacy of an intervention under assumed ideal conditions (Roland and Torgerson, 1998). However, a more cautious reading would point out PCTs still embody many assumptions behind epidemiological research of which social science researchers have been critical, including often retaining the RCT method as the gold standard for producing healthcare evidence (Cartwright, 2007, Zuiderent-Jerak et al., 2012).

Despite widespread criticism of the rhetoric of neutrality often attached to methods of HTA fact-making and its displacements of alternative approaches (May et al., 2003), little is known of the knowledge making processes of PCTs and how such 'purification' (Latour, 1993) is achieved, particularly at the level of research protocol production. A small number of sociological studies focusing explicitly on PCTs cite perennial difficulties like attracting sufficient quantities of patients and clinicians as participants (Jansen et al., 2006); getting results noticed among regulators and practitioners upon trial completion (Kelly, 2010); or struggles social actors within healthcare systems face in scaling-up findings as 'evidence' (Will, 2007). Such science studies oriented accounts have argued persuasively that PCTs are forms of regulatory science 'co-produced' within the parameters of their host health care systems. A recent edited collection (which included contributions from some of the above-mentioned authors) characterise PCTs as exemplars of 'mode 2' knowledge production (Moreira and Will, 2010). This widely-used concept refers to a more 'contextualised' form of knowledge making, distinct from 'mode 1' research associated with disciplinary structures in single institutions like universities. Mode 2 emerges within cross-disciplinary settings, closer to contexts of application where 'science' and 'society' co-construct one other, making it an altogether

more ‘socially robust’ form of knowledge making (Nowotny et al., 2001). Building from these empirically-oriented accounts, it is suggested abstract notions like ‘social robustness’ work best in relation to exploring PCTs when treated as a *topic* of analysis, rather than explanatory resource (Jensen, 2010). Despite laying this groundwork, case studies of PCTs to date have tended to zoom-in at later temporal stages of PCTs. This paper therefore builds on this literature by focusing on how a PCT collective sought to construct this form of research within the constraints of an earlier and quite distinct socio-material setting. The primary material is taken from a meeting that took place *prior* to the launch of a multi-centre, pragmatic randomized controlled trial on a maternal health intervention already partly used in the NHS. Hosted by a university clinical research team, the trial sought to obtain evidence through which future guidelines and regulatory decision-making could be based on whether an intervention be adopted as a standard part of NHS care. The meeting included the Trial Management Group (TMG) who were the protocol authors, along with trial steering committee (TSC) and data monitoring committee (DMC) members who were independent monitors of the trial. This temporal focus opens-up questions of ‘co-production’ specific to this underexplored stage of PCTs, including exactly *how* a cross-disciplinary collective navigated dual demands for being ‘systematic’ (for instance in attending to the RCT and its conventions) *and* ‘pragmatic’ (in accommodating the messy world of clinical practice). Furthermore accessing this meeting enables one to elaborate on which ‘scientific’ and ‘societal’ components get discussed, re-worked, taken into account, and/or re-ordered into the trial protocol; which claims are played-down or even silenced; and which spokespersons are able to make such claims.

### **The Trial Protocol**

The empirical material is drawn from a larger ethnographic study with an academic clinical research team hosting this trial, which worked on maternal health in the NHS through PCTs, observation studies, and systematic reviews. The fieldwork included interviews, document analysis, non-participant observations of research and educational projects, and the group’s weekly team meetings. However, the decision to zoom-in on this particular trial meeting is deliberate, as this occasion revealed some of the difficulties of designing trials of this sort within the conventions of the research protocol, with potential weaknesses and adjustments to the near-final version made audible by the participants themselves. An informative account of guideline development meetings in French oncology suggests these committee’s actions are not reducible ‘simply to a decision about a pre-set number of choices, but [that development] often leads to novel, unexpected solutions’ (Knaapen et al., 2010). Likewise the focus here on a meeting between TMG, TSC, and DMC to ‘fine-tune’ the research protocol can be cast as an occasion that exhibited its own interesting ‘dynamics’

and 'peculiarities' (ibid). I build on this interest in meetings, by arguing this constituted an important epistemic instrument in the formation of such a research protocol (in addition to prior and subsequent smaller meetings, conference calls, and emails referred to among the collective). Such occasions of bringing cross-disciplinary collectives together enact closure rather than consensus (Knaapen et al., 2010), suggesting participants would strive here for a protocol which is considered 'good enough' and 'workable'. However, for informants in this study, the protocol's 'robustness' is a distinct kind of challenge, as unlike with guideline makers, it is committee members themselves who will have to follow the protocol document as the trial proceeds and who will be made more directly accountable for its perceived successes and failings.

