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Managing Clinical Research in the UK

Evidence on the challenges of conducting clinical research projects in the UK

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ISBN 978-0-902683-97-6
Designed by warwickdesign, www.designatwarwick.com

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Preface

This report presents the findings from a two-year project which commenced in October 2007 and was funded by the Engineering & Physical Sciences Research Council (EPSRC)[1] through a healthcare management research programme developed by the Warwick Innovative Manufacturing Research Centre (WIMRC). The study was conducted by a research team from the Innovation, Knowledge & Organisational Networks research centre (IKON), based at Warwick Business School at the University of Warwick, and the School of Management at Queen Mary University of London.

The project team consisted of:
Professor Jacky Swan, University of Warwick
Professor Maxine Robertson, Queen Mary University of London
Dr. Sarah Evans, University of Warwick

Acknowledgements
We are grateful to our funders, the EPSRC through a WIMRC research programme, which enabled us to conduct this research project. The project was supported by a Specialist Scientific Advisory Board (for details, see Appendix 1), and the project team would like to thank this group for their guidance and advice throughout this project. Our thanks are extended to all individuals who participated in this research, by taking part in an interview or by completing the survey. We would like to extend our thanks to the following organisations for their assistance with administering our survey:

Association of the British Pharmaceutical Industry (ABPI), Association of the British Healthcare Industries (ABHI), BioIndustry Association (BIA), Contract Clinical Research Association (CCRA), Institute of Clinical Research (ICR), NIHR Clinical Research Network, NHS R&D Forum, CHAIN Network, Knowledge Transfer Network, and the London Biotechnology Network.

Disclaimer:
This report is published by the IKON Research Centre. The members of the Advisory Board and the interview participants and survey respondents participated in an individual capacity and not as representatives of, or on behalf of, their individual affiliated companies, universities, organisations or associations. Their participation should not be taken as an endorsement by these bodies.
All quotations are personal views and are quoted anonymously.

1 "The Management & Organisation of Clinical Trials" (RIBK 9223) - The research was funded by the Engineering and Physical Sciences Research Council (EPSRC) via the Warwick Innovative Manufacturing Research Centre.

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Executive Summary

Over the last decade UK scientists, clinicians and industrialists have expressed growing concern about the 'translational gap' between basic scientific discovery and innovation that will benefit patients. High quality clinical research is key to closing this gap and underpins innovation and improvement in health services. Clinical research is also central to the UK's pharmaceutical, biotechnology and medical devices industries, which combined are an essential component of the UK's economy. Yet the UK clinical research base is increasingly under threat from global competition and the time and cost of research and development continues to be a major challenge. The successful management and organisation of clinical research projects will be pivotal to overcoming these challenges in the future.

This report presents the findings from a 2-year EPSRC-funded study[1] which was undertaken to systematically explore the challenges of organising and managing different models of clinical research.

Aim: To identify the key social, organisational and managerial factors that influence clinical research projects with a view to improving the clinical research process and reducing the costs and risks of development.

The study employed a multi-method design incorporating:

Phase 1

(i) A systematic literature review of previous work in this area, containing 129 articles.

(ii) 57 interviews with key stakeholders which focused on the challenges of conducting different types of clinical research in the UK.

Phase 2

(iii) A large scale survey generating data on the management of 247 clinical research projects conducted in the UK.

Major findings

There has been an ***overall improvement*** in the proportion of projects that complete within time over the last decade. However, this improvement is largely related to improvements in time to recruit patients, whilst the project set-up stage continues to be a significant challenge. There is a slight drop in the proportion of projects that reach the anticipated recruitment target expected from UK sites within agreed time frames.

Projects led by pharmaceutical companies were more likely to complete on time and to patient recruitment targets, as compared to other projects led by commercial organisations and those led by non-commercial research groups. 45% of pharmaceutical-led projects completed on time, compared with 32% of non-commercial studies, and 24% of projects led by other commercial organisations. 68% of pharmaceutical-led projects completed on budget, compared to 64% of non-commercial studies and 48% of projects led by other commercial organisations.

From the analysis of the data derived from both phases of the study, the greatest challenges affecting the management of clinical research were found around four areas:

- **Regulation & Governance:** Successfully completing the governance approval process was identified as a particular challenge for project management. In particular, different types of research organisation naturally conduct different models of research, all of which experience dissimilar pressures in managing the regulatory and governance process. Researchers that do not adopt standard randomised controlled trial (RCT) models face particular challenges in the approvals process.

- **Knowledge & Expertise:** Retaining project team expertise was critical for successful project management. This underpinned many of the problems (e.g. recruiting and retaining patients) commonly associated with the conduct of all models of clinical research. However, skills shortages create particular difficulties for non-commercial and smaller commercial research organisations.

- **Networks & Strategy:** Project management is reliant on the development of successful working relationships between the research organisation and other key groups within the sector. Each research

1 "The Management & Organisation of Clinical Trials" (RIBK 9223) – The research was funded by the Engineering and Physical Sciences Research Council (EPSRC) via the Warwick Innovative Manufacturing Research Centre.

organisation must shape their strategy for research to fit in with the UK strategic context and to facilitate successful networking with other stakeholder groups.

- **Incentives & Drivers:** To develop and maintain a network of relationships, research organisations and policy makers must develop insight into what incentivises different organisations, communities and individuals to engage in clinical research. In practice this may require balancing dissimilar or even antagonistic actions. The heterogeneous groups that are critical to the UK's clinical research sector require different levels of support to incentivise involvement with research projects.

The major findings were found to be:

1. The major predictor of success in terms of completing a project on time, with sufficient patients and on budget, was the ***ability to retain a project team***.

2. This finding highlights the importance of ***local knowledge and expertise*** in managing clinical research in the UK. Project management requires the development of ***practical nuanced knowledge*** that develops through on-going relationships with stakeholders across numerous organisations and clinical sites. When project teams are disrupted, often much of this local knowledge is lost, adversely affecting project outcomes.

3. Changes to the governance system that were introduced following implementation of the EU Clinical Trials Directive and Research Governance Framework appear to have had little effect on set-up time. For projects conducted over the last decade, the average time to *prepare and submit an application, and receive an outcome* for approvals was found to be 114 days (R&D), 91 days (ethics) and 77 days (regulatory). For projects that obtained approval from *2007 onwards*, the average time to prepare and submit an application, and receive an outcome for approvals was found to be 102 days (R&D), 90 days (ethics) and 83 days (regulatory). These figures are significantly longer than MHRA and NRES figures on approvals, suggesting that ***preparation time continues to be a major challenge***.

> "Project management requires the development of practical, nuanced knowledge

4. All research groups, other than pharmaceutical firms, experience significant difficulty in obtaining information, completing paperwork and ensuring that the features of their models of research correspond with the requirements for regulatory and R&D approval.

5. The greatest impediments to conducting clinical research in the UK were considered by researchers and managers to be ***time and cost***. In addition, ***R&D approval***, ***contract negotiation*** and ***NHS research culture*** were also considered major impediments.

6. There was considerable variation in the time taken to obtain R&D approval across the UK. In conjunction with problems of contract negotiation, this suggests that there remains considerable variation across NHS Trusts with respect to these two aspects of conducting clinical research.

7. The regulatory and ethical approval processes are viewed as having improved in recent years. The introduction of the NIHR Integrated Research Application Scheme (IRAS) and the Coordinated System for gaining NHS Permission (CSP) were considered to be a significant improvement in terms of ease of conducting research in the UK.

8. The development of productive relationships between research organisations and other stakeholder groups is influenced by the different drivers that promote involvement with a project. Research organisations need insight into how different organisations, communities and individuals are incentivised, which may in practice require balancing dissimilar or even antagonistic actions.

9. Distinct features of NHS Trusts act as incentives for research organisations to select particular recruitment sites. The findings highlight that the ***resources provided by a site***, and the ***reputation of a Trust*** for patient recruitment, together with the ***reputation of the lead clinician***, were important aspects which influenced the selection of sites for the projects reported.

10. Clinical Researchers believed that their expertise of planning and designing the project, such as ***inclusion criteria & recruitment strategy and presenting***

an interesting topic, were more important factors for recruitment than explicit incentivisation through the provision of rewards, such as financial and non-financial remuneration.

11. Different types of research organisation have different priorities which influenced their motivation in developing a clinical research project. ***Financial reward*** was important for commercial groups. ***Research group reputation and informing UK policy*** were more important for non-commercial research.

The full report presents detailed findings and recommendations as to the many different challenges that influence the ease of managing clinical research projects within the UK. It is proposed that it is constructive to consider the relationship between the macro-level system that may generate operational and management challenges for the research organisation, and the issues experienced with the day-to-day management of clinical research projects. We suggest that the current system tends to operate as a ***'one size fits all model'***, where projects that do not confirm to the features of the Randomised Clinical Trial (RCT) model of research experience greater challenges with overall project management. However, policy response to these challenges needs to recognise and support *all* the research groups that constitute the clinical research sector within the UK.

1. Study overview & context

Over the last decade, UK scientists, clinicians and industrialists have expressed growing concern about the 'translational gap' between basic scientific discovery and innovation that will benefit patients. High quality clinical research is key to closing this gap and underpins innovation and improvement in health services. Clinical research is also central to the UK's pharmaceutical, biotechnology and medical devices industries, which combined are an essential component of the UK's economy. Yet the UK clinical research base is increasingly under threat from global competition and the time and cost of research and development continues to be a major challenge. The successful management and organisation of clinical research projects will be pivotal to overcoming these challenges in the future.

This report describes the findings from a study which was undertaken to systematically explore the challenges of organising and managing different models of clinical research in the UK context. The management of clinical research projects entails complex working relationships amongst research organisations, industry managers, scientists, academics, contract service providers, clinicians, patient groups and charities. Increasingly, for some models of research, these relationships operate on a global basis. The ease with which clinical research can be conducted is also strongly influenced by both the strategic/market environment and by national policy and regulation. These macro institutional factors can pose major coordination challenges for the successful management of clinical research projects at the micro level.

This multilevel research study identified and mapped the macro-level issues surrounding clinical research in the UK, and systematically explored how these influenced the organisation of research and project management at the micro-level. The purpose of this research was to identify the key social, organisational and managerial factors that influence the management of clinical research projects. Specifically this research aimed to:

- Map alternative models of clinical research and identify the key challenges they generate, from the perspectives of the different research groups and key actors.
- Identify the macro institutional and policy drivers that frame the strategic environment within which research is conducted within the UK.
- Identify the barriers and enablers influencing the day-to-day management and organisation of clinical research projects within the UK.
- Explore the relationship between the macro-level context and the day-to-day challenges associated with managing different models of research.

The findings inform understanding of how and why clinical research projects succeed or fail and what kinds of management and organisation are required to support success. Following an overview of the research context and design, we report on the completion rates of UK clinical research projects included in our study. The challenges of managing and organising clinical research are then addressed across 4 major themes, with associated recommendations on how policy makers and clinical research communities might tackle these challenges.

1.1 Research context

This research was conducted following significant changes that have affected the management of clinical research projects within the UK context. In particular, the last decade has seen extensive modifications to the European and UK regulatory and governance approval processes aimed at improving the quality, safety and timeliness of clinical research. At the same time the threat to UK clinical research has increased significantly, following the development of research capabilities in countries previously unable to compete. In light of these changes, UK government, strategists and policy makers have given increased attention to, and have made major investments in, the healthcare research environment. This has resulted in the introduction of a number of initiatives which have influenced the context within which clinical research projects are organised.

The UK's position

A report, published by the Academy of Medical Science (AMS) in 2003 set out a number of recommendations to strengthen the UK's clinical research industry. It was stressed that this action would require the joint efforts of several government departments, including those with remits for health, business and industry, enterprise and innovation, and education and skills, together with the Medical Research Council (MRC) and major medical

charities. As a result of concern expressed about whether the UK was actually fully exploiting the research potential of the NHS, the UK Clinical Research Collaboration (UKCRC) was established to bring together the major stakeholder groups that influence clinical research, with the aim of improving the overall UK research environment. Of particular concern was the fact that the amount of commercial research conducted within the UK was declining, and that the UK's position in this respect was falling relative to other countries.

A 2005 report reviewed the UK's position with regard to commercial research (McKinsey, 2005), and set out the current state of this industry. It identified a variety of hurdles that the UK would need to overcome, in both the short- and long-term, in order to strengthen the value and position of the UK in the global industry. Whilst advising that the UK was on a par with competitors for quality, that report expressed concern about the time taken, high cost and the level of reliability provided by the UK for commercial research.

A more recent report has expressed further concern that the UK is continuing to lose its 'market share' (Kinapse, 2008). Recommendations were informed by two workshops that brought together representatives from government, the NHS and industry. These suggested that the UK needed to further define and develop strengths in specialised areas such as oncology, medicines for children and early stage clinical research. However, this report still positions the UK as being able to deliver in all areas of commercial clinical research. The value placed in the findings of these earlier reports, together with the 'Industry Road Map Groups' that were set up by the UKCRC, highlights that the clinical research sector is considered to be of strategic importance for the UK.

Regulation & ethical review

In 2004, the UK Government implemented the EU Clinical Trials Directive (European Union, 2001). This resulted in changes to the regulatory approval process within the UK and the formation of the Medicines & Healthcare Regulatory Agency (MHRA). UK regulation was standardised to EU requirements, which practically resulted in changes to the process of obtaining regulatory approval. As the new system was most aligned with the process that industry typically already followed, in general the largest impact of these changes was felt by academic groups conducting medicines research. Previously many clinical trials of this type would either have applied for a Clinical Trial Certificate (CTC) or simply been notified under the Clinical Trial Exemption (CTX) or the Doctors and Dentists Exemption (DDX) scheme. The discontinuation of this 'exemption' scheme meant that all medicines research had to conform to the same regulatory standards. Both commercial and non-commercial groups were required to apply for a Clinical Trials Authorisation, and needed to adhere to new regulatory principles for pharmacovigilance, manufacturing and general inspection of standards of research. Thus, for certain research groups, and in particular academic and NHS-led models of research, considerably more detailed information about each project needed to be provided, together with further documentation, demonstration of 'good practice' and adherence to regulatory inspections. Whilst there was considerable support for the case for change, in general, regulatory adherence became a more time consuming and bureaucratic process.

Medical devices research is subject to different regulation. This has also been affected by various related EU Medical Devices Directives and, in particular, the substantial amendments that took place in 2003 and 2007 related to marketing and clinical use of these products (European Union, 2002). In addition, a 2008 EU Directive for Medical Devices has been passed by Parliament and is due to fully come into force in March 2010 (European Union, 2008).

