Challenges to learning in clinical research: Networked innovation within a regulatory regime

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Abstract

This paper considers how the organisational and institutional arrangements – particularly the regulatory context - that surrounds the clinical research process influences biomedical innovation and restricts the opportunity for learning to take place. We explore how different stakeholder and collaborating groups engage in inter-organisation learning within this field, and, in particular, consider the effects of power interplays at the interstices of these different groups involved. One stakeholder group - the global pharmaceutical industry - is particularly powerful within the network. Their model of clinical research – the Randomised Controlled Trial (RCT) – has been adopted to largely structure the regulatory regime. This, coupled with the power that regulatory groups yield within the clinical research process, means that other groups who use different models of clinical research find it difficult to integrate knowledge about the specific attributes of their research, and so have relatively little influence with regards to shaping the regulatory regime to better fit their type of research. We describe how, in this context, knowledge sharing and learning is highly informal, ad hoc and localized, as less powerful groups strive to find ways to conform to the strict regulatory regime within which they operate. However, this ultimately limits the type of innovation that occurs within the UK context, as research using non-standard models are limited by the extent to which they can integrate knowledge about their exceptional context through the network of stakeholders and re-shape the system to enable their novel research design to be able to proceed within it.

Key words

Clinical research, networked innovation, regulatory context, network power

1. Introduction

One of the strongest components of the UK economy is the innovation occurring in the pharmaceutical and biotechnology sectors, but there is growing concern about a decline in the UK's clinical research base, and the 'translational gap' between basic scientific discovery and innovations that will directly benefit patients (McKinsey, 2005). Clinical research is the branch of this medical science where the safety and effectiveness of medicines, medical devices, diagnostic products and clinical prevention, diagnosis, treatment & management regimes are tested within research studies using human participants. This paper considers how the regulatory context - that drives the clinical research process - influences biomedical innovation and restricts the opportunity for knowledge integration during clinical research which is necessary for successful innovation. Whilst previous research has emphasised the opportunities for learning and knowledge sharing at 'the interstices' of organizations in the biomedical sector (Owen-Smith & Powell, 2004; Addicot et al, 2006), there has been little focus on the restrictive impact of regulatory regimes on these processes. It is the lack of connectivity between the regulatory regimes and clinical research processes which this paper addresses.

We first discuss previous work that describes clinical research as an exemplar of 'networked innovation' – conceptualising this as innovation that occurs through an ongoing communicative process driven largely by collaborative rather than hierarchical or market based mechanisms, although it may also contain elements of both (Powell et al, 1996; Swan and Scarbrough, 2005). We argue that this work significantly underplays the impact and constraining influences of the regulatory system in shaping knowledge flows in the context of clinical research. We then describe the methods we used to gather and analyse the empirical data referred to in the analysis. This is followed by discussion of the regulatory context within which clinical research is organised, where we reflect in particular on the impact of one major change to the regulatory context, the UK's implementation of the EU Medicines Directive in 2004. The analysis, drawing on both a systematic review of the literature on clinical research and our own empirical data, focuses on the problems of knowledge integration during the clinical research process, given (i) recent changes in the regulatory context and (ii) more broadly the context in which clinical research occurs.

Our empirical analysis shows, first, how the different stakeholder and collaborating groups engage in inter-organisational learning, and considers where knowledge about the regulatory process is sourced from, and the barriers that restrict the opportunity for knowledge integration by different stakeholder groups within the network. Second, we consider the effect of power interplays at the interstices of the different stakeholder and collaborating groups involved with the process of clinical research. With a few exceptions, previous work on networked innovation in the biomedical domain has largely neglected the role of power in shaping the collaborative process. Our findings demonstrate that one stakeholder group, the global pharmaceutical industry, is particularly powerful within the

network, and that the model of clinical research that serves their interests – the Randomised Controlled Trial (RCT) – largely structures the regulatory regime. Because of this relationship, and the coercive power that regulatory groups yield within the clinical research process, other stakeholder groups who rely on different models of clinical research find it difficult to integrate knowledge about the specific attributes of their research models, and so have little influence with regards to shaping the regulatory regime to better fit their type of research. Our analysis, however, also highlights the way in which the medical devices sector has begun to address some of these problems, arguing that this may serve as an exemplar of the ways in which barriers to knowledge integration may be overcome for models of clinical research that do not conform to the dominant model. In conclusion, we reflect that while, on the one hand, these coercive pressures restrict opportunities for less powerful groups to shape regulatory regimes that govern the production of knowledge and innovation in this field, on the other hand they also appear to stimulate learning at local levels as actors seek to 'work around' the significant constraints that the regulatory systems pose.

2. Theoretical framing: Networked innovation & the coercive power of the regulatory regime

The biomedical sector has been described as a major area where inter-organisational learning and collaboration are crucial for innovation. Indeed, Powell et al (1996) argue that *"in a field of rapid technological development, such as biotechnology, the locus of innovation is found within the networks of inter-organisational relationships that sustain a fluid and evolving community*". This reflects broader recognition that, as knowledge is becoming more widely distributed, the locus of innovation is shifting from within organizations to 'the interstices' of collaborating groups and organisations (Swan & Scarbrough, 2005).

Clinical research involving human participants relies, by definition, on interaction between different stakeholder groups, including pharmaceutical and biotechnology firms, non-commercial and academic scientists, clinicians, patients, regulators and funding bodies. For example, firms can simply not conduct drug trials on humans without recourse to ethical and regulatory regimens, clinicians and patients. However, there is also significant variety in the models of clinical research adopted. Some research models are focused on the development of new clinical interventions which are not yet licensed for marketing, such as new medicinal pharmaceuticals (e.g. a new cancer drug) or medical devices (e.g. a heart pacemaker). Other clinical research may focus on the evaluation of marketed drugs and devices, or may analyse surgical procedures, or assess diagnostic tools. Research may also have the purpose to evaluate 'best clinical practices (i.e. prevention, diagnosis, treatment and disease management regimes), including surgical procedures, complex interventions (interventions which contain several interacting components, such as combined medicinal and physiotherapy treatment with an exercise regime) and service delivery.