The protocol meeting was centred around a large (1000 women) multi-centre RCT design involving women treated with anti-epileptic drugs to control for seizures in pregnancy. The trial's primary objective was to evaluate the effectiveness of two strategies for monitoring dose levels among this population and whether the presence of a blood test actually lowered seizure rates (compared with an arm of the trial where participants were blinded from blood test results). The clinical background related to a lack of standardization to how this population was being routinely managed through anti-epileptic drug treatments in the NHS. The production of a highly-powered, well-designed RCT was explicitly stated in the protocol as providing a scientific evidence-base through which to make future decisions on whether these blood tests ought to become standard<sup>1</sup>. Research protocols are largely obligatory in the organization of modern large-scale health research projects, as both epistemic and regulatory devices (Keating and Cambrosio, 2012), which 'codify' the design of trials (Montgomery, 2012). Their presence is required in order to gain funding and regulatory approval from agencies like NIHR-HTA funding pragmatic multi-centre trials (Busse et al., 2002). By enforcing a highly deductive model of science, protocols are held as fundamental to 'ensure smooth running and successful conclusion' to a clinical trial (Holloway and Mooney, 2004), as they are held to protect the purity and integrity of the trial's design (Montgomery, 2012). Protocols are not the products of individuals, but clinical collectives consisting of academic researchers, clinicians, and administrators. The meeting of the trial's sub-components (TMG, TSC, DMC) is a regulatory convention pre-specified in a number of clinical research guidelines, with the formal purpose of ensuring steering and data monitoring committees have checked the protocol and are willing to serve as independent auditors of the project (Ellenberg et al., 2002, Cambrosio and Keating, 2009). In addition to fulfilling this regulatory concern, the meeting afforded the collective an opportunity to express doubts about how the protocol 'script' will likely be followed (or not) and to reaffirm or re-distribute where future accountability and credit is to be assigned among trial components. The specific timing of the meeting was important for framing what could be recommended regarding the protocol. The chief

investigator announced at the start of this meeting that given the levels of evaluation and auditing the protocol had already been through<sup>2</sup>, members of TSC and DMC should use this occasion in particular for the raising doubts:

This is a very important element- this meeting is being held before the first patients are recruited. The project has already been peer reviewed and funded through peer review. It has been submitted to the ethics committee, so it has an input from ethics. So I think we are at the stage where we have done everything that could have been done to obtain scientific, critical and independent review. If the document in front of you is in some way unsatisfactory to you then you should let us know very quickly, because once the patients start getting into the study the opportunity to bring about changes will become limited.

The protocol document itself followed a pro-forma structure, including sections such as *Background, Study Design, Eligibility (inclusion criteria), Study Procedures, Data Management and Quality Procedures, Health Economic Design*, reference list, and an *Appendix* including a detailed *Data Monitoring Committee Charter*. A summary located near the beginning of the protocol stated that the trial design was ‘specifically chosen to resemble clinical practice’. Whilst this might be an empirically telling statement from the participants, the word *chosen* does not provide a particularly satisfactory sociological version of how the protocol was developed. Indeed this seems consistent with a literary style for reporting knowledge characterized by ‘purification’ (Latour, 1993) or ‘ordering’ of research which seeks to conceal ‘mess’ (Law, 2004). Instead of imagining the trial collective has *chosen* a protocol to represent an ‘out there’ clinical reality, authors in science studies argue a notion like *construction* enables a more authentic version of how new clinical knowledge emerges through the ‘in-here’ of the clinical trial’s extended apparatus (Law 2004).

### **Constructing Clinical Facts**

Despite there being few empirical studies which have focussed on this stage of pragmatic clinical research, previous constructionist accounts of EBM and HTA research provide some important signposts. Drawing on conceptual touchstones of science studies, Moreira has portrayed modes of HTA research as a matter of re-ordering a complex healthcare organisation like the NHS into a research ‘laboratory’ (Moreira, 2012). Of course the very positioning of healthcare research within formal programs like NIHR’s HTA program and its attendant infrastructure has important consequences for the forms of knowledge which can and cannot be performed. Moreira’s earlier attention towards the making of systematic literature reviews and meta-analyses is a case in point, as he described how researchers responded towards multiple levels of accountability, being

constantly faced with dilemmas to satisfy both 'rigor' and 'relevance' criteria, which impacted in this setting on decisions about which texts to include and exclude from their secondary analyses (Moreira, 2007).