The 2004 medicines regulations also brought changes to the UK ethical assessment process through the legal establishment of ethics committees. Although not under the direct scope of this legislation, the ensuing changes had repercussions for the ease of management of other models of clinical research, including non-medicines & non-intervention research (e.g. surgical research, complex interventions, healthcare evaluation and medical devices).

The issues associated specifically with the 2004 regulatory changes for medicines clinical research have been addressed by two high profile Sensible Clinical Guidelines Meetings, held in 2007 and September 2009 (Yusuf et al, 2008; Groves, 2009). This group debated the situation specific to the Randomised Control Trial (RCT) model of clinical research and stated that barriers to the ease of managing projects were created through the UK's interpretation and implementation of the EU Directive. They argued that this has resulted in an overly complex and detailed procedure to obtain, and then adhere to, regulatory approval, with overzealous monitoring and inspection standards (Duley et al, 2008). As a group, they state that an increasing number of national, local and institutional approvals are now required before trials can be

initiated. This is adding considerably to the time and cost of RCT-based clinical research, but they question whether there is "*good evidence that the layers of complexity, approvals, processes, and laws to protect subjects entering RCTs have actually achieved their purpose*" for safeguarding the science and ethics of trials (Yusuf et al, 2008). Whilst the set of position papers released from these two meetings may represent only the interpretations of the clinical researchers who attended, the fact that these views are expressed at all underlines the need for policy groups and regulators to develop an appreciation of the types of challenges that are perceived to affect the management of UK clinical research projects.

The NHS and the National Institute for Health Research (NIHR)

In 2001, a new framework for the governance within England of research in health and social care was produced. This was subsequently amended in 2005 in light of the 2004 regulatory changes (Department of Health, 2001; Department of Health, 2005). This had implications for all clinical and non-clinical research – both commercial and non-commercial - which used NHS staff and/or resources undertaken by NHS staff. For clinical research projects, this influenced, in particular, the process of obtaining permissions to use NHS sites. The 'Darzi Report', published by the Department of Health in 2007, highlighted further that better development, use, and adoption of innovation through well managed clinical research was a vital aspect of the future vision for the NHS (Darzi, 2007).

The 2002 Consultant Framework (Department of Health, 2002), and its subsequent amendments, has also had indirect implications for the ease of conducting clinical research within the UK. The rewards system it set out resulted, overall, in increased pay for Consultants. However, the terms of the contract emphasised remuneration in return for their role in delivering services and healthcare, and it was felt that this contract placed less emphasis on rewarding clinicians to participate in research. Concurrently, as the specialist registrar training route has decreased the time taken to train as a Consultant, it is now felt to be not as important for clinicians to have conducted their own research projects in order to qualify. Overall, this appears to have altered the direct incentives for clinicians to become involved as investigators, and has changed the context for collaboration between clinicians and research groups.

The 'Best Research for Best Health' report, published in January 2006 (Department of Health, 2006), set out the UK Government's strategy for health research. The underlying aim of this report was to set out 5-year plans for supporting clinical research in the UK. As a result, the National Institute of Health Research (NIHR) was created to act as a virtual body for a framework to "*position, manage and maintain the research, research staff and infrastructure of the NHS in England as a virtual national research facility*". In addition, an implementation programme was developed covering such areas as research capacity development, research systems and governance, and research infrastructure.

Several initiatives to support research systems and governance, such as the Integrated Research Application System (IRAS), the Coordinated System for gaining NHS Permission (CSP) and the Research Passport Scheme have been developed. In addition, bipartite and tripartite model Clinical Trial Agreements (mCTA) and model Clinical Investigation Agreements (mCIA) have been developed through the NIHR to support and speed-up contract negotiation between the NHS, commercial organisations and contract service providers for pharmaceutical and medical technology industry sponsored research, respectively.

The study reported here has captured current attitudes of researchers regarding the extent to which they perceive that these four initiatives will ease the management of projects. More recently, during the summer of 2009, Research Support Services were set up through the reconfiguration of NHS Trust R&D Departments which aim to improve the quality, speed and efficiency of research and research processes in the NHS.

Evaluating challenges affecting clinical research

A NIHR workshop, held in April 2009, brought together senior researchers, funders, regulators, NHS and University leaders and managers and representatives of NIHR and the Department of Health to identify the current barriers to clinical research and review the work being done to reduce them. Whilst a number of particular challenges for the UK were proposed, we caution that systematic study to generate empirically-grounded research evidence is paramount to support a defensible evaluation of these challenges. The Office for Life Sciences (OLS) was created by the UK government in recognition that action was required to support the UK life sciences industry. A Life Sciences Blueprint was presented in July 2009, which set out a *"package of actions to transform the UK environment for life sciences companies"* (Office for Life Sciences, 2009). Within this report, areas such as supporting collaboration between the industry, academia and the NHS, maintaining a highly skilled workforce, stimulating investment, and supporting the UK industry through global

marketing are discussed, and it is intended that detailed delivery plans will be developed to support each of the actions presented.

It is clear, from the emphasis of several working parties and the reports by industry and professional groups, that addressing the challenges associated with the clinical research process is considered to be of strategic importance. However, we highlight that the impact of the numerous 'bureaucracy busting' measures developed by government departments should be properly evaluated, and in such a way that takes into account their effects (even unintended) on varied types of research organisation that comprise the sector as a whole.

The research presented here was specifically aimed at mapping the challenges that influence the *management of research projects for all different models of UK clinical research*. The findings have been developed through analysis of data collected through a rationally designed multi-method research project. Thus, this empirical study reviews the challenges associated with managing medicines, medical devices, surgical, complex intervention and healthcare evaluation projects. It is inclusive of the various components of commercial industry, including global pharmaceutical companies, medical devices organisations, smaller biotech and start-up companies and contract services organisations, together with the non-commercial research sector, including academic research centres, university clinical trials units, and research groups based within the NHS, charities, and other 'not-for-profit' organisations.

1.2 Research design

The research design focused on identifying and evaluating the barriers and enablers, at the institutional and project levels, to conducting both the set-up and recruitment stages of different kinds of clinical research projects. The research comprised two phases and employed a multi-method design incorporating:

PHASE 1: Qualitative

i **Systematic literature review of previous work in this area.**
The systematic literature review generated 129 core articles from 5,191 found in the biomedical, healthcare and industry, social science and business and management literatures. From this review a schematic model was developed categorising, in broad terms, the institutional-level and project-level factors that influence the management of clinical research in the UK.

ii **Qualitative semi-structured interviews with key stakeholders on challenges of managing clinical research.**
Interviews were carried out with 57 individuals from key stakeholder groups within the clinical research sector, including both commercial and non-commercial research groups, individuals from professional, industry and charity groups, and individuals from regulatory, government and policy organisations. Interviewees were selected using a snowballing technique through initial advice from a multi-stakeholder Specialist Scientific Advisory Board (for details, see Appendix 1). This enabled identification of individuals who had experience of managing different types of research, plus senior members of key industry, professional, trade and charity associations. In addition, interviews were conducted with senior members of major groups that influence the UK context within which research is conducted, including government and affiliated organisations, policy makers, regulators and funding groups. This kind of non-probability convenience sampling is appropriate when the research is exploratory and population parameters are unknown (Saunders et al., 2000). The views expressed during interviews are participants' personal opinions, and thus the data presented is not representative of particular organisations. All individual responses remain confidential and are presented anonymously.

Interviews were semi-structured, each lasting around 1 hour. Discussion covered a range of issues entailed in managing clinical research including: networking and collaboration; drivers, motivation and incentives; regulation and governance; organisation (including project management) and culture; and knowledge, expertise, skills and training. Thematic analysis of data delineated the types of challenges affecting different research groups and different research models. This revealed barriers and enablers within the UK context and examples of how these are being overcome.

PHASE 2: Quantitative

iii **A large scale survey generating data on the management of 247 clinical research projects conducted in the UK.**
A survey tool was developed based on the analysis conducted during Phase 1, together with advice from the Specialist Scientific Advisory Board. The survey was administered in Spring 2009 through collaboration with key associations within the clinical

research sector, including the Association of the British Pharmaceutical Industry (ABPI), Association of British Healthcare Industries (ABHI), BioIndustry Association (BIA), Institute for Clinical Research (ICR), Contract Clinical Research Association (CCRA), the NIHR Clinical Research Network, the NHS R&D Forum, Warwick Clinical Trial Unit, London Biotechnology Network, CHAIN and Knowledge Transfer Network. It targeted clinical trials managers and other individuals with direct experience of managing clinical research.

The survey tool collected data about the set-up and patient recruitment stages of 247 clinical research projects. Each respondent provided details about the setting-up and conduct of **one** 'recently completed' clinical research project and about project outcomes. Data were collected on ongoing projects where this was their first experience. Project descriptions were checked to ensure, in so far as possible, that individual responses represented different clinical research projects.

Data were captured on different models of research - including commercial and non-commercial, and medicines, medical devices, complex intervention and service delivery & healthcare evaluation – and on projects conducted between 1999 and 2009 (the majority commencing 2006 or later). The final section of the survey collected data from the respondents about their *current* attitudes around the UK clinical research context. These data provide insight into opinions toward present impediments of managing research in the UK and perceptions towards recent policy initiatives.

1.3 Scope & structure of this report

The findings presented in this report are based on analysis of qualitative data drawn from interviews with key stakeholders, coupled with results from the survey. It is important to note that responses represent individuals' own experience and are not necessarily representative of the views of their organisations as a whole, or of the associations which assisted us in administering the survey. All data are presented anonymously.

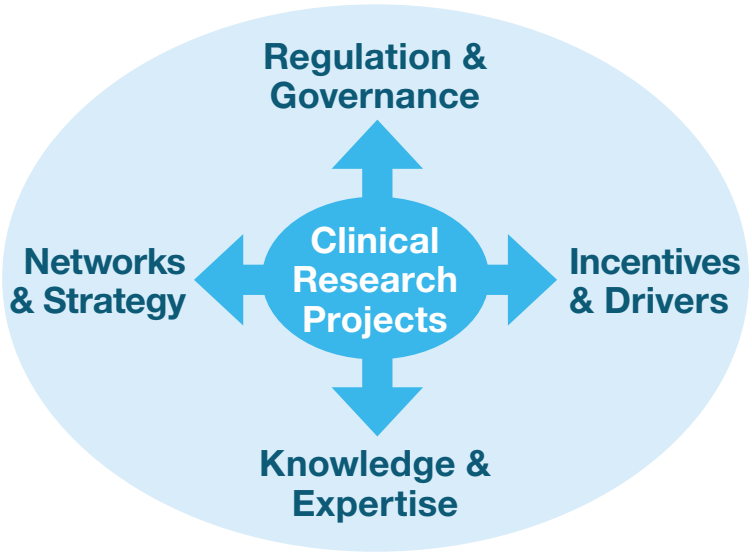
Our analysis provides behavioural data on the performance of research projects. It also provides valuable insight into how certain groups view particular aspects of managing clinical research projects. It is important that other stakeholders, including policy makers and the regulatory/ governance bodies, recognise that such views exist, even where they may not concur with them. This is because attitudes and previous experience shape whether or not people will initiate or engage further in clinical research in the UK. In short, if the UK context is seen as overly challenging, then research organisations and individuals may chose to conduct projects elsewhere, or stop engaging in clinical research altogether.

We caution that attitudes are not always reflective of actual behaviours and, hence, we collected behavioural data on specific experience as well as attitudinal data in our study. This was not a whole population study, however. Whilst we controlled for bias through various sampling and post hoc techniques, as well as through triangulation of different data sources, this always remains a possibility.

This report is set out as follows. First, we present survey data together with an overview detailing success measures across 247 projects, including set-up stage, patient recruitment and budget management. We begin with project completion success over the last decade, and differences between projects managed by different types of research organisation. We report a non-linear multinomial regression model analysis which identified aspects which predict successful project completion, together with features of research which influence ease of completion. We then report in detail on the challenges that are experienced by groups of researchers from different organisations, by combining data from both phases of this research. The greatest challenges were identified in the following four areas:

Regulation & Governance: Successfully completing the governance approval process was identified as a particular

Figure 1.3.1 *Schematic model depicting areas where challenges for day-to-day project management are experienced*



challenge for project management. In particular, different types of research organisation naturally conduct different models of research, all of which experience dissimilar pressures in managing the regulatory and governance process. Researchers that do not adopt standard randomised controlled trial (RCT) models face particular challenges in the approvals process.

Knowledge & Expertise: Retaining project team expertise was critical for successful project management. This underpinned many of the problems (e.g. recruiting and retaining patients) commonly associated with the conduct of all models of clinical research. However, skills shortages create particular difficulties for non-commercial and smaller commercial research organisations.

Networks & Strategy: Project management is reliant on the development of successful working relationships between the research organisation and other key groups within the sector. Each research organisation must shape their strategy for research to fit in with the UK strategic context and to facilitate successful networking with other stakeholder groups.

Incentives & Drivers: To develop and maintain a network of relationships, research organisations must develop insight into what incentivises different organisations, communities and individuals to engage in clinical research, which, in practice, may require balancing dissimilar or even antagonistic actions. The heterogeneous groups that are critical to the UK's clinical research sector require different levels of support to incentivise involvement with research projects.

2. Managing clinical research projects: Overview & completion rates

An overview of the 247 projects represented in our survey is provided here, together with completion rates and predictors of successful project outcomes. Variation in outcomes following major changes to the UK clinical research system (between 2001 and 2004) and differences between projects managed by different types of research organisation are considered. Findings from a non-linear multinomial regression model highlight the critical aspects for overall successful project completion.

2.1. Overview of survey sample

Key features of the data:

- 247 clinical research projects reported
- Projects reported from the perspective of individuals' experience of project management
- Profile of survey respondents: All roles across the sector
- Representative across the research sector, including both commercial and non-commercial research enterprises.
- Types of clinical research: medicines, medical devices, surgical, complex interventions and non-interventional healthcare and service delivery evaluations.
- The majority of projects commenced ***after 2005*** and typical length was in the range of 13 and 24 months.
- Project start dates range from 1999 to 2008.
- Included both short projects of 6 months to longer projects of greater than 4 years.
- 16% of the sample received regulatory approval before May 2004, 31% between May 2004 and the end of 2006, with 52% receiving regulatory approval after this date.

Figures 2.1.1 and 2.1.2 illustrate the profile of survey respondents. These included research centre managers, clinical investigators, project researchers and analysts, research nurses and clinical and affiliated roles. A proportion held a combined role, such as centre manager *and* Clinical Investigator (CI). 57% of projects were led by non-commercial research organisations, including clinical trials units and other types of health research centres based at universities (40%) and other 'not-for-profit' research groups, including NHS-led projects and charity-based groups. 43% of projects were led by commercial organisations, including pharmaceutical companies (27%) and other (smaller) commercial groups (16%) including medical devices organisations, biotech and start-up companies and projects that were primarily led by contract research organisations.