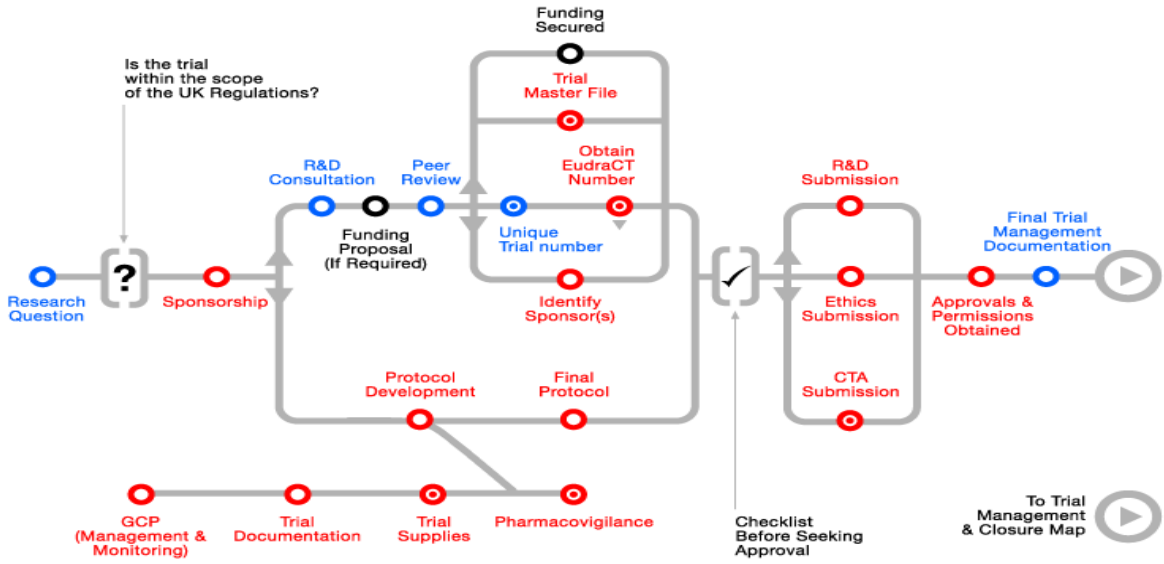
Reflecting on the different models for clinical research, there are also many different forms of organisation for conducting it, including large multi-national pharmaceutical research, smaller start-up biotechnology organisations, commercial organisations developing medical devices, university-based clinical trials groups and non-commercial research groups (e.g. academic, NHS or charity-based). In addition, the management of some, or all, aspects of research may be contracted to other organisations, which include private commercial contract research organisations (CROs) and university or NHS-based research service units. These different stakeholder groups involved with different models of clinical research must collaborate with other relevant groups, including regulators, ethics committees, NHS R&D departments. Depending on the specific model of research, they may also interact with other groups including government funding bodies (e.g. the National Institute of Health Research - NIHR), regulators (the Medicines & Healthcare Regulatory Authority (MHRA) and the National Institute of Health & Clinical Excellence (NICE)), Clinical Research Networks, end-users/purchasers such as the NHS, charities, patient groups, and professional & trade organisations.

Previous work, then, has, not surprisingly, described innovation in the clinical research field - and in the biomedical domain more broadly - as highly interactive or 'networked', relying on collaborative forms of organizing and reciprocal exchanges of knowledge and learning amongst the parties involved. For example, the development of 'integrative' and 'relational' capabilities (Owen, Smith et al., 2002) have been found to be crucial for innovation in this field (Swan et al, 2007). The former relates to the need to integrate knowledge across diverse interest groups and the latter to the need to form collaborative relationships across the organizations involved. However, the impact on the development of these capabilities of the relative power of the different stakeholders involved, including the coercive pressures exerted by highly institutionalised regulatory regimes, has largely been overlooked in existing work in this area.

This research draws, then, from a networked innovation model to explore the critical importance of stakeholders' ability to learn within the clinical research field but examines this in relation to the wider institutional arrangements – in particular regulatory regimes – in which this learning takes place. A networked innovation model avoids simplistic notions of linearity in knowledge flows. Instead, innovation is conceptualized as occurring through dynamic, highly interactive engagement and collaboration that promotes knowledge sharing, knowledge integration and learning across groups and organisations engaged in ongoing processes of communication (Hardy and Lawrence, 2003). Networked forms of innovation, whilst differing in scale and scope (and being variously described, as 'networked', 'interactive', 'open' and 'distributed') are found to be increasingly prevalent across organizations as broad ranging as open source, biomedical, manufacturing and non governmental organizations (Hardy and Lawrence, 2003). Whilst power has featured in some analyses, networked innovation has, however, usually been discussed without recourse to wider institutional and systemic pressures than shape learning at the local level.