HTA is a largely global scientific-regulatory movement, interacting with overlapping movements in medical research such as EBM and health economics, that claim to provide a rational scientific basis on which to allocate scarce resources and ensure clinical effectiveness in health care contexts (Lehoux, 2006). Clearly then one would expect PCT research to be delimited by this epistemic and regulatory context, especially considering researchers in such settings are themselves one the major groups to benefit from their profession's configuring as 'disinterested outsiders' in the HTA movement (May et al., 2003). This label is meant ironically: May and colleagues strongly rebuke such rhetorical maneuverings by showing the entire journey of clinical fact-making does not proceed in anything like a disinterested or neutral fashion. Rather their summary of several HTA trials measuring ICT interventions in the NHS shows how evidence emerged contingently, reflecting specific socio-technical arrangements in which some networks and forms of knowledge were privileged above others. The privileging of method (the RCT, the systematic review) constituted 'formal proof' through which HTA's normative claims for re-working of healthcare settings were often based (May et al., 2003, 698). Will (2007) draws on a distinction by Latour to argue that whilst the legitimating claims of clinical trials rely on modes of rhetoric resembling certain 'Science', the actual processes of designing and running trials resembles messy 'Research'. Interestingly through analysing legitimating claims found in official documents about clinical trials in the UK, Will found that evidence from PCTs encountered credibility problems among decision-makers precisely because they appeared to this audience more 'Research' than 'Science'. Another sceptic, this time in the Netherlands, argues one of the consequences of the application of RCT methodology within PCTs is to impose a narrow, a priori, experimental worldview on complex medical and organisational processes (Jansen, 2010). Indeed research in a constructionist mode has for some time argued the propensity of traditional epidemiological models like RCTs to measure at the population level and privilege outcomes (with a potential view to re-ordering how future populations receive care) does much silencing of settings as messy, complex, and multiplicitous as routine clinical practice in health care systems (Dehue, 2002, Mol, 2008). If what gets counted as knowledge is that which is *measurable*, this places sociological significance on what gets counted and discounted in the making of a trial and how this is foreclosed by the trial's methods, and associated epistemic and regulatory procedures (Wehrens and Bal, 2012). Paraphrasing Berg and Timmermans (2000), I take-up this line of thought by observing the kinds of 'ordering' the PCT protocol produces and its 'others'.

## The Meeting

The research in this paper emerged from a four month period of ethnographic fieldwork conducted amongst an academic clinical research group in the UK. During the period I interviewed the entire group and two senior research managers in their faculty's hierarchy; and attended and observed directly hour-long weekly team meetings eight times as a non-participant. During this fieldwork I was invited by the leader of the group to a meeting about a trial on which he was chief investigator.

At the start of the meeting I explained the objectives of my research and that the meeting was going to be recorded on an audio device. The leader of the group (chief investigator of the trial) had also circulated an email the previous week to inform those in attendance of my presence. All present were requested to sign an informed consent form. For purposes of anonymity I have omitted certain details like the names of people, places, and organisations. The audio recording was later transcribed verbatim onto the NVivo software package. The transcript was coupled with fieldnotes recorded by hand during the meetings to jog the memory and record observations that could not be captured through the audio device, like the set-up of the room. As well as being given a copy of the protocol draft under discussion, later I also received a copy of official minutes. The findings in the paper emerged iteratively through coding of the transcripts, derived through constantly interpreting and comparing empirical materials whilst drawing on theoretical concepts and arguments. Following Strauss's open-ended guidance, the basic question I asked of the data was:

What is actually happening in the data? What are the basic problems faced by the participants? What accounts for their basic problems or problem? (Strauss, 1987, 31)

More specifically, this meant asking what are the challenges and practices of producing a research protocol for this form of trial? I hope the findings reveal an evocative (if inevitably partial and incomplete) insight into the kinds of struggles pragmatic-fact making in modern healthcare systems like the NHS can entail.

The location of the meeting was a board room in a building belonging to the host university. The room contained a long table in the middle, around which those in attendance sat, including me. On arrival a paper copy of the draft protocol which had been circulated via email was waiting at each seating position on the table. Once sat down we all were requested by the chief investigator to introduce ourselves – mentioning our names and our different roles in respect to the projects. The meeting was composed of various professions including statisticians, epidemiologists, neurologists, obstetricians, administrators, and a sociologist<sup>3</sup>. Some of the independent committee members had been flown in from overseas and accommodated in a hotel. The independent members were hand-

picked by the trial management groups, who could call on people with whom they were familiar and would likely prove cooperative with the trial (Trial coordinator interview).

During the meeting an interaction order emerges through which alterations to the protocol are enabled and mediated. Although all committee members are in theory equally able to input into the meetings I attended, some emerged as are 'more equal' than others in respect to challenging the protocol in the course of the discussions. The chief investigator asked the trial coordinator read step-by-step through each section of the protocol we all had in front of us. The act of announcing each section came with a pause, which was the cue for other members in the room to voice any concerns with what was contained in the section she was announcing. Pauses in talk and blank expressions were taken by the chairpersons as a cue for satisfaction and thus to move onto the next section. Whilst the coordinator read out loud the title of each section, simultaneously the chief investigator issued explanations and justifications for most sections (but not all). The latter thus assumed the position as a primary spokesperson and figure towards whom complaints about sections ought to be addressed by those present. The practice of minute-taking served several functions, including audit and ensuring that what is agreed-upon in the meeting is faithfully reproduced in subsequent changes to the protocol. It was the chief investigator who emerged as the spokesperson for the minutes – and therefore a crucial mediator between the talk of the meeting and the subsequent protocol changes. One of the most common tactics suggested in meetings was to hold specific follow-up meetings. Again it was the chief investigator who typically prompted such suggestions, with the TMG assumed to be responsible for formulating solutions to cited problems which would be presented back to independent participants whom they considered relevant, in order to seek agreement. This tactic appears to affirm the ethnographic observation of guideline-making meetings, in which problems and situations are not 'solved', but rather 'settled' (with some and not others assuming the authority to do so). It is also responsive to the fact this meeting was finite in terms of time and no doubt participants' attention. The substantive issues discussed and (partially settled) in respect to the pragmatic protocol will now be unpacked further.