Figure 2.1.1 *Profile of role of survey respondents – Role within the projects reported*

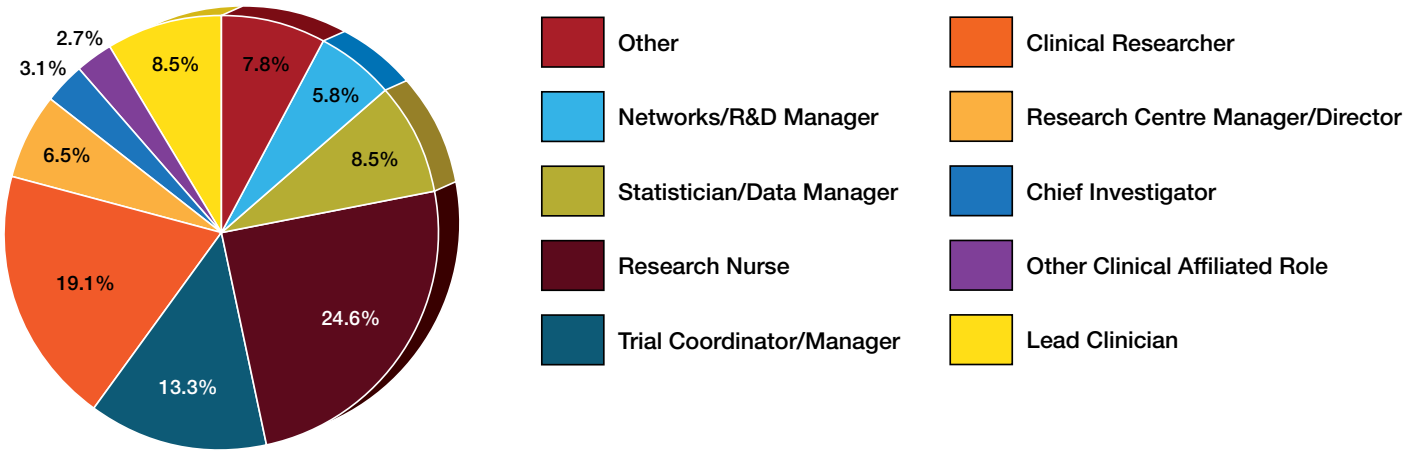
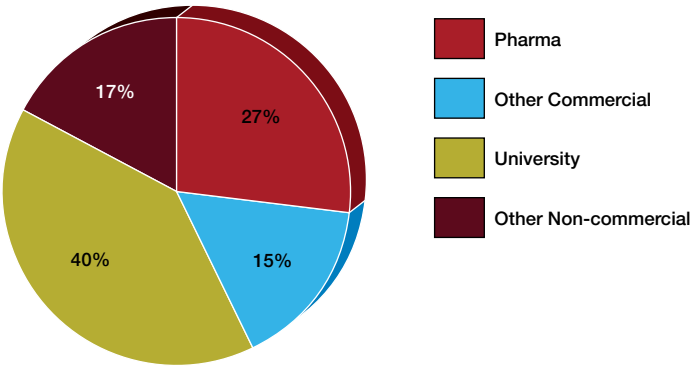
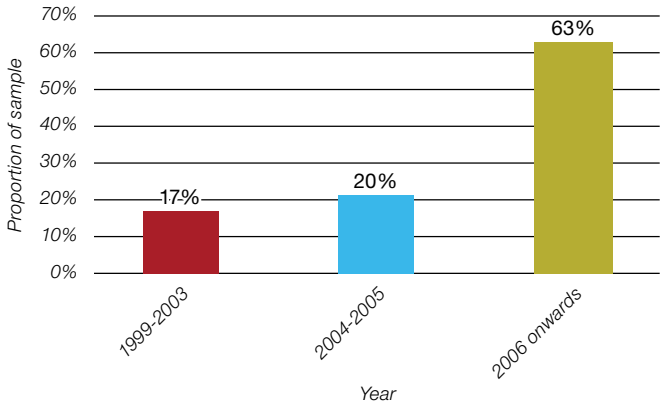


Figure 2.1.2 *Profile of lead organisation of projects*



The majority of the responses depict experiences of recent projects, with 63% reporting projects which commenced during or after 2006 (Figure 2.1.3). However, the design of the survey also enabled the collection of a representative sample of projects that took place earlier than this date. These data provide baseline data that help to show how changes in the UK context have influenced the management of projects over time.

Figure 2.1.3 *Profile of the year projects commenced*



The majority of projects (56%) were trials investigating pharmaceuticals or medicines, with the remainder focusing on medical devices or surgical research, complex interventions, or were for the purpose of service or general healthcare evaluation (Figure 2.1.4). Unsurprisingly, commercial and non-commercial organisations tended to have different foci of investigative intervention or evaluation. 83% of the commercial groups were researching medicines products, while the projects led by non-commercial groups spanned a broader range of investigative interventions and evaluation types (Figure 2.1.5).

Figure 2.1.4 *Profile of investigative clinical intervention or evaluation of projects*

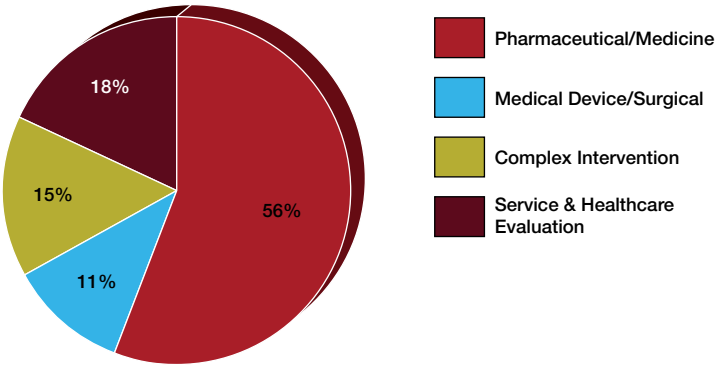
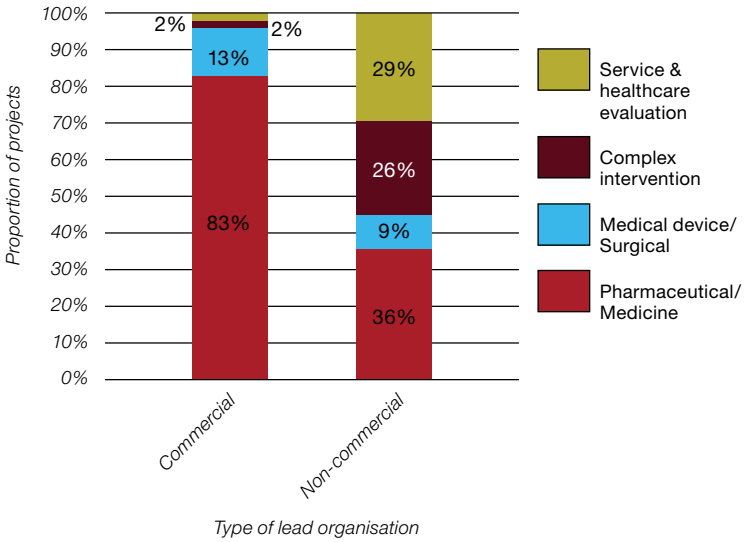


Figure 2.1.5 *Profile of variation between lead organisation of investigative clinical intervention or evaluation of projects*



The projects were inclusive of a range of disease areas (Figure 2.1.6). Cancer trials constituted the largest sample (26%), which perhaps reflects the emphasis on cancer research within the UK. For the purpose of the findings presented later in this report, we combine the related disease areas, respiratory, cardiovascular, stroke and diabetes into one broad disease group (RCSD) (Figure 2.1.7).

2.2 Time taken to complete projects

Data were collected on whether the overall project finished within the time that had been allocated within the project plan, from the point when the protocol was developed and project management team established, to the point where data had been collected, analysis undertaken and the project closed. Data were also obtained on whether the set-up and recruitment stages were completed within the time allocated. Completion of set-up is to the point where the first UK patient could be recruited in the study, and

Figure 2.1.6 *Profile of disease areas of projects*

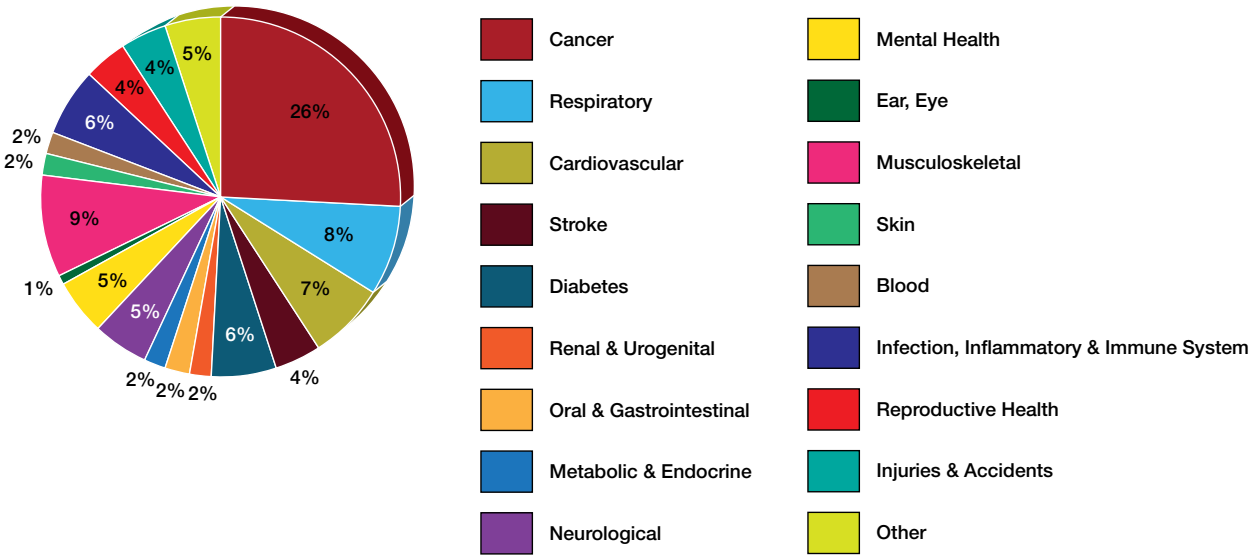
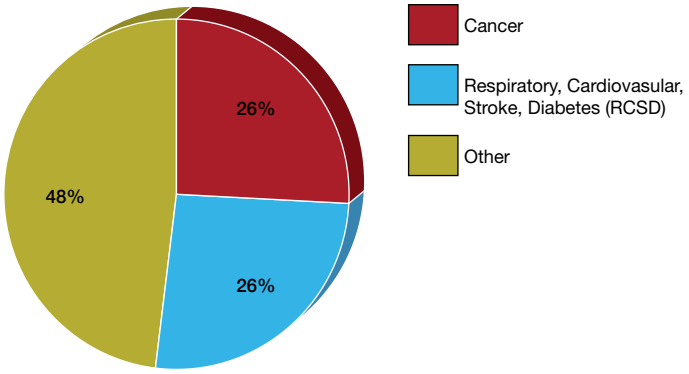


Figure 2.1.7 *Profile of disease groupings of projects used for analysis within the report*



thus includes the time taken to recruit the project team, negotiate access and obtain necessary approvals and permissions to enable the first clinical site to be opened. The patient recruitment stage is inclusive of the time taken from when the first patient could be recruited into the study, to the point of closure of the last UK clinical site.

There has been an overall improvement in the proportion of projects that complete within time over the last 2 years (Figure 2.2.1). This improvement is largely related to improvements in time to recruit patients, whilst the project set-up stage continues to be a significant challenge (Figures 2.2.2 and 2.2.3). Overall, the proportion of projects which are terminated before completion, terminated at the set-up stage, or during the patient recruitment stage, has not altered over the last 10 years.

The general trend showing improvement in project completion over time is countered by a slight drop in the proportion of projects, from 2004 onwards, that reach the anticipated recruitment target expected from UK sites within the timeframes set (Figure 2.2.4). These findings may reflect a change in project management strategy, resulting from a greater pressure to terminate a project when it has not recruited to target, rather than providing additional time to recruit further patients. For projects led by global pharmaceutical companies, UK sites increasingly constitute only a small proportion of recruitment sites included in a study, and thus low recruitment achieved from the UK can be more easily compensated by non-UK sites, enabling pharma-led projects to still complete on time.

Figure 2.2.1 *Proportion of projects completing on time: Categorised by year of project commencement*

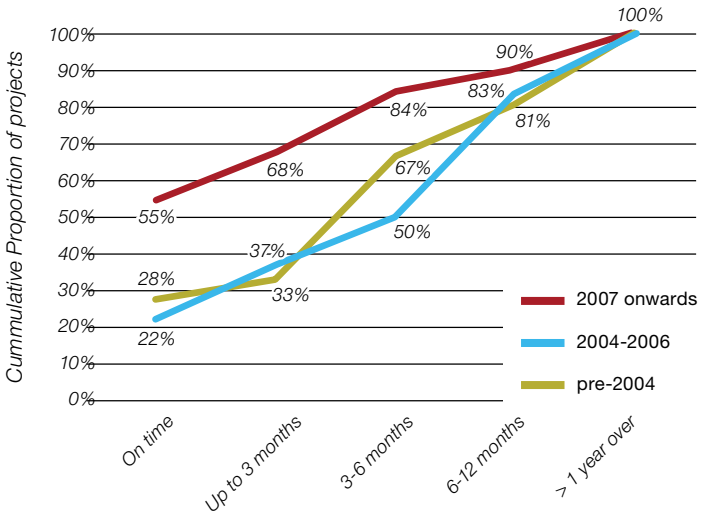


Figure 2.2.2 *Proportion of projects completing set-up stage of project on time: Categorised by year of project commencement*

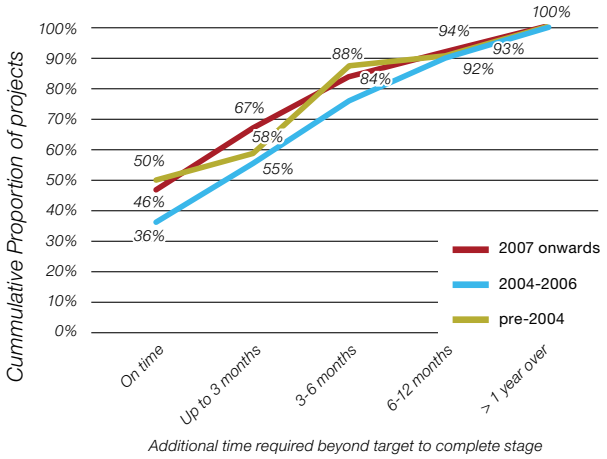


Figure 2.2.3 *Proportion of projects completing recruitment stage of project on time: Categorised by year of project commencement*