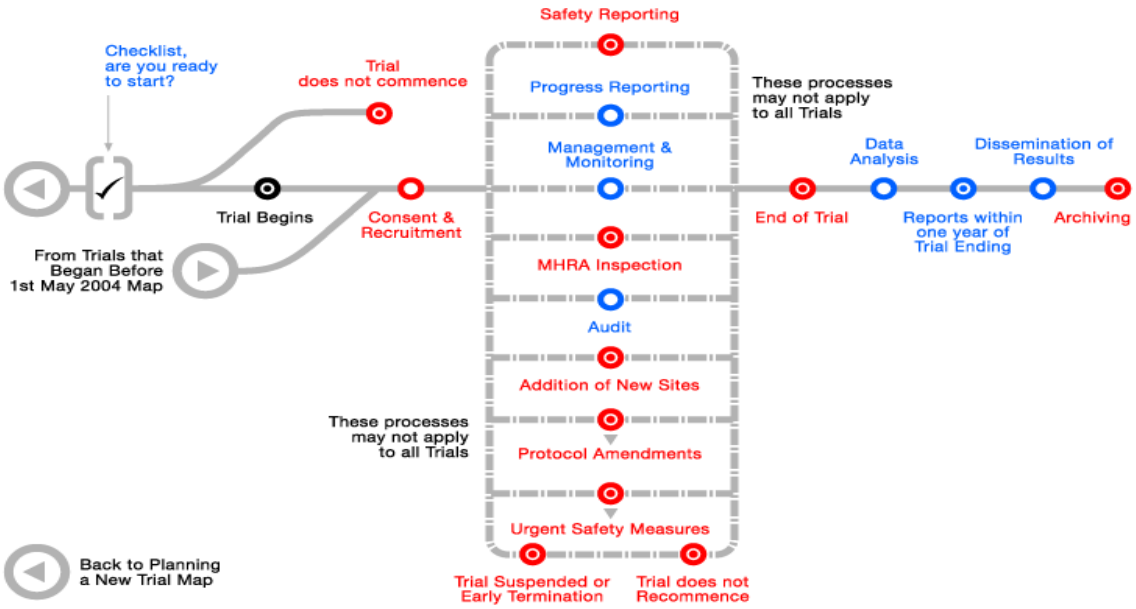
Unlike many of the sectors where the networked innovation model has started to emerge, e.g. software (Linux, IBM), consumer goods (Proctor & Gamble, Johnson & Johnson) etc., the biomedical sector operates in a highly regulated environment where the regulators have significant coercive power over the clinical research process. Moreover, the regulators, somewhat paradoxically given the iterative and recursive nature of clinical research, impose a strict linear regulatory path to approval consisting of distinct phases and stage gates which directly control the pace and progress of the knowledge production process. The following two diagrams illustrate a typical path for setting up a single pharmaceutical clinical trial research project within the UK system (figure 1), and the various requirements that need to met during project management (Figure 2).

Figure 1. Stages for setting up a trial in the UK[1]



[1] Route maps produced by the Department of Health (DH) and Medical Research Council (MRC) as part of the Clinical Trials Toolkit. Available at: http://www.ct-toolkit.ac.uk/route_maps/map_landing.cfm?cit_id=250 [accessed 02/04/09]

Figure 2. Stages for management and closure of a clinical trial in the UK[2]



There have been recent changes to the regulatory regime in Europe around pharmaceutical clinical research aimed at making the process more streamlined and efficient. However in practice the features, standards and practices associated with only one of many clinical research models - the randomized controlled trial (RCT) - have been used to determine the new regulatory guidelines and processes. The RCT is arguably one of the most simplistic models of clinical research, comparing one potential new drug against a placebo. RCT's are typically undertaken by global commercial pharmaceutical companies for the purpose of generating safety and efficacy data to support an application for marketing approval. In practice, as we have already described, there are many other models, which are often undertaken by small academic teams and biotechnology firms, and in combination, these conditions imposed by the regulators are creating significant problems for those engaged in clinical research which does not conform to the RCT model. Therefore, as Swan & Scarbrough emphasise (2005) it is important to also consider the role of power exerted by different stakeholder groups in shaping the networked innovation processes within the clinical research field, for an understanding of the pressures exerted on models of research represented by less powerful stakeholder groups, and how these groups fit their research into a regulatory system which is influenced by the more powerful RCT model. Their analysis suggested that "understanding the politics of networked innovation depends on understanding the generative (and sometimes degenerative) relationship between power, knowledge integration, network formation and the role of technology" (Swan &

[2] Route maps produced by the Department of Health (DH) and Medical Research Council (MRC) as part of the Clinical Trials Toolkit. Available at: http://www.ct-toolkit.ac.uk/route_maps/map_landing.cfm?cit_id=248 [accessed 01/04/09]

Scarbrough, 2005). They stress moreover that the institutional context and the role of technology are also important influences on the networked innovation process although leave such issues largely unexplored.

Clearly we can turn to institutional theory to gain insights into influence of regulatory regimes on networked innovation. Hence, DiMaggio & Powell (1983) suggest that, because organisations which share a field also have similar pressures exerted from the same institutional constraints, and market and bureaucratic forces, they tend to become more similar, but without necessarily becoming more efficient. This process of isomorphism assumes that the norms and formal rules of institutions will shape the actions of those acting within them. DiMaggio & Powell (ibid) identify, further, three mechanisms through which isomorphism may occur. Firstly, coercive pressures result from the cultural expectations of society, and formal and informal pressures from other inter-dependent organisation or official bodies. Coercion may occur because stakeholder groups hold critical resource sources for the organisation, or because of the power held by organisations with legitimised governance mechanisms. The second type of mechanism is mimetic process, which is where isomorphism is produced "when organisations mimic other organisations in the face of uncertainty" (Heugens & Lander, 2009). Thirdly, they describe normative pressures, which are associated with professionalization and the need to establish legitimacy within the sector. When applying this theory to our research topic, this would suggest that, given the power of the regulatory regime to exert both coercive and normative pressures (i.e. via legally binding approval mechanisms and professional standards), and the dominance of the RCT model of clinical research, that the organization of clinical research conducted in the field would become increasingly similar to the dominant RCT model. However, a limitation of, at least early, institutional theory is an overly deterministic assumption that organisations will passively re-shape to conform to these institutional pressures. Heugens & Lander (2009), for example, draw on the age-old tensions within organisational sociology of the structure versus agency debate, and question whether organisational field-level factors can explain the differences in the pull of isomorphic forces across organisational fields.