### **Deciding What Gets Measured**

One of the important themes which emerged as a feature of discussions in the meeting concerned what was to get 'counted' within the protocol design, what would not, who could decide, and on what basis this was explained and justified. A series of questions raised by a statistician from the DMC provided a revealing set of insights into how assumptions about 'mess' in respect to the pragmatic trial protocol were then ordered by others present in the meeting.



An initial query the DMC statistician raised was whether those present were content with how the trial's database would classify participant responses. For example, should a clinician in the unblinded, experimental arm 'ignore' the results of the blood test, would this be counted as deviation from the protocol or simply clinical judgment (and therefore an ordinary part of 'routine clinical practice' which PCTs are supposed to measure)? The TMG neurologist responds:

Well it has to be judgment. Because there will be scenarios where the women have got to take tablets the night before and the level has fallen, and then the clinician has to make a judgment not to change the drug, because they were aware that she has taken tablets the day before.

What the DMC statistician imagines could count as participants deviating from the protocol, the neurologist states can be counted as 'normal' mess which the pragmatic trial encompasses. The following statement from the DMC statistician, reveals whether there were adequate procedures in place for recording this relevant information (in the protocol as it currently stood):

DMC Statistician: For monitoring purposes will that be recorded?

TMG Neurologist: ... It is actually included on the form, the reasoning for why did you [the clinician] decide to change [the patient's dose] or not.

This led the DMC statistician to question what information was being collected about each patient and whether this ought to be extended:

DMC Statistician: Yeah because it is a pragmatic clinical trial it is important to know if it is only a subgroup of eligible women who agree [to participate in the trial]...

DMC Neurologist: Yes but the trouble is for the clinician who is vetting in a busy clinic where you have only got five or ten minutes with a patient, you might think of the trial, but before you know it they will be on call and they won't have written the name down or got all the data, so it will be very incomplete.

DMC Statistician: Maybe yes.

DMC Neurologist: But I know why you think we should be collecting it – for the generalisability of the result [DMC Statistician: Yeah]. Can I just say for a trial like this that generalisability is better than it has been for many, many epilepsy trials in the past.

In response to the statistician's request – informed by interest in a technical criteria of improving generalizability of results – the neurologist puts forward a 'pragmatic' attitude, first by referring to

‘the realities’ of an imaginary NHS clinic, then by arguing the trial will produce generalisability relative to previous trials on this medical condition. The neurologist thus expresses confidence in the relevance of the trial, whilst conceding it might not fulfil a more abstracted and idealised version of robustness put forward by the statistician. The neurologist appears then to argue that the reality constituted through the pragmatic protocol is *relevant enough*, a remark reminiscent of how Moreira’s (2007) systematic reviewers approached rigour and relevance tensions. Furthermore the neurologist expects the protocol as it stands would tame the messy reality of clinical practice, but extending the scope of information requests would risk overwhelming the ‘busy NHS clinic’. Here the reality being brought forward through statistical procedures is ‘brought down to earth’ and coordinated with the reality of ‘a busy NHS clinic’, with the cost of increasing amounts of data into the trial coming in terms of increasing labour of participating clinicians collecting the data. The passage suggests, although PCTs may be characterised on a general level as more ‘Research’ than ‘Science’ (Will 2007), criteria of ‘Science’ were being fed back into the discussions about protocol design by the DMC statistician, given that this is an important repertoire through which the study would be held to future account. Disagreement on this matter was noted in minutes, with the idea to obtain information from some centres and not others put forward as a possible solution to be decided on by the TMG. Thus whilst this exchange may appear in many ways an iconic moment of ‘socially robust’ knowledge making, the decision on the final content of the protocol need not necessarily incorporate different forms of knowledge symmetrically (see also Montgomery, 2012).

### **Participants ‘messing things up’**

Empirical studies have shown during data collection stages of clinical trials, clinicians need not have detailed technical knowledge of research protocols in order to implement them (Ziebland et al., 2007). One unavoidable issue for trial designers is the fact that clinicians and patients provide quite diffuse interpretations when implementing research protocols in practice (Lawton et al., 2011). Indeed researchers often accuse medical practitioners of not properly following their protocols or ignoring them altogether (claiming sabotage) (Timmermans and Berg, 2003). How forms of ‘sabotage’ were imagined which were particularly problematic to the PCT and how those involved sought to negotiate these issues is the focus of this section. Those who spoke in the meeting seemed acutely aware that the NHS constituted a particularly unruly ‘laboratory’ for the PCT, where those tasked with recording the data are distant, and accountable and attentive to far more than the epilepsy trial database. The potential problem for participants to go ‘off-script’ was exemplified in a query by the DMC statistician, who was concerned about the extent to which the seizure rates of women captured in the trial database would be ‘truly’ representative of how they were being

managed by trial-registered NHS clinics. In particular, the statistician raised the question of how the trial could cope with events occurring 'outside' the participating clinic which might influence a woman's seizure rates (and are therefore 'off the grid' of the trial). The DMC obstetrician then provides a scenario where a patient has a seizure and is rushed to accident and emergency, where they are treated in a way which changes their blood serum levels. This presents a problem for the trial in determining whether subsequent seizure rates are affected by the treatment received in casualty rather than by the clinician participating in the trial:

DMC Obstetrician: Someone [in casualty] could have been treating a patient in entirely the wrong way [from the trial's perspective] through no fault of their own so that potentially could dilute the effect [of the intervention on seizure rates]. That will happen, it's a pragmatic trial and you have to take it on the chin- you just have to know that has happened and involve the info.