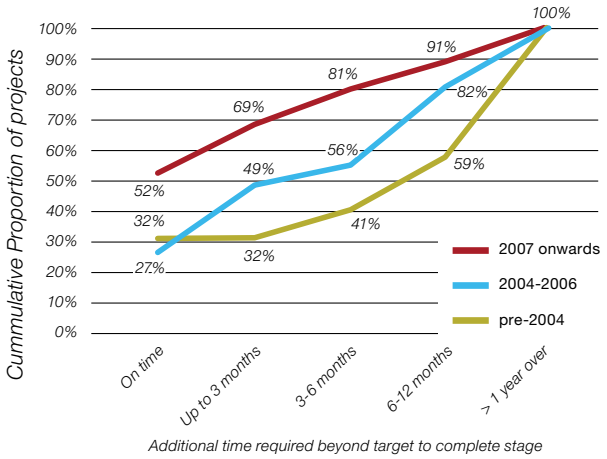
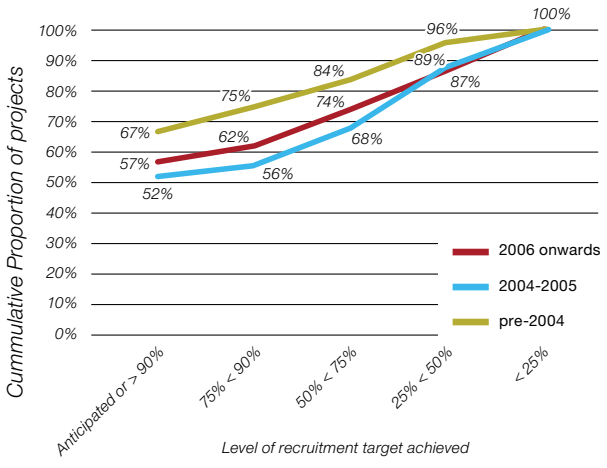


Figure 2.2.4 *Patient recruitment target achieved: Categorised by year of project commencement*



2.3 Influence of lead organisation on overall time taken to complete projects

One of the main objectives of this study was to identify the challenges associated with managing different models of research. Different types of lead organisation are founded on different market and strategic imperatives, and hence projects typically favour different models of research. Thus, global pharmaceutical companies characteristically develop 'straightforward' RCTs. In contrast, small-start-up organisations are reliant on developing innovative new products, whilst non-commercial research typically focuses on areas important within the UK context, including essential medicines, cost-effectiveness comparisons of interventions, and NHS-specific service & healthcare evaluations.

Projects conducted by different types of lead organisation exhibit different levels of success in terms of the time taken to complete different stages of a project, and achieving patient recruitment targets within the planned timeframe (Figures 2.3.1, 2.3.2, 2.3.3 & 2.3.4).

The 'pharma' group encompasses large global pharmaceutical companies. This group reports the largest proportion of trials completing on time (45%), with only 17% running over the planned time by more than 6 months. This trend is seen across both the set-up and recruitment stages of the project and also with the recruitment target achieved. This group also represents the highest recruitment of patients to target (73%). Therefore, pharmaceutical organisations are more successful achieving project completion and recruitment targets, relative to other organisations within the clinical research sector.

The 'non-commercial research' group comprises university clinical trials units, together with clinical research projects managed by other groups within universities departments, NHS organisations and charity and other 'not-for-profit' research collaborations and centres. This group report wide variation in success. Around one third of projects complete on time, and 58% achieve target numbers. Slightly under one third of projects over-ran by more than one year. In general, this group are experiencing comparably less problems at the set-up stage of the project, with 43% completing this aspect of the project on-time, and only 20% taking greater than 6 months additional time. However, whilst 36% are completing the patient recruitment stage on-time, around half of the projects reported were running over by more than 6 months during this stage of the project.

The 'other commercial research' group includes projects which were conducted by other 'for-profit' organisations

including medical devices companies, biotech and start-up organisations. This group also includes projects which were primarily managed by contract research organisations. It is this group of research organisations which are experiencing the greatest difficulty completing projects within the designated time. Only 24% of projects complete on-time, and half reported running more than 6 months over. In particular, this group encountered greater difficulty with completing the patient recruitment stage. Only 43% of projects achieved target recruitment, with the same proportion achieving less than half of the recruitment target. In addition, many of the projects also ran considerably over the time allocated for this stage of the project

Figure 2.3.1 *Overall time taken to complete project: Categorised by lead organisation*

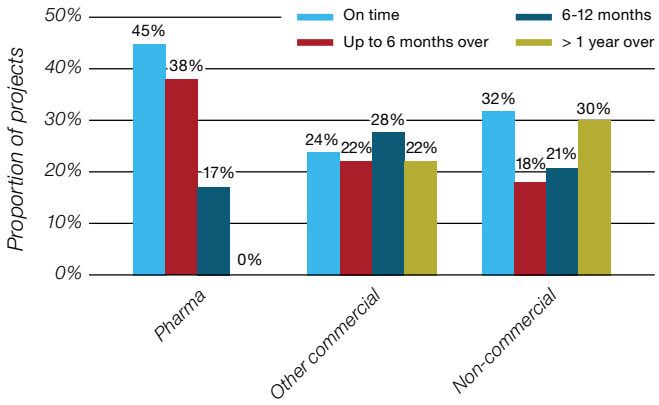


Figure 2.3.2 *Overall time taken to complete set-up stage of project: Categorised by lead organisation*

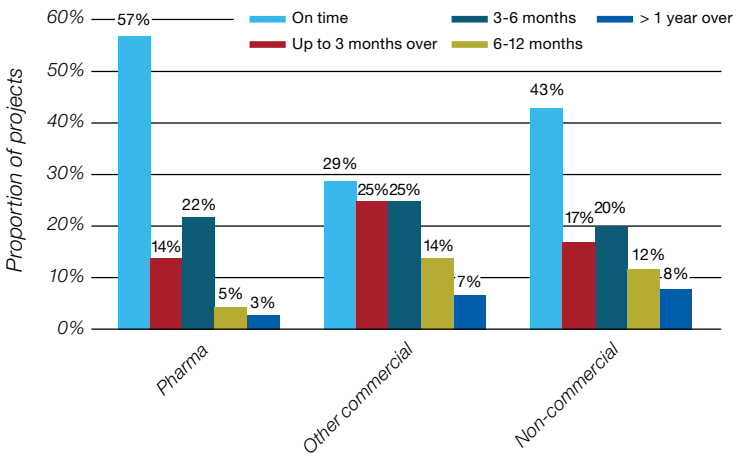


Figure 2.3.3 *Overall time taken to complete recruitment stage of project: Categorised by lead organisation*

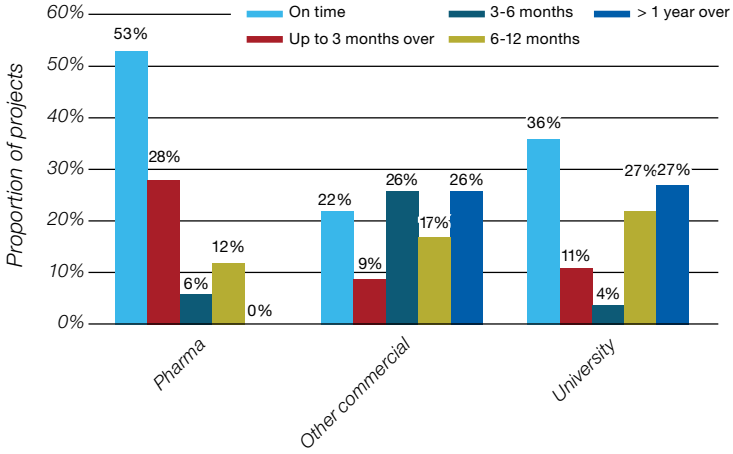
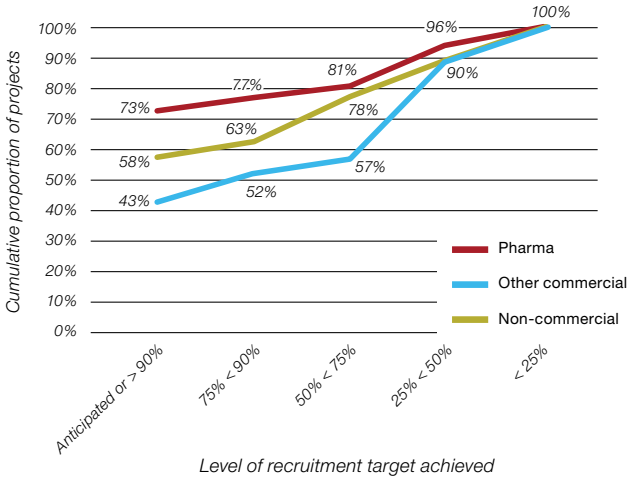


Figure 2.3.4 *Patient recruitment target achieved: Categorised by lead organisation*



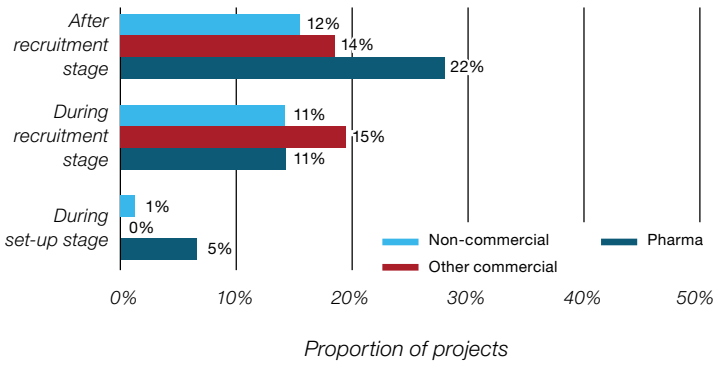
The proportion of projects terminated by different types of research organisations illustrates that different strategies are employed by different parts of the sector (Figure 2.3.5). Pharmaceutical organisations have a greater proportion of projects which terminate either during the set-up stage or after closure of the recruitment stage. Commercial pressures mean that these organisations are more likely to drop an entire project if it does not show promise. Moreover, global pharmaceuticals are more likely to have alternative non-UK locations to conduct trials meaning that UK sites can be dropped whilst still continuing with a research programme. This strategy contributes to the proportionally lower number of projects which run considerably over time. In contrast, many of the organisations within the other commercial groups are small companies with only one or two investigative products. Hence, even when project management challenges are

experienced, these organisations need to persevere with a research programme to obtain some results.

Finally, non-commercial projects are typically tied to fixed-term public funding and are under pressure to demonstrate findings of both academic *and* policy/patient benefit. They also incorporate a comparatively more complex range of design and methodological approaches. This can influence project management strategy - projects typically terminate only when the funding (and any extension granted) ends, even when considerable difficulties are encountered earlier. This could help to explain why some non-commercial projects take considerably longer than expected.

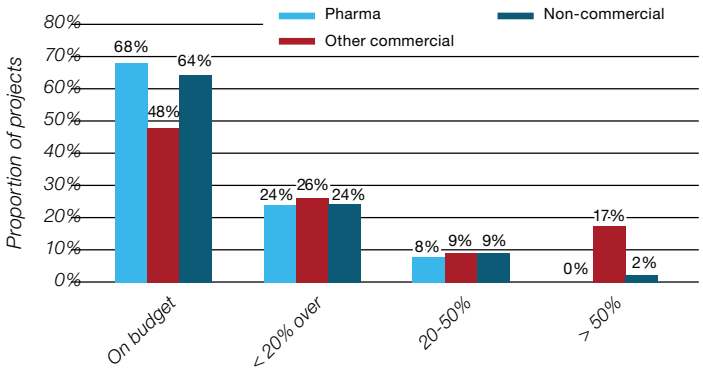
It was apparent from the first phase of our study that many of the clinical research projects led primarily by Clinical Research Organisations are inherently tricky as other research organisations have already experienced delays before making the decision to outsource. The projects reported by the 'other commercial' group include organisations, such as biotech, start-up and small medical devices companies. These may have less experience in managing clinical research projects and are therefore likely to experience greater challenges. Whilst the focus of medical devices research can vary widely, the nature of this type of research can include research into interventions with high levels of risk (e.g. where surgery is also included) or which require complex patient recruitment, and thus are more challenging to manage successfully.

Figure 2.3.5 *Proportion of projects terminated: Categorised by lead organisation*



Almost two thirds of the projects reported for pharmaceutical companies and non-commercial research organisations complete within budget, with less than 10% of these running more than 20% over budget (Figure 2.3.6). The group of other commercial organisations experience greater challenges with budget management - less than half complete on budget and around 17% were reported to have run over budget by more than 50%. This group constitutes organisations, such as start-up companies, which typically have the least experience of managing a clinical research project and may struggle with commercial expertise.

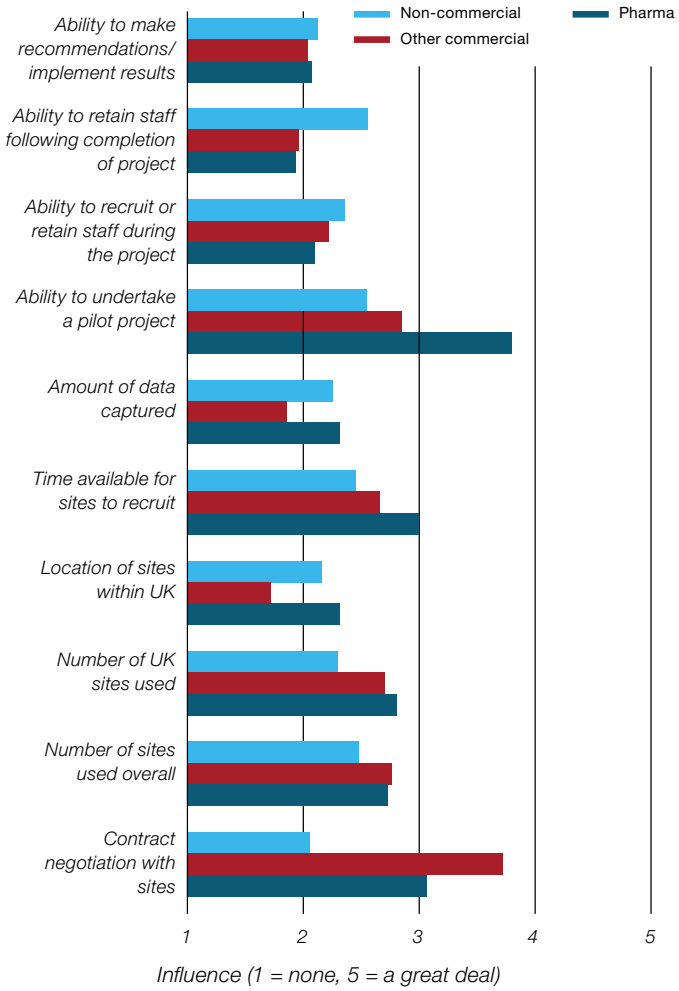
Figure 2.3.6 *Project completion within budget: Categorised by lead organisation*



The findings indicate that different types of research organisation experience different financial and budget pressures (Figure 2.3.7). Data about commercial organisations found that budget pressures considerably influenced the ease of their contract negotiation with NHS sites. This reflects that all types of 'for-profit' organisation have to engage in more complex discussions about financial payment and reimbursement for use of NHS resources as compared with non-commercial organisations.