Therefore, within our analysis of networked innovation below we consider both the impact of the regulatory regimes and ways in which actors interpret, explore and reshape such regimes in order to accomplish their work at the local level. We consider how differently-placed groups respond to macro-level institutional pressures exerted from the regulatory regime, and also how these pressures influence the models of innovation that are occurring within the clinical research field. In particular, we examine how the stakeholder groups respond to the institutional pressures at the meso-level to make the system work for their model of clinical research. Therefore this paper explores how knowledge flows within clinical research in the context of tensions between the networked innovation process where inter-organisational learning and collaboration is necessary for biomedical innovation, and the role of the macro-level coercive power of the regulators, and the isomorphic pressures for the different models of clinical research to conform.

3. Methodology

The findings presented in this paper are part of an ongoing 2-year research project[3] which commenced in October 2007 exploring the management and organisation of clinical research and aimed at establishing the major barriers to UK clinical research. The analysis uses data collected during the first phase of this project which draw on two sources (i) a systematic literature review which combines a search of both the management & social sciences disciplines, together with the biomedical, clinical & allied professions and healthcare industry fields, and (ii) detailed qualitative interviews with multiple stakeholders from the clinical research field.

The approach used for the systematic literature review was developed using insight from David Tranfield's evidence-informed system for synthesising existing research for the management field (Tranfield et al, 2003). Tranfield recognised that "concern with the poor utilization of research evidence by policy-makers and practitioners is a phenomenon shared by many physical and social science disciplines", (Denyer & Neely, 2004), and developed his approach using the experience and traditions of other disciplines (in particular the Evidence-based Medicine (EBM) movement developed in the 1990s) to respond to criticism that reviews within the management field lacked rigour and relevance. Although as researchers we are founded in the management and social sciences disciplines, a principal source of literature for this analysis came from the biomedical, clinical & allied professions and healthcare industry fields, which are paradoxically the types of data more traditionally associated with EBM movement within the medical discipline. The aims of our review mean that it is inappropriate to apply the assumptions underlying the EBM movement of hierarchical study designs that prioritise randomised controlled trials above other evidence even whilst using literature from the healthcare field (Dopson et al, 2003). Instead we focused on applying the systematic stages of conducting a review as outlined by Tranfield et al (ibid), to ensure that the selection and analysis of literature used for our research into the challenges associated with managing clinical research can be justified as being based on a methodical rather than ad-hoc method.

Written sources are a principal part of scientific and medical communities, and this analysis of written sources for empirical investigation into the clinical research field are an established and suitable approach for sociological investigation. As Prior (2001) states "in a literate culture such as ours one of the most important of all available data sources is lodged

[3] This two year research project "The Management and Organization of UK Clinical Trials" commenced in October 2007. We would like to thank the Engineering & Physical Sciences Research Council (EPSRC) and the Warwick Innovative Manufacturing Research Centre (WIMRC) for funding this research.

within documents. Strangely – given the significance that writing plays in our culture – the role of documents in social research is widely underestimated. Yet we know that routine scientific (and clinical) work is executed as much through writing as it is through conversation". Therefore, our literature review included a wide range of papers published in biomedical, clinical and industry journals, including not only standard peer-reviewed research, but also editorials, letters, and discursive or general commentary pieces. In addition, the analysis presented in this paper also reflects on 'official' documents that relate to the governance of clinical research, and specifically the ethical approval application form. The literature search used the OVID databases of MEDLINE, EMBASE, Allied and Complementary Medicine (AMED), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, the Health Management Information Consortium (HMIC), and the Web of Science database. From a total of 5,191 articles identified from the search terms and strategies limited to the years 2001 to 2008, 142 articles were selected for review.

A detailed qualitative interview-based survey was conducted with two main groups of key stakeholders from the clinical research field (i) individuals with experience of managing and conducting a range of different models of clinical research, including academic/ non-commercial, commercial/ contracted research organisations and, (ii) individuals representing organisations involved with influencing how research is managed and conducted in the UK, including regulators, policy makers, professional & trade organisations, charity & patient groups. Interviewees were originally identified via members of our projects' expert Scientific Advisory Board (SAB), and members were experienced in different aspects of the clinical research field, including global pharmaceutical, contract research organisations and university-based academic research. Through the roles of SAB members, we also had support from major professional and trade organisations and policy bodies relevant for this sector. From these initial contacts, additional interviewees were identified using a 'snowballing' technique. This kind of non-probability convenience sampling is appropriate when the research is exploratory and population parameters are unknown (Saunders et al., 2000).

The primary aim of these interviews was to gather rich detailed information about the challenges involved with managing and conducting clinical research in the UK, and in particular in order to obtain a representation of how these issues affected different models of research. The interviews included discussion of how major policy and governance changes influenced the ease of managing a clinical study in the UK, and specifically reflected on the role of the regulatory system in influencing the organisation of research. In total, we conducted 58 interviews. With regards to qualitative interviews, Murphy & Dingwall (2003, p.93) suggest that these "allow researchers to explore the ways in which informants themselves define the experience and practice that are the focus of the research… they open up the possibility of challenging the researchers preconceptions about what is important or significant". This research adopts a social constructivist approach which views that the data obtained must be interpreted within the context and parameters of

the social setting of the interview, rather than as an actual depiction of reality, and therefore a subjective rather than objective epistemology was assumed (Denzin & Lincoln, 1998; Silverman, 2001).

By using a combination of qualitative data from both literature and interviews, our empirical findings are based upon analysis of rich detailed information, enabling us to explore the features of networked innovation within this context of the clinical research field. We are able to explore the dimensions of power within the collaboration of the different collaborating groups and organisations which need to interact at the interstices' of this network, and consider how the regulatory context influences the innovation which takes place within this sector.