TSC Neurologist: You can't avoid it.

Unlike scenarios where 'sabotage' is inferred and blame attached (Timmermans and Berg, 2003), here the conversation focuses on what would be considered a morally acceptable deviation from the protocol, which nonetheless poses problems to the PCT design and their capacity to make later claims about outcomes which are 'certain'. The DMC obstetrician adopts a 'pragmatic attitude' to cope with the risk laid-out in this scenario, suggesting pragmatic trials entail 'acceptable' forms of deviation from the protocol that cannot be controlled or avoided. This justification seeks to recognise that in constituting the NHS as a 'laboratory' for the pragmatic trial, they are not able to arrange 'ideal' experimental conditions (the assumption of the 'explanatory attitude') (Roland and Torgerson, 1998). Again what emerges from these exchanges was that the messiness of day-to-day clinical practices and variations between participating centres is not necessarily considered a liability, so long as these details can be recorded and managed within the trial's research apparatus. Having well-designed, easy-to-follow forms was cited as a key mediator to help overcome these concerns. These conversations appear to stem from the anxiety that, whilst participants do not all respond in a uniform way to the trial's procedures, the credibility of the findings will rest on an assumption they have. Here a means of coping and 'taking on the chin' the mess of routine clinical practice was the argument that trust should be placed in participants.

DMC Statistician: Okay. Could they [participant clinicians] order these tests outside of the trial?

TMG Neurologist: Aha. Of course. We can't stop them.

DMC Statistician: And are you monitoring that?

TMG Neurologist: Well we would expect them to document it on the form if they had done it.

TSC Neurologist: It's very difficult that because it could really mess things up if they're checking themselves and changing doses based on what they found.

DMC obstetrician: Can you not make a request that if they do something like that then they let the trial know? I think they might do it and not tell us, but if they have agreed to take part in the trial... presumably they think it was a question worth answering - then surely they will say 'look we did this for a very particular reason'.

Despite acknowledging the risk that participant deviation 'could really mess things up', it was also argued participants were ultimately likely to be supportive of trial's aims and methods and therefore act in close accordance with the procedures laid out for them by the trial designers – otherwise they would be acting irrationally having agreed to participate. As such for the protocol to 'work' relies upon a mutual relation of trust between those designing the trial and those participating in it. The conversation was moved on after the statistician accepted the assurances that these considerations were already accommodated in the current iteration of the protocol text they had before them. This suggests that the issue was considered as 'resolved' (formally at least) and was not made visible to external agencies in the minutes.

### **Intervening without Interfering**

A highlighted risk of setting-up a pragmatic trial to measure 'naturalistically' the effectiveness of the intervention in this trial, was having a protocol design might interrupt and interfere with participants' 'ordinary' course of clinical practice. One distinction which came about in discussions was a subtle differentiation made between 'intervening' in routine clinical practice through introducing a clinical trial and 'interfering' in it. By definition the trial protocol is intervening in clinical settings, as it is setting-up a script participants adhere to which they otherwise would not be following. Yet once the trial is in place in the clinical setting and participants are randomised into one of its arms, a 'naturalistic' assumption kicks in. This distinction was captured in the following quote in which the TMG neurologist explains to the room the process by which patients were to be randomised and blinded into the trial:

TMG neurologist: [Once their patient is randomised] [T]he clinician is then informed and is then asked to act appropriately and manage appropriately the patient. So we are not telling

them what to do. So all of the planning the woman and the clinician have no idea about. That's the basic idea.

The randomisation and blinding procedures were significant in preventing the intrusion of individual subjective judgments by participants which would 'bias' the results and undermine later confidence that the protocol design had faithfully represented the 'reality' of how effective the intervention is in routine clinical practice. This is characteristic of a particular mode of thought where the world is divided into objects and subjects, where subjective interpretations risk over-running experience and being imposed onto the 'out there' world. To avoid the trappings of over-active selves mechanical rules are followed (Daston and Galison, 2008), with randomisation and blinding being two cases in point, along with the more general procedures of following protocols, guidelines, and standards (Keating and Cambrosio, 2012). What seemed striking about the extension of the RCT logic into the domain of 'pragmatic' trial was just how fragile the distinction between 'intervention' (acceptable) and 'interference' (unacceptable) seemed within discussions in the meeting. One of the means of anticipating and minimising 'interference' of the trial machinery in the 'naturally occurring' course of clinical practice, was to ensure that the practical and administrative procedures through which clinicians 'normally' obtain test results would not be 'excessively' disrupted by the presence of the trial. Below the trial coordinator asks clinicians how they would 'normally' obtain test results in their everyday NHS clinics:

Trial coordinator: Will seven days be enough time for them [clinicians] to act [as normal]?