Respondents from non-commercial organisations believe that financial issues adversely affect their ability to retain staff following completion of a project. Typically, non-commercial projects are financed by fixed-term grants from external funding bodies, and the continuing employment of research staff is dependent on whether the organisation successfully receives funding for a subsequent project. To actually retain staff, research organisations need to engage in time consuming negotiations with public funders before they can provide new contracts. These, often protracted, negotiations can make it difficult for a subsequent project to be confirmed by the time the initial project has been completed, and consequently research staff may leave before new contracts are confirmed. For all organisations, financial and budget pressures are considered to have influenced negatively the number of UK and overall number of sites used.

Figure 2.3.7 *Influence of financial and budget pressures on project management: Categorised by lead organisation*



2.4 Predictors of project management success

Non-linear multivariate regression analyses models identified major predictors of successful project management outcomes (Table 2.4.1). The most critical predictor is retaining a project team, accounting for significant variation in success of overall project completion recruiting to target *and* completion of the recruitment stage of a project. This highlights that the nuanced expertise held by project team members is critical to many aspects of setting-up and conducting a project.

The number of submissions for regulatory approval is also identified as a predictor of successful project completion. If a team has to re-submit a regulatory approval application, there may be underlying issues with the project design and focus, and this may account for problems with achieving efficient and timely completion of the recruitment and set-up stage.

Ease of contract negotiation also predicted variability in project completion, and completion of the recuitment stage, suggesting that this is a major challenge when managing a clinical research project.

Completing the patient recruitment stage is influenced by the retention of the project team, contract negotiation and the time taken to receive R&D approval. The latter two factors reflect the variability of time taken by different R&D offices to provide permissions to use NHS sites. Retaining a project team is also crucial aspect for achieving target recruitment, together with the time taken to obtain the R&D approval for the first site to be used in the study.

Table 2.4.1 *Critical predictors of project completion*

Stage of project	Aspect of project management	Proportion of variance accounted by model
Overall project completion:		**14.2%**
	Retaining a project team	
	Ease of contract negotiation	
	Number of submissions for regulatory approval	
Completion of set-up stage:		**n/a**
	No significant individual predictors	
Completion of recruitment stage:		**14.3%**
	Retaining a project team	
	Ease of contract negotiation	
	Time taken to receive R&D approval (Average time)	
Recruitment to target:		**17.7%**
	Retaining a project team	
	Time taken to receive R&D approval (First site)	
Completion within budget:		**8.2%**
	Project completion on time	

Table 2.4.2 presents an analysis of the ways in which project type predicts project outcomes. In particular, the later phases of medicines research experience the greatest difficulty. In addition, projects where the focus is on acute rather than chronic conditions are less likely to complete on time. The type of clinical site setting also has an influence, with sites based within secondary and tertiary care experiencing greater difficulty completing on time compared with primary care sites. For the set-up and recruitments stages of the project, it is the involvement of children and later phase medicines research which effects whether a project completes on time. Obtaining regulatory and governance approval is more challenging for research that includes children, as there will be particular ethical and

safety concerns associated with these projects and often less previous data about similar research interventions available as bench-mark comparisons. It is more difficult to successfully complete recruitment for projects focusing on cancer and research about acute conditions, as these present particular challenges when attempting to identify sufficient patient numbers. These findings exemplify some of the major challenges experienced when conducting different models of clinical research.

Table 2.4.2 *Types of research project that predict ease of project management*

Stage of project	**Type of Project**	**Proportion of variance accounted by model**
Overall project completion:		**13.0%**
	Chronic compared with acute conditions	
	Phase of medicines research	
	Type of clinical site – Secondary compared with primary/ tertiary	
Completion of set-up stage:		**9.4%**
	Research involving children	
	Phase of medicines research	
Completion of recruitment stage:		**8.6%**
	Research involving children	
	Chronic compared with acute conditions	
Recruitment to target:		**41.9%**
	Research involving children	
	Phase of research	
	Disease group – Cancer compared with other disease areas	
	Chronic compared with acute conditions	

3. Regulation & Governance

This section considers the challenges experienced when applying for regulatory and governance approvals. Findings are presented on how changes to the regulatory & governance framework that have taken place over the last ten years have influenced respondents' experiences of managing this process. The findings also show that problems encountered in completing the process and obtaining regulatory approval & governance permissions vary systematically across the model of research and lead research organisation.

3.1 Preparation and submission of regulatory & governance approval applications

As seen in Section 1.1, there have been considerable changes to the regulatory system and governance framework for clinical research in the UK – in particular the UK's implementation of the EU Clinical Trials Directive that came into force in May 2004, and the creation of the 2001 Research Governance Framework for Health & Social Care. The former led to changes not only to the regulatory process through the formation of the Medicines & Healthcare Regulatory Agency (MHRA), but also to the UK ethical assessment process through the legal establishment of ethics committees. The latter had direct repercussions for the process of obtaining permissions to use NHS sites and resources for clinical research projects.

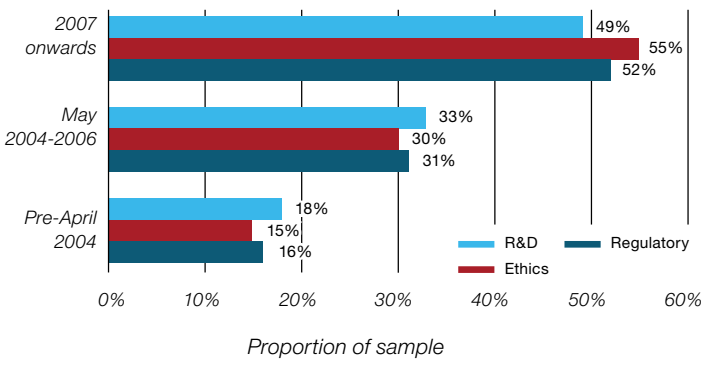
The 2004 changes to the regulatory system seem to have had the most impact in academic medicines research. Previously many clinical trials of this type would have been applicable for a Clinical Trial Exemption (CTX) or would had been notified to the regulatory bodies under the Doctors and Dentists Exemption (DDX) scheme, and thus received an exemption from following the full process of obtaining regulatory approval. The discontinuation of this scheme meant that all medicines research had to conform to *the same* regulatory standards, and both commercial and non-commercial groups were required to seek regulatory approval for Clinical Trial Authorisation (CTA). This resulted in a need for certain research groups to provide more detailed information about their project. Each project needed to demonstrate adherence of 'good practice' for regulatory inspections, and in general regulatory adherence became a more time consuming process.

Although the focus of the EU Directive was on standardising the regulation of medicines research across all EU countries, the ensuing changes have had repercussions for the ease of management of other models of clinical research. Projects such as non-medicines & non-intervention research (e.g. surgical research, complex interventions, healthcare & service evaluation and medical devices) were not under the direct scope of this legislation, but were affected by the parallel changes to the ethics review process. In addition, medical devices research has been subject to changes incurred through the various related EU Medical Devices Directives, as major amendments came in during 2003 and 2007.

It is important to note here that the data collected within this study on the time taken to obtain approvals incorporates, not just the duration of assessment by review bodies, but also the time taken to obtain information about the review process, and to prepare and submit documentation. Therefore the findings presented in this report are distinct from figures generated by the approval bodies themselves, which refer to the duration from the point where an application has been submitted to receiving a decision. The time taken to obtain R&D approval refers to the average time it took to prepare the documentation and secure permission from all NHS Trust R&D departments involved in the study.

Overall, 59% of respondents in our survey reported that their projects required medicines regulatory approval for a clinical trial authorisation, 99% required ethical approval and 91% required NHS research governance (R&D) approval to use NHS clinical sites. The survey collected information about projects conducted over the last ten years. Only a small proportion of the sample sought regulatory, ethical and R&D approval prior to April 2004 (Figure 3.1.1). Therefore the majority of the data relate to recent experiences with the regulatory & governance approvals system.

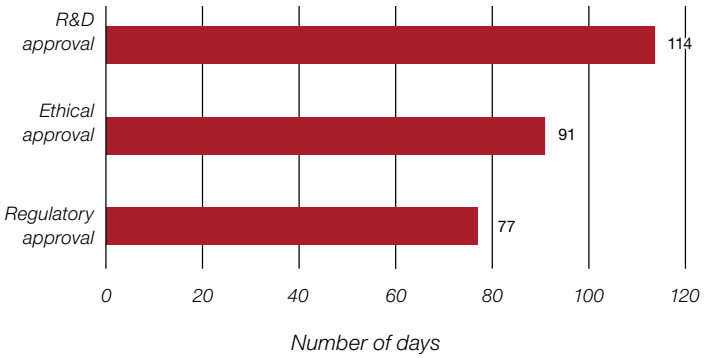
Figure 3.1.1 *Date approvals were sought by projects in sample.*



The average time to *prepare, submit and obtain* an outcome for approvals (Figure 3.1.2) was found to be:

- R&D: 114 days
- Ethics: 91 days
- Regulatory: 77 days

Figure 3.1.2 *Average number of days to prepare, submit and obtain approvals taken by projects reported within the survey*



3.2 Managing projects in the context of changes to the approvals system

Findings presented in Section 2.2 (Figure 2.2.2) suggest that changes to the regulatory & governance system that were introduced following implementation of the EU Clinical Trials Directive appear to have had little effect on overall set-up time of a project. The survey data charts changes to time taken to prepare for and obtain approvals over the last decade. Around half of respondents reported on projects that took place from 2007 onwards, and around 15-18% refer to projects from before May 2004. The results demonstrate that over the last 10 years, the time taken to prepare, submit and receive approval from the three main types of regulatory and governance review have followed different trends (Table 3.2.1 and Figure 3.2.1).

The time taken to prepare for, and receive MHRA regulatory approval for a Clinical Trial Authorisation increased slightly between 2000 to 2009. Data produced by the MHRA indicate that changes to the process in 2004 resulted in only slight reduction to the time taken for an assessment to be reviewed following submission (remaining at a little under 30 days (MHRA, 2009)). We surmise therefore that some researchers may be experiencing additional challenges with preparing application documents. Certain groups of researchers find the 'new' system more complex, and take additional time to understand and prepare the documentation. In particular, for those groups that had previously received regulatory exemptions, inevitably the overall time to prepare, submit and receive approval with the post-2004 system will be much longer.

For ethical review, the 2004 changes appear to have had little effect on the time taken to prepare and submit an application to receive a positive ethical outcome - approval times have remained stable around the 90-day mark. Data from NRES indicate that since 2004, the duration of their review of applications has remained stable at around 35 days (NRES, 2009). Overall, our findings suggest that changes to the approvals process have had little effect on researchers' overall ability to manage the process of ethical review.

These findings highlight that the greatest challenge associated with managing the approval process centres on negotiations with NHS Trusts and the time taken to receive R&D permissions to use NHS sites. The average time for the projects to prepare documentation and engage in consultation to receive positive outcome from an NHS Research Governance office initially increased considerably following changes in 2004, but more recently have fallen back to pre-2004 figures at around 100 days. These findings may reflect that additional time was required for researchers to obtain information and learn about the new processes at the start of the decade, and that new documentation and procedures were being interpreted, perhaps differently, by the various NHS Research Governance offices across the UK, following the publication of the 2001 NHS Research Governance Framework.

The time taken for the last R&D approval to be received (i.e. the Research Governance office that took the longest to provide a decision within a multi-site study) was reported to have decreased over the 10-year time period. This may reflect that in general, NHS Research Governance offices have streamlined the process, and that some of the most serious barriers to obtaining R&D approval have been confronted. However, the time taken to obtain R&D approval from the last site in a study is considerably longer than the average time, so there still is significant variability and unpredictability in the time taken across different Trust Governance offices within the UK.

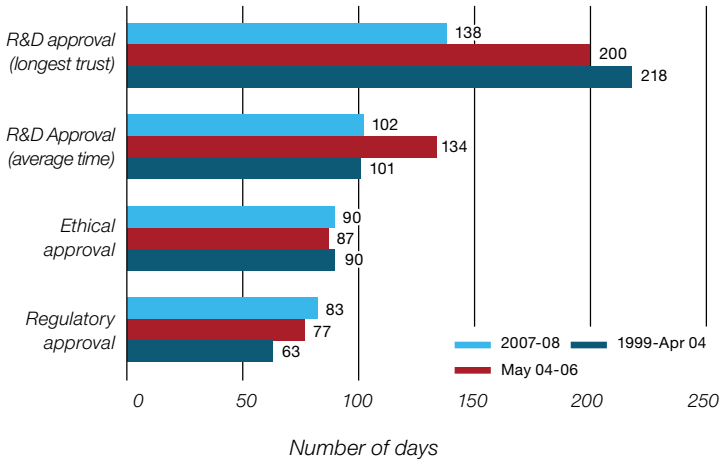
The maximum 30-day (14 days for early phase studies) and 60-day turn-around following submission by regulatory and ethical bodies, respectively, have been welcomed by researchers. This has been attributed with providing

research groups much greater control over project management, allowing them to plan more accurately how long regulatory and governance applications will take. There is a strong desire for a similar maximum time to be guaranteed for R&D approval by NHS Research Governance offices. If such an initiative could be implemented this would greatly assist preparation and planning of projects.

Table 3.2.1 *Number of days taken to prepare, submit and receive a positive outcome from regulatory & governance approval bodies: Categorised by year of approval application*

Year	Regulatory approval	Ethical approval	R&D approval (average time)	R&D approval (longest Trust)
99-Apr 04	63 days	90 days	101 days	218 days
May 04-06	77 days	87 days	134 days	200 days
07-08	83 days	90 days	102 days	138 days

Figure 3.2.1 *Average number of days taken to prepare and receive a positive outcome from regulatory and governance approval bodies: Categorised by year of approval application*



It is also important to note that these data on preparation and approval times are from the researchers' perspective**.** Whilst they may seem high compared to official figures on approval times, they do reflect the day-to-day experiences of setting-up and managing a clinical research project, at least as reported by the respondents in our survey.