4. Empirical findings

4.1 Biomedical innovation within the European clinical research regulatory regime

The Medicines & Healthcare Regulatory Authority (MHRA) is the government agency that is responsible for ensuring that medicines and medical devices used in the UK are safe and effective. Medicinal products (i.e. pharmaceuticals) are subject to legislation from the EU Clinical Trials Directive 2001, which the UK implemented in April 2004. They require marketing authorisation from the MHRA before they can be placed on the UK market to be prescribed by doctors or sold to patients. To obtain this license, they must demonstrate its safety, efficacy and quality, information which is generally acquired from a clinical trial, for which a clinical trial authorisation license is also required to conduct research using human subjects. Whilst information on the quality of the product and its non-clinical safety will have been obtained before the clinical trial programme commences, clinical trials typically begin with micro-dosing (phase 0) or small studies (phase I) in a controlled population of healthy volunteers or patients and, as data are gathered and initial safety demonstrated, expand to larger scale studies in patients (phase II and III). Medical devices are covered by the EU Medical Devices Directives and amendments which have been implanted into UK law, and they must obtain a CE-mark before they can be marketed in the UK. Studies involving non-CE marked medical devices carried out in the UK may be regulated as clinical investigations under the Medical Devices Regulations 2002 and require approval from the UK Competent Authority, which are ultimately governed by the MHRA.

As already highlighted, much of the clinical research undertaken in the UK does not involve a new (non-marketed) drug or device. There are many other models of research, such as trials of licensed drugs (e.g. phase IV marketing trials), clinical evaluations of CE-marked medical devices, research into complex interventions and service delivery and non-intervention research. Whilst not subject to direct MHRA regulatory approval, these are governed by a multitude of legislation and guidelines, and subject to adherence to other processes and approval requirements. All research using participants and/or resources from

the NHS require approval from a Research Ethics Committee (REC), a process which is over-seen by the National Research Ethics Service (NRES) before they can conduct research. In addition, permission to conduct research is required from each relevant NHS Hospital or Primary Care Trust, of which the research governance applications are overseen by the Trust Research & Development (R&D) Departments. In addition to the EU Clinical Trials and Medical Devices Directives, there is a large amount of legislation and guidelines that together provide ethical, quality and 'good practice' standards for the process of conducting clinical research in the UK. The precise relevance of particular legislation and guidelines, and adherence to particular governance procedures, depends on aspects such as the type of clinical research being undertaken (e.g. whether it is a medicine, medical device, complex intervention, service delivery of other models of research), the stage of research (e.g. whether marketing approval has been granted) and the type of stakeholder group (e.g. non-commercial research may be subject to requirements from funding bodies; commercial marketing research may be designed to fit in with requirements from NICE).

Other forms of governance include international standards such as the Declaration of Helsinki which was first agreed in 1975 (several major and minor amendments have since been made) and aimed at harmonising principles to be used worldwide by which all research using human participants should be founded upon. The International Conference on Harmonisation of Technological Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines were developed through consultation of the regulatory bodies from Europe, USA and Japan and industry. The purpose was to reduce the need for duplicate testing carried out during the research and development of new medicines through new recommendations providing greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration. Developed from this are a number of other 'Good Practice' guidelines which are worldwide standards which govern the research process (collectively referred to as GxP), which include Good Clinical Practice (GCP) for hospitals and clinicians conducting research on new drug or medical technologies on human participants, Good Manufacturing Practice (GMP) for the control and management of manufacturing and quality testing of food, pharmaceutical products and medical devices, and Good Regulatory Practice (GRP). In the UK, a 2nd Edition of a Research Governance Framework for Health & Social Care was produced by the UK Department of Health in 2005 and outlines the principles of good governance for all research conducted in the UK.

Other relevant guidelines may be more specific to the type of study or topic of investigation or produced by professional, trade or funding organisations, such as by the Association of Medical Research Charities (AMRC), Association of the British Pharmaceutical Industry (ABPI) or the Royal Colleges of Medicine, Surgery or General Practice. The International Organisation for Standardization (ISO) has several standards that are relevant for the type of clinical research that investigates medical devices. Therefore, the guidelines and regulations which constitutes the governance of the clinical research field is complex, and requires considerable knowledge to understand how to proceed successfully with the

process. However, as Gertel & Stark (2008) illustrate in their discussion of regulation of medical devices, it is not as simple as just following guidelines, as these may appear to conflict.

> "While drug development and approval processes have referenced the International Conference on Harmonisation (ICH), the processes for devices are caught between two worlds: that of ICH, and that of International Organisation for Standardisation (ISO). Companies with experience in the ICH context must assess applicability of these standards to the world of devices. This is not always self-evident, since ISO and ICH do not agree on some requirements and, often, ISO is silent on issues that are emphasized in ICH."

Instead, in practice successfully negotiating the regulatory regime in order to engage in, and complete clinical research requires a more informal understanding of how to practically negotiate the different steps.

There have been many recent changes to these institutional and organisational arrangements governing clinical research in the UK, with perhaps the most significant changes specifically affecting research into medicines/ pharmaceutical products. These arose following the various European governments' implementation of the 2001 EU Medicines Directive (which the UK implemented in April 2004). One of the main objectives when developing this directive was to reduce the risk to human participants involved in research, and in theory the system should improve research the research process through standardising procedures across European countries. However, the new system of monitoring and oversight procedures that form the regulatory regime for clinical research has been depicted as a highly complex, costly and bureaucratic process (Williams, 2006; Griffith, 2008; Gajic et al., 2004; Murray & McAdams, 2007, Bollangrada et al., 2007). However, despite this, these same commentators have suggested that the changes have had the overall effect of ensuring that the regulatory process is more streamlined and efficient, through features such as making the guidelines about requirements and timeline for each stage more explicit, a greater commonality of paperwork and timelines applied throughout each European Union country, and standardised procedures and criteria for GCP and GMP. Nevertheless, as the next two sections will indicate, the changes to the regulatory system may not have improved the process for all types of clinical research, as we will argue that the process was dominated by one particular research type, the commercial RCT model conducted by commercial global pharmaceutical companies, and that the powerful relationship between this one stakeholder group with the regulators, has resulted in difficulty for other types of research to fit into the system, and also to influence changes to incorporate knowledge about the features and requirements of their model.