TMG neurologist: Yes it should be. Well the thing is I would expect the results of the blood test to be fed back to them within seven days. Maybe seven days and a few days to act upon it.

TSC neurologist: Yes that is how clinical practice usually works- you [the clinician] get the result of the blood test when you go back to the clinic a week later. It is not like you spend your whole week hunting it down. It comes to you. So that's absolutely what happens within normal clinical practice.

The initial assumptions written into the protocol about what counted as 'normal' procedure were 'double-checked' by the trial coordinator to seek assurances the trial design incorporated standard practice for obtaining test results in NHS clinics. The assumption seems to be that even if the procedures for obtaining test results may be altered slightly, this was not sufficient *enough* to suggest it had altered how the clinician would otherwise have managed the patient. The general claim that pragmatic trials are modelled on the image of the health care systems in which they are

based (Will, 2007, Kelly, 2010), is manifested in this particular temporal stage, with participants mediating between trial design and the mundane particularities of the NHS. The above quotation gives a clear example of the limited experience and expertise of trial designers in relation to certain parts of the protocol and the need to check and cross-check to ensure the document is 'workable' and 'robust' according to various scientific and regulatory standards. On this occasion, the meeting could be moved on as both the TMG and TSC neurologists agreed the protocol would not unduly disrupt organisational routines, and the pragmatic trial would not *interfere* with the 'natural' setting it sought to measure.

## **Discussion and Conclusion**

This paper has focussed on a meeting between TMG, DMC, and TSC in order to analyse the challenges of arranging a 'laboratory' for a PCT in the UK NHS. The findings suggest a number of struggles characterised this situation, which often involved participants mediating and negotiating between the 'purity' of the RCT design as laid out in the protocol format with the 'messiness' of routine clinical practice. The pragmatic trial protocol appears then to require sufficient (not absolute) taming of the messy reality of the NHS clinic without undermining the pre-defined, systematic criteria of conducting this mode of research. The account of how these 'disinterested outsiders' (May et al., 2003) went about producing a document which they hoped would 'tame' clinical practices into a new reality offers a number of glimpses into some of the issues in arranging a healthcare system like the UK NHS as a laboratory for pragmatic clinical research. As with other modes of evidence-based inquiry (Moreira, 2012), representing 'routine clinical practice' as a research object is premised on ideas of restricting individual judgment – a liability which is to be circumvented via following stepwise, mechanical procedures, such as research protocols (Daston and Galison, 2008). Yet in the 'busy clinic' scenario put forward by meeting participants (usually with a clinical interest), a threat to faithful reading of the protocol by clinicians also stems from the amount of attention they are able to give a protocol, rather than a deliberate, conscious deviation away from it (by 'saboteurs', Timmermans and Berg, 2003). Ultimately then the designers rely on trust that participants will want to take part and adhere 'faithfully' to the protocol by taming their own subjective judgment for the greater good of the trial and future patients. These scenarios appear to draw mainly on personal experiences and evoke abstracted, idealized types of participants and NHS clinical settings. Although these efforts to inscribe 'social robustness' into the protocol would hardly be considered sufficient on their own for ensuring successful adoption of the protocol, one can at least infer that by meeting to discuss such issues the collective and regulators considered this occasion important in assisting this process.

Many of the tensions described in this paper reveal that the protocol was to be acted-upon and held to account by a number of audiences, according to different criteria and at various moments in time (Moreira, 2007). At times these different demands appeared to align, yet at others they did not. As the purpose of the meeting was to produce a protocol which was 'good enough' rather than perfect and within this finite setting issues raised were often more 'settled' than 'solved' (Knaapen et al., 2010), with those issues not settled noted in the minutes and deferred to subsequent meetings and communications. Here some participants exhibited the authority to call for further meetings, invite others to join, and close discussions and move onto the next item in the protocol, whereas others did not come forward in such a manner. Primarily those assuming this authority were members of the trial management group, particularly the Chief Investigator and Clinical Lead (Neurologist) of the trial. A number of the settlement moves and tactics suggested authority to act on suggestions raised in the meeting rested with the TMG, as 'authors' of the trial, although this was somewhat counter-balanced by the need to gain support from independent committee members. The findings from the meeting also indicate the overwhelming majority of time and conversations focussed on the 'primary objectives' of the RCT, with 'secondary objectives' like qualitative research being met with mute responses in the room. Although conclusions cannot be derived from this single observation, it at least raises the important future question of how 'order' and 'mess' are negotiated across the division-of-labour of pragmatic trials, for instance between quantitative and qualitative modes of research. Which forms of knowledge 'count' and how this is achieved in the making of pragmatic trials is a question that deserves further attention.