There is a perception by certain research groups that following changes to the regulatory and governance system, obtaining all approvals became more cumbersome due to a large increase in the documentation that was required to satisfy legal and governance framework requirements. In addition, changes to the amount and type of documentation required for ethical review is also perceived by some (especially those groups previously exempt) to have considerably increased.

…"With the EU Directive, there were lots of other things that fell apart at the same time. Our local ethics form, the information sheet used to be a maximum of two pages long. The one I showed to a patient this morning was 18 pages long. It had obviously been with the lawyers for an extensive period before the company signed it off. These documents now feel as if they increasingly are designed to enable a lawyer to sign it off, not to be tested. You think of all the simple communications that fail in real life... Quite how we expect people with widely varying educational levels to take in an 18-page information sheet, and we've got to increase our recruits of ethnic minorities."

Data produced by NRES (NRES, 2009) highlights that since May 2004, when a 60 day turn-around for ethics approvals was implemented, there has been little change in the time taken to receive an outcome following submission. Since 2005 the time taken has remained around 35 days. Our data indicates further that there has been little change in the time taken to *prepare and obtain* ethical approval since 2000, which remains at between 87-90 days. We surmise therefore, that in general, researchers are putting similar levels of effort into the preparation of application documents, which accounts for approximately two thirds of the time they take to obtain ethical approval.

…"The ethics board they are improving things, but the last three of four years have been a nightmare. You haven't got long enough. You have to basically write a thesis to get it there, and there are restrictions. It's just unbelievable what they will and what they won't do. They have very conflated protection stuff. It's gotten the worst that it's ever been in many ways, but I hear it is going to be resolved."

Recent attempts to integrate and streamline the approvals process, including the Integrated Research Application System (IRAS) and Coordinated System for gaining NHS Permissions (CSP), have been welcomed (Figure 3.2.2). In particular, researchers in both commercial and non-commercial organisations are hopeful that the Research Passport scheme and the bipartite/ tripartite model Clinical Trial/ Investigation Agreements (mCTA/ mCIA) for NHS & commercial collaboration could solve some of the issues at the NHS research governance and contract negotiation stage.

However, there is a perception that the changes are not happening quickly enough to secure a future for UK clinical research (especially commercial research) in the face of

global competition. Many suggested that site specific information required by each NHS Trust could also be considerably lessened, enabling uniform procedures to be followed and identical documentation to be used. This could reduce the burdens imposed by different NHS sites considerably.

In particular, it was felt that if some Trusts could 'buy-into' a streamlined process which reduced the amount of specifically tailored information required, then all Trusts might start to follow suit. Respondents reported, further, that the performance of Trusts in this regard was not transparent enough and therefore they relied heavily on insight from personal contacts to inform the selection of sites where it was believed that gaining Trusts R&D approval would be less problematic.

Figure 3.2.2 *Current attitudes towards recent policy initiatives affecting the regulatory & governance approvals process*

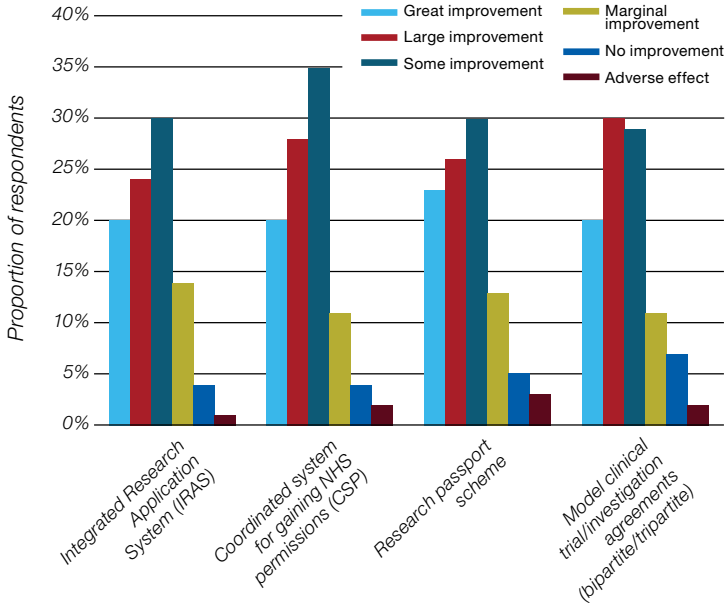


Figure 3.3.1 *Proportion of projects which received regulatory and ethical approval from the first submission; Categorised by type of lead organisation.*

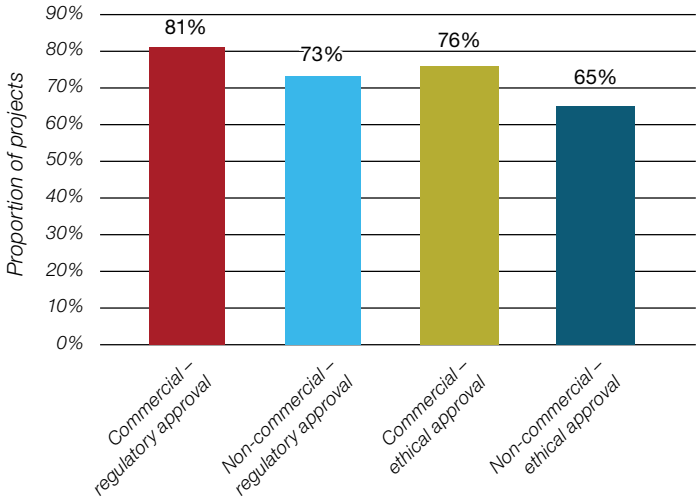
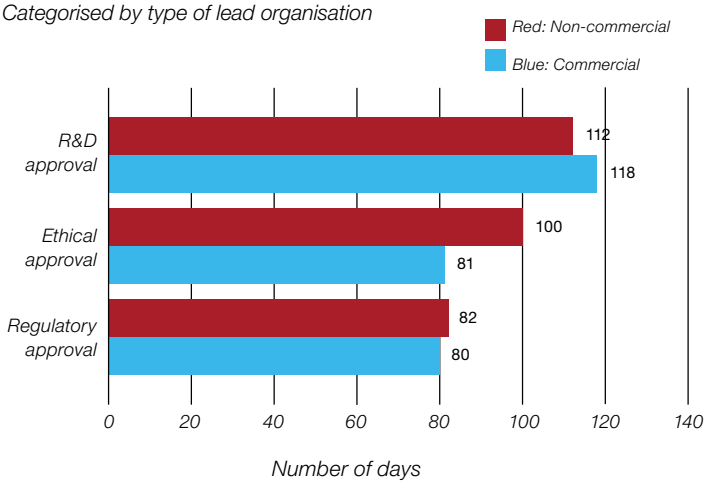


Figure 3.3.2 *Number of days to prepare and obtain approvals: Categorised by type of lead organisation*



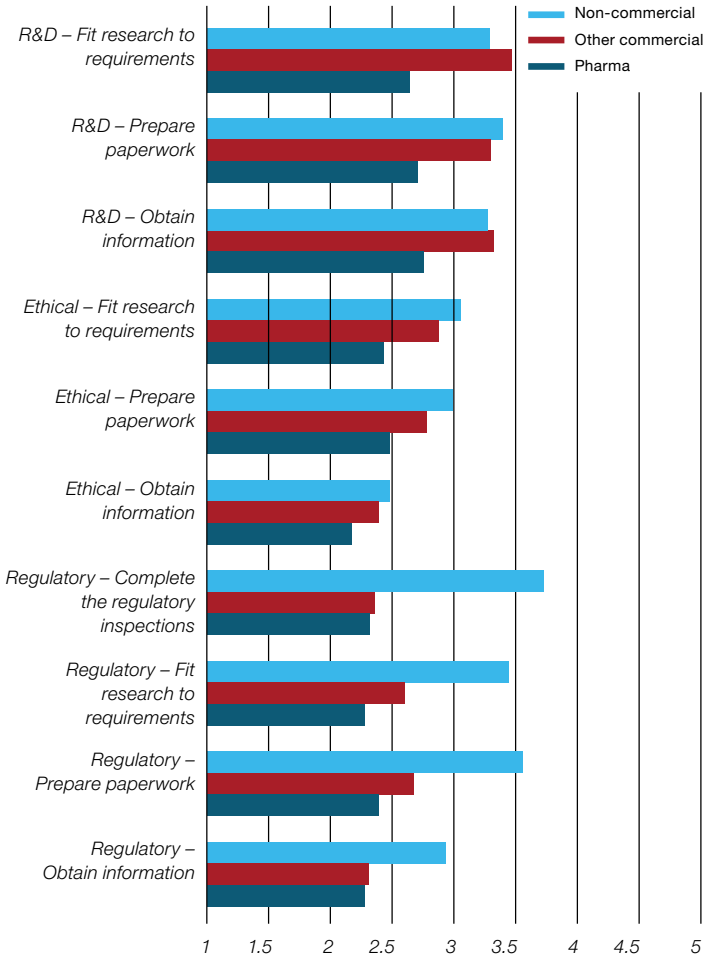
3.3 Different types of organisations have different experiences of the approval process

The survey data indicates that commercial organisations complete the process of preparation and submission of regulatory, ethical and R&D approvals more efficiently than non-commercial research groups (Figure 3.3.1). They are more likely to receive regulatory and ethical approval with the first submission, and overall achieve quicker approval times. Both organisation types take a similar amount of time to prepare and receive regulatory approval, although non-commercial organisations take longer on the ethical approval process (Figure 3.3.2). Commercial organisations take longer to receive Trust R&D approval, which may reflect the intricacy of the contract negotiation which they must engage in.

Non-commercial and other commercial groups experience greater levels of difficulty compared with pharmaceutical organisations with obtaining information, completing paperwork and fitting the features of the research to the approval requirements for the regulatory and R&D approval process (Figure 3.3.3). The structure and greater resources of large pharmaceutical organisations is likely to provide the levels of expertise that are required to complete the approval process efficiently. Overall, a pharmaceutical company will have more dedicated specialist staff, and the structure within a typical company enables them to more easily draw on these resources when needed for a specific project.

Proportion of respondents

Figure 3.3.3 *Ease of completing aspects within the approval process: Categorised by organisation type*



Academic research groups expressed particular concerns about the effect of the 2004 changes to the regulatory system, and the influence this has had on the ease of conducting their model of clinical research. This issue was also recently discussed at the 2nd Sensible Clinical Guidelines meeting in September 2009 (Groves, 2009).

…"When the new regulations came out in 2004, for people who had been working in academic central organisations, which, as far as I could tell, had never been near industry. Suddenly, this extraordinary level of bureaucracy was explained to them. They didn't know where to look, so they started asking these extraordinarily naive questions about how you do the most basic things about making the documentation of your trial reasonably robust. But certainly when the new regs came in and they had to apply to everybody, that was a major shock. I mean the correct form to get your ethics approval now is a huge and worrying document. Most of us think there was a big decline in the number of projects being submitted to coincide with the new regulations because it became very hard to do things. Pilot work, particularly, is much more difficult to do."

Many academic groups felt that they were not sufficiently involved in discussions about the changes to the regulatory framework and that, consequently, their needs were not sufficiently addressed. There is also a perception that the new regulatory system was modelled largely on improving the efficiency of large-scale RCT trials typically conducted by pharmaceutical firms, but showed less concern about the financial implications of the changes for other models of research.

…"It was intended to harmonise research throughout Europe. It was a consequence of discussions between the pharmaceutical industry and the regulators. Academics were not involved; it was not about improving patient safety. That's complete nonsense. It didn't even include the health directorate of the EU. It was the industry directorate of the EU meeting with the pharmaceutical industry."

A recent one-year study into the Impact of Clinical Research of European Legislation (ICREL) organised by the European Forum for Good Clinical Practice (EFGCP) evaluated the impact of the clinical trials directive for various research types across Europe (EFGCP, 2009). These findings highlighted that there has been a considerable reduction in the number of research applications by UK non-commercial research groups, suggesting that this group in the UK context alone, may be experiencing uniquely challenging issues as a result of regulatory changes.

Respondents suggested that the documentation for approval submission compelled them to adhere to certain standard approaches and forms of presentation of their research protocols. It was believed that there could be confusion about how an assessment should be made for a-typical (i.e. non RCT) models of research when presented to approval committees. Whilst appreciating the value of these panels for ensuring good research and ethical practice throughout the UK, many respondents felt strongly that what was conceptualised as 'good practice' was largely informed by what was standard 'good practice' for a Randomised Controlled Trial (RCT).

Firms conducting medical devices research have experienced particular problems with obtaining approvals

due to a lack of understanding from ethics committees about what features constitute good research practice, as the features often differ markedly from more standard RCT types. In particular, pre-marketing studies for medical devices may only require small numbers of patients to generate the level of data required at this stage of product development. However, for many committee members, knowledge of what constitutes a good study is based on an RCT design where a pre-marketing medicines study typically requires large numbers of participants to demonstrate safety & efficacy.

…"The ethics committees work in the same way whether it's a device or pharma or a research project. They're looking at the ethics, whatever the project is. They determine if it's ethical and if it's scientifically valid to be ethical, so they're looking at the same things from an ethical perspective. 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, 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?'. Device control trials are very difficult because finding something to compare any device with can be very difficult. You normally are comparing a procedure as opposed to another product."

The specific issues for medical devices research have been recently considered and presented in a report by the Healthcare Industries Task Force (HITF, 2007). A Strategic Implementation Group was subsequently developed to oversee the implementation of this report's recommendations. This has enabled the specific needs of this model of research to be identified, and actions to combat the specific issues experienced by medical devices research teams have been developed. In particular, the creation of ethics committees that are flagged as having received specific training to evaluate devices research have been welcomed.

3.4. A '**one size fits all**' **model? Delineating risk levels for regulatory & governance approvals**

The role of the regulatory & governance approval bodies in assessing safety, quality, efficacy and ethical aspects of research is well recognised and valued by researchers. However, there is a perception that the risk-levels of different types of research are not sufficiently delineated meaning that some projects are subject to a level of assessment that is not proportional to the level of risk that they represent.

…"There is little emphasis on the risk - the processes are 'one-size fits all', so sometimes the process to get approval seems too onerous."

There is a perception that for many types of research, the balance of ensuring patient safety with what is required from researchers is at a 'tipping point'. It was felt that the ethical review process is too arduous compared with the level of ethical protection that research subjects in many types of project are actually perceived to require. Thus, it was felt that compromises to the design of studies and the overall level of documentation required to demonstrate adherence to 'good research practice' (as interpreted by ethical bodies) was resulting in practical difficulties for project design and management.

…"They [ethics committees] are so paternalistic. The idea citizens can't make some of these decisions themselves without being mollycoddled by ethics committees is ridiculous."

In particular, respondents felt that there was little flexibility in tailoring informed consent processes to reflect the level of risk that a project actually presented.