4.2 Inter-organisational learning

Although, in theory there are many guidelines and 'official' documentation that set out the requirements that should be met at each step of the clinical research regulatory system, our on-going research has demonstrated that in practice successfully negotiating the regulatory regime in order to engage in, and complete clinical research requires a more informal understanding of how to practically negotiate the different steps.

> *"Anyone can read a book on, yes, you have to randomize. If you look at the good clinical practice guidelines you have to follow those rules. Making something work is not through blindly following a set of rules… The way you learn how to do that is by doing it. The experience of people who know… Who've worked out shortcuts and who know how to get through all the approvals, design the study in the appropriate way, use the systems that are available to facilitate recruitment, to facilitate follow-up."*

In particular, research which does not conform to the standard RCT model relies heavily on informal channels and tacit knowledge and understandings largely developed locally by other researchers who have already gone through the process. Smaller organisations, such as biotechnology companies and commercial organisation developing medical devices have often evolved from a scientific or laboratory expertise and have an academic or clinical background, but they may lack expertise that is essential to manage a clinical research project. For example, as the following extract illustrates from the CEO of a specialist contract research organisation describes.

> *"Again, when it comes to devices there's a real lack of knowledge. They're very focused on intellectual property, which they're very good at, but when it comes to CE Marking… Do they know what CE Mark is? That's a good start. Do they know how to get CE Mark? Do they know what it involves? Do they know which directives cover medical devices? That's really a good starting point. When they do a study, what guidelines and standards do they apply to it?... And then after that, it's the general stuff like how difficult is it to obtain hospital approvals."*

Although there are organisations, such as contract research organisation (CROs) that can assist organisations, it is individuals who hold much of the key expertise to the practical every-day management of clinical research. However, our research has also indicated that the structuring of the context within which clinical research is undertaken restricts the opportunity for knowledge integration, in particular for learning about the problems experienced by other researchers during clinical trials. The structure of the clinical research process reinforces a tight cycle of i) secure funding ii) set- up processes, iii) conduct clinical research and iv) report findings. Because of the time and financial pressures experienced by clinical researchers, as the following extract illustrates, often the only real opportunity to share and integrate knowledge about the challenges of actually managing

research beyond the research group directly involved is when the group disseminate their research findings. Even then however the emphasis is on the clinical outcomes rather than the practical experiences and problems experienced during the process.

> *"It's sort of folklore. I don't know of any data that actually showed that. It's odd because the whole business of trials is evidence-based medicine, but the things that we say about trials are not evidenced based themselves... There are very few formal ways of sharing knowledge and information with other people, or at least none that I'm aware of... Internally, I guess we do. We try to make sure that everybody internally is up to speed and doing things in the same way. We have sets of standard operating procedures and training in GCP, training for chief investigators and that sort of thing to try and standardize things internally."*

There can therefore be considerable difficulty in acquiring knowledge about the practice of clinical research. This is particularly problematic for research with a more unusual focus, particularly methodologically or practically more difficult, as although research may have previously been attempted in this area, it is also far more likely to have failed. Due to the structural cycle of the clinical research process where findings are only usually reported following *successful* completion, those research teams that have experienced the most severe problem such that the project has ultimately been terminated, will never have the opportunity to formally disseminate the issues they have faced. Therefore, the structural conditions within the sector also operate as a barrier for knowledge integration across clinical research teams and the regulators around the challenges of managing these atypical research projects

4.3 Power

A key aim of the EU Directive was to reduce the risk to human participations (Griffith, 2008). However in practice it was largely regulatory and ethics knowledge associated with the RCT clinical research model which was defined and applied in the new procedures by the regulatory bodies. Specific knowledge associated with other models of clinical research was not considered or integrated into new regulatory procedures, as one of our respondents highlighted.

> *"It was intended to harmonize research throughout Europe. It was a consequence of discussions between the pharmaceutical industry and the regulators. Academics were not involved… It didn't even include the health directorate of the EU. It was the industry directorate of the EU meeting with the pharmaceutical industry… For academic trials, which it wasn't really intended to regulate, it's created a lot of extra work. There are extra levels of approval."*

This indicates the lack of knowledge integration around other models of clinical research into new regulatory procedures, as the process of introducing new standards and the content of the procedures that were introduced were determined predominantly by arguably the two most powerful stakeholders operating within the sector. Clinical researchers engaging in various other models of clinical research have had to establish ways and means of 'fitting' their research into the dominant model applied by the regulatory regime in order to demonstrate their adherence to the new standards and procedures that have been imposed. The following extract from an individual representing a regulatory body highlights how they recognised that the changes conferred particular challenges for academic research to change how they manage research to comply with the new requirements.