Hitherto the significance of protocol making has been under-researched in studies of pragmatic clinical trials, albeit some have commented on their propensity to prove restrictive during later stages trials (Berg, 1997, Faulkner, 2008). On the basis of my findings taken from a period prior to the 'launch' of the trial, I would like to propose that meetings constitute important epistemic instruments in the making of pragmatic trial protocols (Knaapen et al., 2010). In particular, this meeting was important in anticipating and responding to the known restrictedness of research protocols. Given a general incapacity to adapt protocols to emergent problems once the trial was underway, different professionals involved either in the design or the independent monitoring of the trial met on this occasion to discuss weaknesses or put forward scenarios of where the protocol could be derailed, and, if needs be, make adjustments in order to avoid such issues. Interestingly in this pragmatic trial setting, the very restrictiveness of having a protocol which must be stuck to necessitates a strong version of 'socially robust' knowledge making (c.f. Nowotny et al., 2001). After all it was those present in the room that would themselves have to follow the 'script' of the protocol and be made more-or-less accountable for its failings. One of the advantages of the meeting was

then that the abstracted, purified statistical and epidemiological procedures in the near-final version of the protocol could be adjusted and attuned to the 'realities' of a 'busy NHS ward', about which clinicians in the meeting exhibited considerably more experience. These meetings, as well as satisfying routine audit procedures, therefore also afforded a space in which the trial protocol could be attuned to the 'pragmatism' needed to constitute NHS as a clinical research 'laboratory' for these trials. This would suggest that medical sociologists interested in clinical fact-making could accord more attention to the importance of meetings in coordinating and enabling the scientific and administrative feats of clinical trials and other forms of clinical fact-making in health care settings.

## Notes

1. The trial protocol also included two secondary objectives: evaluating cost effectiveness and acceptability of the monitoring strategies, and a qualitative study into women's experience of the trial and epilepsy care in the NHS more broadly. These additional criteria are themselves an interesting addition to the scope of PCTs within HTA program, as it suggests statistical evidence (even if highly powered through a large sample size and produced via an RCT) was not sufficient by itself to inform regulatory decision-making. The trial's health economist was absent from the meeting and was said not to need to attend meetings until later stages of the trial. A qualitative sociologist announced the progress of her research during the meeting, however, this elicited no response and the meeting was moved on to the next topic by the chief investigator. How such components get integrated into trials (or not), though an important question, is beyond the scope of this analysis. As the meeting paid very little attention to these secondary objectives, I will focus here only on how the primary objectives of measuring clinical effectiveness were handled in preparing the protocol.
2. By the time of this joint meeting, the protocol had already been subjected to various auditing checks, negotiations, and iterations prior to the 'start' of the trial. These stages included: internal university indemnity review, review from the clinical trials unit of the medical school, university ethical review, NHS ethical review, confirmation about study sponsorship from their medical school's R&D Department, and contract signing by the Department of Health. Prior to this of course, the TMG had also produced an application to NIHR-HTA, which was itself evaluated by panels of statisticians and clinicians (Trial coordinator Interview).
3. The TMG consisted of the chief investigator (the principal investigator of the clinical research group I had been observing), project coordinator (a senior lecturer in the research group), a trial manager (employed full time by the research group), a neurologist who was clinical lead of the trial, an administrative trial coordinator, a sociology professor from another



university, and a statistician from the host university; the TSC was represented by a chairperson who was a epidemiology professor from an overseas university, a statistician from the host university, a neurologist and an obstetrician (both consultants in the NHS); and the DMC was chaired by an overseas statistics professor, a statistician from the host university, a neurology consultant and obstetric consultant (both NHS).