…"We feel that consent ought to be appropriate for what these people are consenting to, the consent procedure. If you're talking about a surgery that could be fatal, it's reasonable that the patient should chat with a consulting surgeon and have 24 hours to think about it, discuss it with family, and then come back with some more questions, maybe spend an hour chatting with a nurse and another 10 minutes with the consultant. It is a major decision. If a sample is taken in exactly the same way as usual, but it could get processed one of two ways in the laboratory, which are totally different, say one is looking at it under a microscope and the other is doing a molecular test. We think the consent should be quite different"

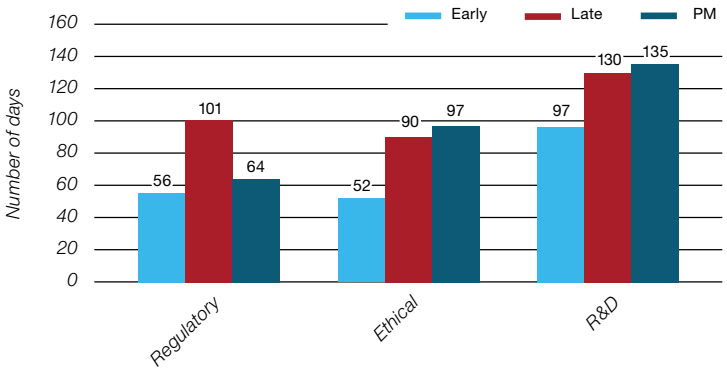
Throughout this research the findings underline that there is a belief that assessment of what constitutes 'good' research is based on the procedures followed within a Randomised Controlled Trial (RCT). Researchers who engaged in projects that did not conform to this standard research model experienced greatest difficulty.

In particular, it was felt that it can be more difficult to fit research that exhibits non-typical features into the standard paperwork and requirements of the approvals processes.

…"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."

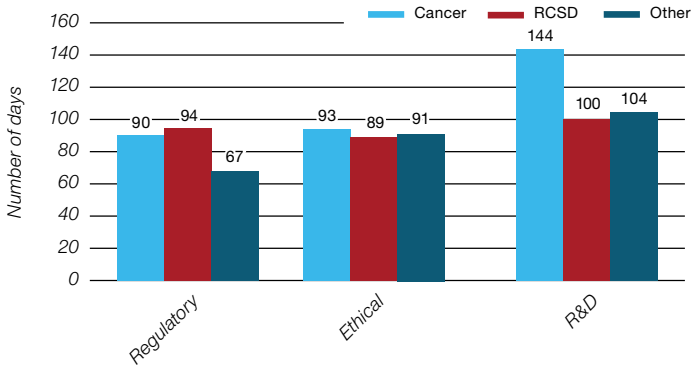
That said, the findings also demonstrated that late phase studies (2b & 3) take the most time to prepare and submit to obtain regulatory approval and these types of projects also are less likely to receive approval with the first application (Figure 3.4.1). For ethical and NHS R&D review, early phase research proceeds considerably quicker than late phase and post-marketing studies, which also have a greater number of ethical approval submissions approved with the first application (88% compared with 65% for late phase and 56% for post-marketing studies). These findings reflect the different remit for review that the different governance approval bodies are subject to. For regulatory approval, projects need to demonstrate safety and efficacy, which is most critical for projects designed to obtain marketing approval. Many early phase research projects are small, and there are relatively less ethical concerns and fewer overall local issues for NHS Trusts, whilst there are greater concerns about the ethical value of research findings for post-marketing (PM) research.

Figure 3.4.1 *Number of days to prepare, submit and obtain approvals: Categorised by medicines research phase of project*



The data indicates that cancer trials tend to experience a longer time to prepare and negotiate access with NHS R&D departments as compared with the disease group comprising of 'Respiratory, Cardiovascular, Stroke and Diabetes' (RCSD) studies and 'other' disease areas (Figure 3.4.2). This perhaps reflects a degree of saturation of NHS sites in terms of their capacity to run further cancer trials. In addition, much cancer medicines research inherently carries greater liability concerns for NHS Trusts.

Figure 3.4.2 *Number of days to prepare, submit and obtain approvals: Categorised by disease area of project*



Projects which are assessing treatments, typically in the form of evaluating new medicines, experience greater delays with obtaining R&D approval. This model of research generally present comparably greater liability concerns as compared to other models (such as prevention trials and healthcare management & evaluation studies – Figure 3.4.3). However, researchers engaged in prevention trials experience the longest time to prepare and submit ethical approval applications. This may reflect that many of these studies necessitate very specific design features that are not typical of the majority of studies that are reviewed by ethical bodies, such as requiring novel participant identification and consenting processes.

These non-typical design features are also generally associated with project types with a focus on acute conditions and/or rare diseases. These face greater difficulty in identifying and planning, in advance, an appropriate target patient population. These types of research thus experience greater delays with obtaining R&D approval and also experience a slightly longer time obtaining ethical approval (Figures 3.4.4 and 3.4.5). Whilst not necessarily inherently of greater ethical concern, researchers may need to engage in more detailed debate about the appropriateness and ethical merit of the incorporation of novel and even innovative approaches that are not typical for the standard type of project (e.g. an RCT that conforms to standard design features) reviewed by these bodies. Overall healthcare management & evaluation studies experience the least issues, indicating that in some instances there is evidence of

a delineation of risk levels occurring during the regulatory & governance review process.

Figure 3.4.3 *Number of days to prepare, submit and obtain approvals: Categorised by clinical purpose of project*

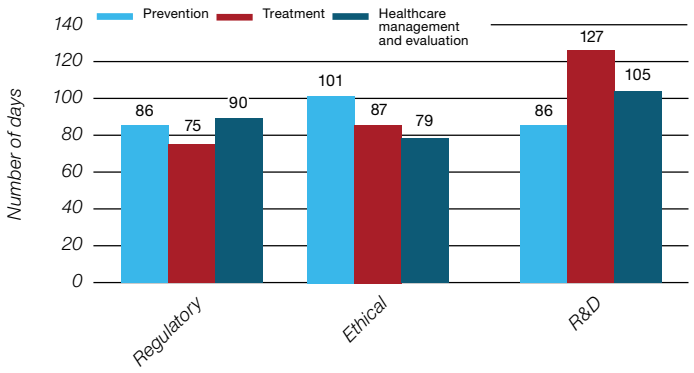


Figure 3.4.4 *Number of days to prepare, submit and obtain approvals: Categorised by projects about acute compared with chronic diseases*

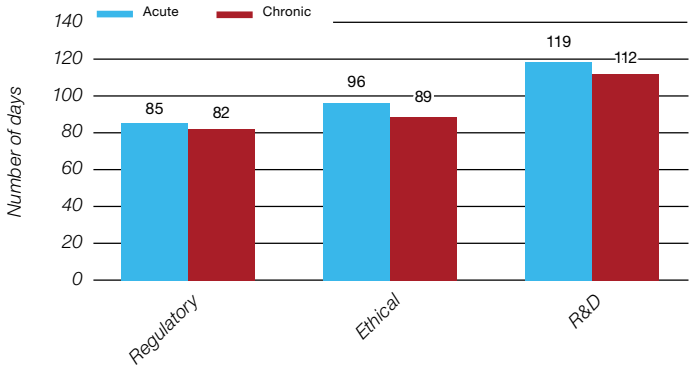
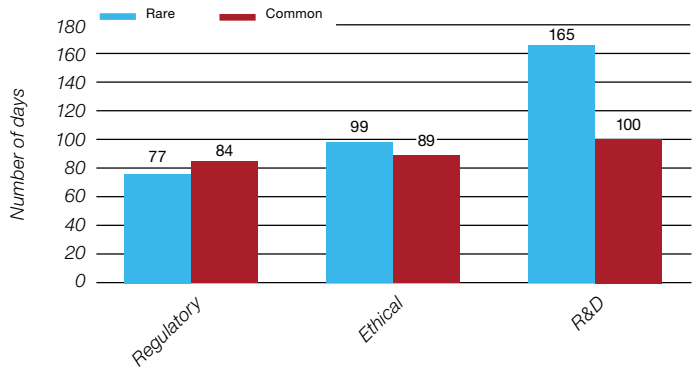


Figure 3.4.5 *Number of days to prepare, submit and obtain approvals: Categorised by projects about rare compared with common conditions*



The findings from this study highlight that additional challenges are experienced when research does not conform to a standard RCT model, as it can be more difficult to fit research that exhibits non-typical features with the standard paperwork and requirements of the approval system. Particular types of research which are valuable for supporting *UK* healthcare, such as essential medicines, preventions research, and healthcare & service evaluation are less likely to conform to the features of the RCT model.

Research into rare conditions, acute diseases and prevention trials also often face greater challenges for patient recruitment, meaning that it is more likely that non-typical approaches, such as non-standard identification and consent processes, will be incorporated in the research design to counterbalance these issues. The data indicates that research that focuses on rare diseases and acute conditions takes longer to obtain approval and are less likely to receive regulatory and ethical approval from the first submission. This suggests that researchers need to engage in greater effort to justify the need for a-typical features, and there is a greater likelihood that an application will be rejected.

Overall, many researchers reported that they felt discouraged from including innovative features that were non-typical to review bodies (e.g. incorporating novel recruitment methods). They felt that this would potentially increase the overall time taken to obtain approvals, as they would need to engage in additional discussion to justify their approach, and it was more likely that the application would require re-submission.

…"Trying to do prevention studies is pushing the boundaries and there are different issues. So what we wanted to do was a huge study, essentially randomising a million women to the majority. What we wanted is to streamline the consent procedure because it would be impossible to spend 20 minutes getting full consent from each woman when you're talking about a million women. We feel that this would be some sort of population consent and that various groups would say, yes, this is ethical, and then it would be an opt out. So we would be advertising at screenings that this is what's going to happen. If you don't want that and you still want to be screened, you can request to have the usual form. If not, you're going to be in the trial. Here's a phone line if you want to talk about it, but your GP or nurse won't be able to discuss it very much."

Recommendations

i. The process for obtaining R&D approval from NHS Research Governance offices should be streamlined and made transparent.
ii. Performance data on R&D approval times for different NHS Trusts should be publically available for comparison
iii. Standard documentation and information should be used across all NHS Trusts, with a guaranteed turn-around for decisions.
iv. Information on how to obtain approvals (including regulatory, ethics and R&D) should be provided in the form of a 'one-stop-shop', with clearly signposted pathways for different models of research. Applicants should demonstrate they have consulted this information.
v. Examples of completed documentation (such as the 'mock forms' for a medicines and biotechnology product which are provided by the MHRA) should be provided by approval bodies for different models of research.
vi. The regulatory & governance system needs to reflect the particular ***risks*** and endemic features of different models of research. Training for committee members should include greater detail about how to assess the risks of different models of research.
vii. The system of 'flagged' ethics committees for medical devices should be further extended with dedicated ethics committees being set up for other different models of research.
viii. The regulatory & governance system should actively encourage the inclusion of innovative forms of research. There should be different routes provided through forms, and greater flexibility to include novel approaches.
ix. Members of approval bodies should receive training in how to assess novel approaches for research design to ensure that assessment of non-standard research features accurately assesses the risk.

4. Knowledge & Expertise

This section considers the knowledge and expertise that are required to conduct clinical research, and some of the challenges in accessing knowledge and developing appropriate levels of expertise The findings highlight that projects led by different types of research organisation experience varying levels of difficulty accessing knowledge and developing appropriate levels of expertise to support successful project management.

4.1 The importance of practical nuanced knowledge

Survey data depict that retaining a project team is one of the most important aspects that influenced whether a project successfully recruited the required patient population and finished on-time (see section 2.4). This suggests that individual team members' expertise is extremely important for successful project management, which relies upon very practical, nuanced or 'local' knowledge that can only be obtained through experience and the development of relationships with individuals from many organisations. Analysis of data across both phases highlighted that it is paramount for a research group to bring together individuals with a particular skill set and range of expertise for a project to be completed successfully and on-time.

The importance of *local* knowledge and expertise is therefore emphasised as critical for successful management of clinical projects in the UK. Sufficient knowledge cannot be obtained purely from written sources, such as that provided by websites and formal, written guidelines etc. Instead expertise must be developed based on more practical insight. Often clinical nurses are essential conduits of local knowledge. Thus, project management requires the development of local knowledge cultivated through on-going relationships with stakeholders across numerous organisations and clinical sites who themselves have had experience of managing different types of research. This research found that when project teams are disrupted, often much of this local or nuanced knowledge is lost which can adversely affect project outcomes.

…"Anyone can read a book on how to randomise. If you look at the GCP guidelines you have to follow those rules. Making something work is not through blindly following a set of rules. It's actually understanding what are the clinical aspects of the design of a trial that would increase its likelihood of succeeding and of getting a clear answer. 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..."

For successful project management, research organisations rely upon team members developing experience and an appreciation of the nuances of how particular clinical sites are actually organised and run on a day-to-day basis. This expertise is often lost if the project team is disrupted across the course of a project.

…"You can try to put the knowledge about sites in a library, but sometimes it's current experience, so you do reach out to the people that are in the field and you say, 'what happened that time?' or you might speak to the project manager from another study who happens to be working with that particular centre, saying, 'did you have some of the same challenges?' We often do that, not so much working with the centres, but for example, 'there was a lull in patient recruiting here. You did some interesting stuff to try to recruit more patients to the study. Perhaps your experience recruiting patients to a breast cancer study is something I could use in recruiting patients to a lung cancer study,' so there's a lot of shared knowledge. What we have as an organisation is know-how, but not necessarily intellectual property. We have experienced knowledge. We have clinical expertise, and we have know-how because it has been practiced. It's just from constantly doing it. And none of that is easy to bottle and put a patent on."

Much local knowledge associated with project management is therefore held by individuals rather than organisations as a whole. Research organisations may attempt to collect and document this information, but due to the tacit nature of this knowledge, this is often not achievable in practice.

4.2 Sources of knowledge

There are obviously many different sources from which researchers can access support and information to help develop their own expertise and skill set to assist with project management. However, the findings highlight that challenges can arise not because of a lack of information,

but because the right information is not easily accessible or not used. In particular, often researchers find that there are too many sources of information and it is difficult to ascertain what constitutes the most up-to-date and accurate advice. Some websites and guidelines are also quite dense and it then can also be difficult to locate the information that is required. In addition, many sources assume a certain level of expertise, and provide information which a novice finds challenging to make sense of as the source assumes an understanding of certain acronyms or specialised terms.