> *"The principal challenges now are not so much to do with commercial research, which is really what I've seen, it's to do with how academia perceive research and how they comply with standards, which are accepted more broadly in the commercial environment, and the harmonization across the European network, in terms of how we've all interpreted what was supposed to be a common set of principles that were the directive."*

There is much 'official' documentation and guidelines that have been produced by the various organisations involved with governing clinical research in the UK. However, these documents act as a disciplining device, as they force researchers to conform the design of their studies to fit within particular expected standards of 'good research practice and design'. One example is the online application form for the Integrated Research Application System (IRAS)[4] which is used to obtain the legislative permissions to conduct research in the NHS which may include direct involvement of participants identified through the NHS (which includes both patients and their relatives, and also NHS employees) or use of NHS resources (such as NHS databases or biological samples) in the UK, and this form is used by the ethics committees. However, even the language used within this form illustrates the dominance of the RCT model of clinical research within the regulatory process. Although there are many different types of research that would be required to use this application form, including clinical research into drugs and medical devices, complex interventions, and service delivery and other types of non-intervention styles of research (e.g. survey and qualitative methods), one of the main aims of the process is clearly aimed at reviewing the high-risk research associated with medical interventions, as demonstrated explicitly by questions focusing on highly sensitive aspects such as exposure to ionising radiation and use of human tissue samples, but also more implicitly through the focus on indemnity schemes and arrangements (A76), and the reference to aspects such as interviews, use of questionnaires and informed consent as "non-clinical intervention(s) or procedures that will be received by participants as part of the research protocol". As one respondent in our studies comments,

[4] We refer to IRAS Version 2.0 throughout this paper

> *"It assumes that all clinical research involves patients being treated, clinical trials, patient follow up and large research teams and groups. This focus undermines the research structures of all other types of research so that the ability to conduct clinical research that is not a trial, does not need a power calculation etc and is relatively small scale is completely overwhelmed with the unnecessary, unsuitable 'RCT' based paperwork."*

Indeed, although the Medical Research Council (MRC) guidance for developing and evaluating complex interventions states that "identifying a single primary outcome may not make best use of the data", the form forces the researcher to define a deductive narrow research objective. In addition, although any research using NHS employees as participants requires ethical approval, such as may be the focus of service delivery research, questions within the form (A49-1) still refer to whether participants' General Practitioners will be informed of participants involvement in the study. Whilst it may be seem reasonable to new researchers that questions such as these would not actually be relevant for certain types of research (i.e. they could complete the question as n/a), it does appear that all research is assumed to have the ethical implications, as one respondent describes.

> *"There is little emphasis on distinguishing between different risks - processes are 'one-size fits all' - so sometimes the process to get approval seems too onerous"*

Consequently, a researcher undertaking qualitative interviews with NHS employees must also demonstrate indemnity arrangements and risk-management processes, such as ensuing appropriate counselling is available should the topic of research raise issues for the participant. Therefore our research has indicated that a high-level of informal learning is required by researchers to understand how to fit the features of their own research within the expected judgements of regulators, such as demonstrating the right level and type of appreciation of ethical issues raised when submitting an application to a REC. However, if a research group is inexperienced with the regulatory process, or are conducting research that has features that are different from the usual model, they are less likely to have an understanding of how to fit in with the judgement of ethics committee members of what involves 'good practice', as the following extract illustrates.

> *"The problem we found with the research ethics committees was their lack of understanding, again, in terms of conducting device studies, which are very different from pharma studies. Remember, they're used to reviewing pharma protocols, not many device studies to be fair, but pharma protocols have thousands of patients and then, all of a sudden, they get a device study which has got five patients. It's an alarm signal to them, but we have to test devices quite often in a feasibility study. The design of the studies – in the early days we used to get*

> *questions from the ethics committees saying, 'why aren't you doing placebo?'... We can't blind the surgeon because he has to do the surgery. He has to be able to see what he's doing. Device control trials are very difficult because finding something to compare any device with can be very difficult."*

So, for example, when the research design does not involve typical features such as randomisation of participants (e.g. questions A61), as much of the committee members understanding of 'good research design' is formed from the RCT model where randomisation is paramount, other types of research can experience delays in obtaining permission as attempt to inform the committees that a particular feature is acceptable in their example. For research that does not conform to the 'best practice' randomized controlled trial (RCT) our data highlighted that it is imperative for their success that they access highly tacit knowledge about how to practically manage the new regulatory demands. Because of the significant power of the regulators, our data has also highlighted that clinical researchers are deterred from challenging the model that has to be applied. For example, one academic researcher described how they were deterred from developing a model of informed consent different from 'the standard' for a large preventative research study as they felt that this would be more likely to cause them greater issues when applying to the regulatory and ethical approval agencies. They felt this would ultimately hinder the progress of their research through the additional time taken as they attempted to provide one REC with an understanding of the details of how their model was still following acceptable 'good practice', but just in a different way from usual. Therefore, this effectively acts as a barrier to knowledge integration and sector level learning around clinical research. In addition, even if one REC accepts a particular model as acceptable, because each REC has little contact with other committees, there is limited opportunity for new knowledge to be transferred sidewise for other RECs to learn from this experience. Pisano (2006) suggested that the organisational forms and institutional arrangements of the biotechnology industry are fundamentally 'flawed', and ultimately limit innovation. He argued that the highly specialised niches of the commercial drug R&D sector were a barrier to innovation as there was little connection between them. We observed that the organisational forms and institutional arrangements, particularly the regulatory regime, limit connectivity specifically by limiting formal knowledge integration around different models of clinical research *in practice.*

5. Discussion

5.1 Patterns of learning

Our findings concurs with earlier work in finding that learning within the clinical research field is often highly informal, ad-hoc occurring at the interstices of collaborating organizations (Powel et al, 1996). Thus, whilst there are many sources of highly codified information (such as guidelines and 'official' documentation about how to proceed through the regulatory approval process), the 'tacit' knowledge of individuals within research groups and the colleagues they connect to is paramount to practically be able to progress

through the process. The regulatory system, with its presumed 'best' RCT model, on the one hand, could be seen as placing significant constraints on learning and innovation in so far as it exerts significant coercive pressure for all clinical research to 'look like' RCT research. Thus isomorphic pressures are clearly at work (DiMaggio and Powell, 1996). However, our interviews also suggest this relative inflexibility or the regulatory regime also forces actors at the local level who are engaged in research that cannot actually follow the RCT route to network with and learn from others in order to develop workable solutions.