## References

- BERG, M. 1997. Problems and promises of the protocol. *Social Science & Medicine*, 44, 1081-1088.
- BERG, M. & TIMMERMANS, S. 2000. Orders and their others: on the constitution of universalities in medical work. *Configurations*, 8, 31-61.
- BUSSE, R., ORVAIN, J., VELASCO, M., PERLETH, M., DRUMMOND, M., GÖRTNER, F., JØRGENSEN, T., JOVELL, A., MALONE, J., RÖTHER, A. & WILD, C. 2002. Best practice in undertaking and reporting health technology assessments *International Journal of Technology Assessment in Health Care*, 18, 361-422.
- CAMBROSIO, A. & KEATING, P. 2009. Who's minding the data? Data Monitoring Committees in clinical cancer trials. *Sociology of Health & Illness*, 31, 325-342.
- CARTWRIGHT, N. 2007. Are RCTs the gold standard? *BioSocieties*, 2, 11-20.
- DASTON, L. & GALISON, P. 2008. *Objectivity*, New York, Zone Books.
- DEHUE, T. 2002. A Dutch treat: randomized controlled experimentation and the case of heroin-maintenance in the Netherlands. *History of the Human Sciences*, 15, 75-98.
- ELLENBERG, S., FLEMING, T. & DEMETS, D. 2002. *Data Monitoring Committees in Clinical Trials: A Practical Perspective*, Chichester, Wiley.
- FAULKNER, A. 2008. *Medical technology into healthcare and society*, Palgrave Macmillan.
- HOLLOWAY, P. J. & MOONEY, J. A. 2004. What's a research protocol? *Health Education Journal*, 63, 374-384.
- JANSEN, Y. J. 2010. *Pragmatic Trials: The Mutual Shaping of Research and Primary Health Care Practice*, Rotterdam, Erasmus University.
- JANSEN, Y. J., BAL, R., BRUIJNZEELS, M., FOETS, M., FRENKEN, R. & DE BONT, A. 2006. Coping with methodological dilemmas; about establishing the effectiveness of interventions in routine medical practice. *Bmc Health Services Research*, 6, 160.
- JENSEN, C. B. 2010. *Ontologies for developing things: Making health care futures through technology*, Rotterdam, Sense Publishers.
- KEATING, P. & CAMBROSIO, A. 2012. *Cancer on trial : oncology as a new style of practice*, Chicago ; London, The University of Chicago Press.
- KELLY, A. 2010. Pragmatic fact-making: contracts and contexts in the UK and the Gambia. In: MOREIRA, T. & WILL, C. (eds.) *Medical Proofs, Social Experiments. Clinical Trials in Shifting Contexts*. Farnham: Ashgate.
- KNAAPEN, L., CAZENEUVE, H., CAMBROSIO, A., CASTEL, P. & FERVERS, B. 2010. Pragmatic evidence and textual arrangements: a case study of French clinical cancer guidelines. *Social Science & Medicine*, 71, 685-692.
- LATOUR, B. 1993. *We have never been modern*, Cambridge, Mass., Harvard University Press.
- LAW, J. 2004. *After method : mess in social science research*, London ; New York, Routledge.
- LAWTON, J., JENKINS, N., DARBYSHIRE, J. L., HOLMAN, R. R., FARMER, A. J. & HALLOWELL, N. 2011. Challenges of maintaining research protocol fidelity in a clinical care setting: A qualitative study of the experiences and views of patients and staff participating in a randomized controlled trial. *Trials*, 12.

- LEHOUX, P. 2006. *The problem of health technology : policy implications for modern health care systems*, New York, Routledge.
- MACPHERSON, H. 2004. Pragmatic clinical trials. *Complement Ther Med*, 12, 136-40.
- MAY, C. 2006. Mobilising modern facts: health technology assessment and the politics of evidence. *Sociology of health & illness*, 28, 513-532.
- MAY, C., MORT, M., WILLIAMS, T., MAIR, F. & GASK, L. 2003. Health technology assessment in its local contexts: studies of telehealthcare. *Social Science & Medicine*, 57, 697-710.
- MOL, A. 2008. *The logic of care : health and the problem of patient choice*, London ; New York, Routledge.
- MONTGOMERY, C. M. 2012. Protocols and participatory democracy in a 'North-South' product development partnership. *Sociology of health & illness*, 34, 1053-1069.
- MOREIRA, T. 2007. Entangled evidence: knowledge making in systematic reviews in healthcare. *Sociology of Health & Illness*, 29, 180-197.
- MOREIRA, T. 2012. *The transformation of contemporary health care : the market, the laboratory, and the forum*, New York, Routledge.
- MOREIRA, T. & WILL, C. 2010. *Medical proofs, social experiments : clinical trials in shifting contexts*, Farnham, Ashgate.
- MYKHALOVSKIY, E. & WEIR, L. 2004. The problem of evidence-based medicine: directions for social science. *Social Science & Medicine*, 59, 1059-1069.
- NOWOTNY, H., SCOTT, P. & GIBBONS, M. 2001. *Re-Thinking Science*, Cambridge, Polity.
- ROLAND, M. & TORGERSO, D. J. 1998. Understanding controlled trials: What are pragmatic trials? *BMJ*, 316, 285.
- STRAUSS, A. L. 1987. *Qualitative analysis for social scientists*, Cambridge Cambridgeshire ; New York, Cambridge University Press.
- TIMMERMANS, S. & BERG, M. 2003. *The gold standard : the challenge of evidence-based medicine and standardization in health care*, Philadelphia, Pa., Temple University Press.
- TIMMERMANS, S. & MAUCK, A. 2005. The promises and pitfalls of evidence-based medicine. *Health Affairs*, 24, 18-28.
- WEHRENS, R. & BAL, R. 2012. Health programs struggling with complexity: a case study of the Dutch 'PreCare' project. *Social Science & Medicine*, 75, 274-82.
- ZIEBLAND, S., FEATHERSTONE, K., SNOWDON, C., BARKER, K., FROST, H. & FAIRBANK, J. 2007. Does it matter if clinicians recruiting for a trial don't understand what the trial is really about? Qualitative study of surgeons' experiences of participation in a pragmatic multi-centre RCT. *Trials*, 8.
- ZUIDERENT-JERAK, T., FORLAND, F. & MACBETH, F. 2012. Guidelines should reflect all knowledge, not just clinical trials. *BMJ*, 345.