Overall our research has shown that studies of networked innovation need to be sensitive to institutional pressures that shape network relationships. Thus, in the clinical research field, although networked innovation should be a major opportunity for learning across boundaries and promoting connectivity in the sector, in practice, regulators remain largely oblivious to the problems experienced by local actors engaged in models of clinical research that do not conform to the dominant RCT model. In this regulated context knowledge sharing and learning is highly informal, ad hoc and localized, as less powerful clinical researcher teams strive to conform to the strict regulatory regime within which they operate. This ultimately influences the type of innovation occurring throughout the clinical research field, as to undertake successful research, less powerful research teams must shape the type and design of their studies to fit into the established system, limiting the use of more innovative methodological approaches because there is a high risk that they may fit less easily into the current regulatory regime. Therefore, to some extent our research fits in with DiMaggio & Powell (1984) normative institutionalism, as there is a level of isomorphism within the clinical research field, which is particularly due to coercive forces exerted due to the relationship between two powerful stakeholder groups, the global pharmaceutical industry and the regulators, resulting in pressure from the regulatory regime for other stakeholder groups that use different models of research.

There is also an assumption that learning within the clinical research field results in novel peer-reviewed publications and that this is how knowledge from this field is captured and is translated within the network. However, there are three major limitations with this model, which ultimately limits learning within this context. Firstly this model assumes that research can reach this point of dissemination of findings. However, in particular for research that has experienced the greatest challenges with managing a project, they may never reach this point, and therefore the opportunity to share knowledge through this outlet is denied. Secondly, this assumes that all stakeholders within the network will access this formal form of knowledge in order to learn. However, disciplinary boundaries may come into play here, and we commented on how even when one REC may learn about a new model of research, that it is difficult for this knowledge to be transferred sidewise to other RECs within the system. This reinforces an informal learning by experienced stakeholder groups, as many respondents commented that they requested the same ethics committees for subsequent projects as they had learnt about the individual perceptions of that particular committee. Finally, much research is focused on the scientific reporting of a clinical research study. This neglected several major opportunities for learning. There is often little

reflection on the practical or methodological experiences, such as practically how the project fitted in with ethical approval requirements. Once a project has reached the point of scientific journal dissemination, there is often little opportunity to take the research further and reflect on dissemination. Whilst for RCTs where the aim of a research project is to obtain a license for marketing approval, the purpose for many other types of research is to incorporate new medical knowledge to change clinical practice.

5.2 Medical Devices

Despite these problems, our data has highlighted that knowledge integration is starting to occur between researchers engaged in developing medical devices and the regulators, which is shaping the regulatory context. As previously discussed, medical devices research is governed under a different set of European regulations to pharmaceuticals. One of the significant consequences of this is that the studies required to support applications for marketing approval of medical devices often only require research studies involving much smaller or even no human participation compared to the more usual medicines research. Recently the medical devices community has been involved in a two-way process of knowledge sharing and integration through which they have been able to shape the regulatory process to better fit the medical devices context. One of the previous problems experienced by medical devices researchers when submitting ethical approval applications was that the committees would judge and make recommendations based on knowledge informed by the characteristics of the 'best practice' pharmaceutical RCT studies. However, more recently the medical device community have engaged in training individuals in some ethics committee about some of the specific features required for 'good practice' clinical research involving medical devices. A proportion of UK ethics committees have now been 'flagged' as having specific expertise to review medical devices, and our data suggests that this is now making ethical /regulatory approval for medical device research a more straightforward process.

Our analysis of the data has highlighted that a key feature of this particular group's ability to integrate knowledge about their specific model of clinical research within the regulatory regime was the successful organisation of small discussion groups. Firstly this research community was brought together and organised into a more formal group which had a strong association with professional/ trade organisations. This structuring and to some extent legitimising of the disparate medical devices companies into a professional association arguably improved both the integrative and relational capabilities of this part of the sector, enabling this research community to set up direct communication channels with policy and regulatory groups. This facilitated knowledge integration about the issues faced by all the stakeholders involved, and for very practical changes to be made to the regulatory process for this particular group.

5.3 Final reflections: Opportunities for learning in the clinical research process – a paradox

This paper has shown how a lack of knowledge integration across clinical researchers and regulators affects the clinical research process. Our research suggests that networked innovation occurring in the clinical research field may differ from networked innovation in other less regulated sectors. In this context knowledge sharing and learning is highly informal, ad hoc and localized, as less powerful clinical researcher teams strive to conform to the strict regulatory regime within which they operate and that they are relatively powerless to change at least in comparison to dominant pharmaceutical firms. This ultimately influences the type of innovation occurring throughout the clinical research field, as to undertake successful research, less powerful research teams must shape the type and design of their studies to fit into the established system, limiting the use of more innovative methodological approaches because there is a high risk that they may fit less easily into the current regulatory regime.

However, this research has demonstrated that considerable amount of learning takes place within the clinical research field, but the type of learning is strongly influenced by the relative power when the different stakeholder groups interact. The regulators knowledge is influenced primarily by only one type of clinical research, the RCT model typically used by global pharmaceutical companies, and they apply their understanding about this type of research to judgements about what constitutes 'good clinical practice and research design' when making assessments of approval for researchers to conduct clinical studies in the UK.

Finally we conclude by reflecting on the paradox that considerable learning does take place within the clinical research arena, as research that does not fit into the dominant RCT model of clinical research must learn how to fit into the regulatory system for successful innovation to occur in this sector. However, this ultimately limits the type of innovation that occurs within the UK context, as research using non-standard models, such as based on radical technologies or incorporating novel design features, are limited by the extent to which they can integrate knowledge about their exceptional context through the network of stakeholders to re-shape the system to enable their novel research design to be able to proceed within it.

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