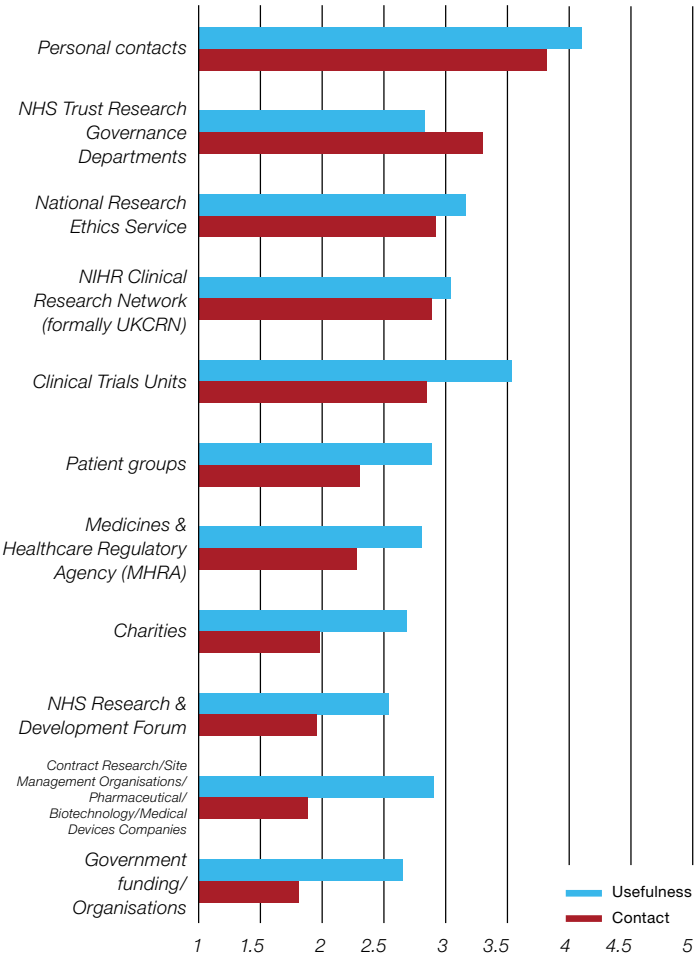
The survey asked individuals about what sources of information and advice they currently use, and perceptions of their usefulness (Figure 4.2.1). Unsurprisingly, personal contacts are the most utilised source of information and advice and are also considered to be highly useful. This again reflects and reinforces the local and highly nuanced nature of the knowledge and expertise that is necessary for project management. Much of the expertise and skills required can only developed through experience, which is usefully supplemented in some cases by documentary sources.

It is notable that although respondents have a high level of contact with NHS Trust Research Governance departments, this source is not viewed as highly useful. This suggests that the advice that is provided may not necessarily be corresponding to the type of knowledge and expertise that researchers actually require to support project management. The National Research Ethics Service (NRES) and Medicines and Healthcare Regulatory Agency (MHRA) however, are viewed as more useful despite there being less actual contact with these bodies.

The findings highlight that contact with patient groups and charities is relatively low. This is surprising as the qualitative findings from the first phase of this study indicated that these groups are considered to be extremely helpful, particularly with highlighting practical issues associated with project design. However, where these sources are accessed, they are considered to be particularly useful.

Our data demonstrated that proportionally less contact was made with professional and trade organisations, this reflects the specialised nature of these sources of advice and information which will only be applicable and relevant for certain groups within the clinical research field. Indeed, where accessed, these avenues of support were rated as highly useful.

Figure 4.2.1 *Groups and sources of information accessed to develop expertise and obtain advice and perceptions of usefulness*



Usefulness (1= not at all useful 5= Extremely useful)
Contact (1= no contact 5 = A great deal of contact)

The analyses of the data collected during the first phase of this research, underline that the development of project management expertise can be usefully supported through engaging with charities and patient groups. These organisations provide sources of information that are very specific to the day-to-day reality of a condition. Through better engagement with the needs of patients, practical ideas of how to organise the patient recruitment stage of a project can be incorporated into the design.

…"There was one study where they were asking elderly people to go into hospital for this trial. The time they were making them come in was mid afternoon, and that meant they were leaving these appointments just as all the kids were coming out of school, and they were having to then travel on the bus. You were getting this lack of participation; people weren't staying in the trial. Those service users were saying, if you just changed the method for how you were doing this trial, changed the times when you do this, you can then influence your participation."

The findings suggest that although support from patient groups and charities is viewed as highly useful, actual contact with these types of groups is actually relatively low. Research groups that do incorporate this support, such as through patient representation on advisory boards, report that this provides then with access to the patient perspective, and that research can be better tailored to be more practically achievable.

…"Historically, there has been this sort of view that clinicians will say, 'I see patients every day; I know what problems they've got. I understand what it's all about.' but it's very different from what people are saying in that relationship, even though things are changing and people are more questioning of treatments and things, from when they're sitting alongside an equal and talking about these issues, discussing them. So it's bringing in those different dimensions that they can think about things differently, and it isn't just always driven by what researchers think people want. It's because there are things that need to be done to help people in different ways. If the research is focusing the wrong way or if it's practically not addressing things in a useful way, then the research itself will not have useful findings and not be useful in practice."

4.3 Project team expertise and skills

The findings (section 2.4) indicate that retaining a project team is critical for successful project management. As much project management expertise is gained through personal experience, much of this knowledge is often lost if a team member leaves. Conversely, knowledge can be gained and shared across organisations through the employment of a new member to the research team.

…"We don't hire anybody that has anything less than three years in clinical research, so we hire very experienced staff rather than as some of the bigger CRO's do who will hire people and put them through a very rigorous training program…They bring their know-how to the table, and we try to have a very open communications policy that we share the collective knowledge and the collective experience so that we can pass that along for the benefit of our sponsors, and that's how it's said in the perfect world."

Individuals bring with them their own experience of sites. However, this can, on occasion act as a disincentive for organisations to develop or provide training for non-experienced individuals. It also encourages a turn-over of more experienced staff as there are often incentives to transfer to other organisations.

…"I went straight from PhD into it and then they trained you up really well, whereas a lot of companies, you have to have the experience. And so it's how to get the experience when you haven't done it before?"

There was particular concern that there was a skills shortage of clinical research associates and project managers. A recent report published by the Association of the British Pharmaceutical Industry (ABPI) stresses that the skills supply for the pharmaceutical industry is at "a tipping point", just at a time when pressures to be increasingly innovative are mounting (ABPI, 2008). In parallel, in universities, many research staff are employed on contracts for the duration of a specific project. This can inevitably lead to retention problems as retaining staff is dependent on receiving new funding at the right time.

…"There is a shortage of people with the right expertise. It is very tough; there's no question about it. You're not only trying to find the right expertise in a particular country, so specifically the UK, you're trying to find the right personality to fit within your company, too, It is very competitive out there. There is a shortage of talent, experienced talent, and then when you take it with us, we not only want experienced talent in the area of clinical research, full stop, on top of it we want oncology expertise. We keep narrowing the universe of candidates we can select from, and we'd love there to be a larger universe of candidates to select from."

A further concern about the skills gap related to recruiting and retaining research nurses. It was felt that clinical research was not perceived as a typical career direction for a nurse and did not offer the same opportunities as a more traditional nursing career. It was believed that the work of a research nurse was not fully understood by some individuals in the nursing profession, and that there was little incentivisation to work in research as again, the work was typically available only on fixed-term project contracts rather than permanent employment. This is an issue that the UKCRN has recently considered.

…"I don't think there is any formal career structure [for research nurses]… I think the problem, too, is that often they're on short-term contracts. They're on a project and the project goes. That, in a sense, is also a problem in trials units unless you've got core support. It's quite challenging. And yet they're the main point of contact with the patient… Absolutely, and at least some of that is what the UKCRN will do. The UKCRN is giving people a longer term contract. But I think the natural

progression, in some ways, is towards being a manager of several nurses. It's not a formal structure I don't think, and that's what we were hoping."

There are many different roles within the clinical research sector, and individuals who work on different aspects of research projects often come from many different occupational and professional backgrounds. However, this complexity in terms of backgrounds and lack of obvious career routes does present challenges in terms of encouraging individuals to work in this field. The research findings highlight that there is a need for clinical research as a career option to be much more widely highlighted to individuals at an earlier stage.

…"Our research staff, people have been at big pharma in the past. Some people have been nurses, study site coordinators. Some people have worked in clinical research their whole careers. Some people have been pharmacists, nutritionists, doctors. Or they come out of biotechs and if they've worked on the preclinical side or the lab side and they've worked on the clinical side. We are a service organisation, clinical research, CRO, vs. someone who's actually developing the compound or at least developing the intellectual property. We're on the service side of things, so all kinds of backgrounds."

…"Recruiting experienced researchers, the issue here is that there is a shortage generally of good people in this area. These people are very much in demand… So what do you do? You try to encourage people to get into this line of work from the beginning. Maybe we should be down at school level encouraging people to get into this line of work. Maybe we should start talking to experienced people like nurses. 'Have you thought about a slight career change over to clinical research?' Maybe you do go all the way to school level. And do enough people know about clinical research?"

It was felt that clearer career trajectories into the clinical research sector could contribute to addressing the skills gaps within this sector. We propose that this is an area that should receive greater attention from policy makers. In particular, a greater appreciation of what incentivises individuals to become involved with clinical research will assist with policy development in this area.

…"So if we don't have enough people going into clinical research, how do you encourage that? Does that mean more science grants, chemistry, biology, whatever, and maybe encouraging more people to pursue a career in this than in accounting, law, when the careers pay as much as when people enter those professions? Maybe people don't appreciate that."

4.4 Expertise required by different models of research

Different models of research naturally face different types of skill gaps. Whilst information and expertise from personal contacts is highly utilised and valued by all groups working in the sector, the support from trade, industry and professional organisations is particularly valued for providing specialist support that is tailored to particular types of research (see Figure 4.2.1).

The survey data (see Figure 3.3.3) also indicates that non-commercial and commercial groups other than pharma experience difficulty with obtaining information, completing paperwork and fitting the features of their research to the requirements for regulatory and R&D approvals.

Research groups which lack experience of the UK regulatory & governance system can also experience particular difficulties completing the approval process in a timely fashion. To be successful, these groups need to obtain an understanding of the nuances of the process and an appreciation of how to present the features of their research project to demonstrate that they meet the appropriate standard.

As part of the follow-up from the 2006 Department of Health 'Best Research for Best Health' report (Department of Health, 2006), the NIHR have implemented a framework for Research Support Services. The remit of this is enacted through the reconfiguration of NHS Trust R&D Departments. The overall aim is to improve the quality, speed and efficiency of research and research processes in the NHS. In the summer of 2009, Research Design Services were set up across different regions within England. Whilst this type of support should be able to counter-act some of the challenges raised here the findings also highlight that to be most effective, *this support needs to be tailored to meet the specific needs of different types of research.* Specifically, particular support is required to assist research projects that do not conform to an RCT model, and which, in many cases, are often developing highly innovative health research interventions.

Our analysis suggests that large pharmaceutical firms have most access to expertise and the necessary flexibility of labour to support projects. With greater numbers of individuals involved in clinical research generally, a more

robust network through which local knowledge can be shared between groups working on different projects from within the same organisation develops. In addition, individuals can be more easily transferred between different projects as time and skills pressure dictate, enabling greater flexibility and availability of management expertise.

Smaller organisations are more reliant on individuals who have specific expertise within smaller teams. There is less flexibility around project management to transfer individuals between projects, when there are particular resource and expertise strains or pressure points. In addition, these organisations are more vulnerable if team members leave, as it is very difficult to preserve the local, knowledge that has been acquired by these individuals.

Public-funded projects typically only enable non-commercial organisations to employ research staff on fixed-term contracts. These types of research organisations are therefore particularly vulnerable once a project draws to a close. Even if the team acquire further funding, which in principal would allow them to retain staff, there are often difficulties in agreeing contracts between funders and the research organisation. The time this can take often leads to research staff being forced to join a project elsewhere and again the valuable, local knowledge may be lost.

Medical devices research organisations can experience difficulty because of the very different licensing route for this type of healthcare product. The findings from the first phase of the research indicate that even when contract organisations are selected for the purpose of supplementing an expertise gap, some of these contract organisations do not have expertise with devices research and do not understand that this falls within a different regulatory process to medicines research.

…"If device companies don't get advice, they may do studies that aren't necessary, and when they do, quite often they don't even know that research ethics committee approval is required. One of the things we get a lot of is a manufacturer has chosen a contract research organisation who is very pharma oriented, and that pharma CRO has unfortunately chosen to try and license the product as a drug, but it's a device, and they've done a clinical trial application on the whole thing."

…"A year in the life of a small device company with maybe only a couple of products and not having a CE Mark is huge. That could affect whether they can stay in business. They don't have these protections in place that drug companies have when it comes off patent in so many years. They've got the market, the drug companies, for a lot of years. They can make a lot of money and rake it back. It's not the same with the device industry. After that, the copies, it's very easy to work your way around a patent for a device. The lifetime of a product is very, very short, affecting the ability to rake back. What you would do is watch somebody else develop a device, slightly modify it, and ride on the back of that. It costs you less. You don't have to do the studies; they can. They get all the costs and then you put it on the market as well. You can't do that in the drug industry. You haven't got that first mover advantage. If anything it's a disincentive. The first movers spend a lot of money, so if somebody else is right on the back of that, not spending that money..."

Data indicates that there may have been a settling-in period for the regulatory approval processes following the major changes that were introduced in 2004, as researchers who had previously been exempt from obtaining approval, had to learn, again typically largely through experience, how to submit applications that were in an acceptable style and format. Many of the recent initiatives aimed at improving the process over the last 2 years are viewed positively. However challenges for managing projects still exist specifically in terms of deciding what constitutes the most up-to-date expertise and knowledge. Confusion thus arises in terms of identifying exactly what changes have occurred and which of these are relevant to a project. Researchers also sometimes lack an understanding of how they might actually benefit from new initiatives. Research groups which conduct few projects may not even realise the extent of changes to the system, or which new initiatives are available to support projects.

Smaller research organisations, such as start-up and biotech companies also experience particular issues with managing the clinical research phase of projects. These companies have typically been set up by laboratory scientists and often these individuals lack the project management expertise, legal/ regulatory knowledge and the business skills which are required for the clinical research stage of product development, and are not able to employ staff with the necessary diverse range of skills and expertise to support project management.

…"They're very good in the laboratory side of things, and then it's transferring that and understanding the challenges, the needs, the timelines, how you make

a clinical trial a success, which is essentially why we established our CRO business in the first place, to pass along this expertise because it is very different than working in the lab. Some of it is down to how quickly you can recruit patients; some of it is about economically managing the trial because it could be that you need to open in a variety of centres in order to recruit the patients within the timelines you want. You have to understand the financial dynamics of that. It could be we can extend the timelines and work in fewer centres, and if you extend the timelines you have time to recruit more patients. So it's just understanding some of those dynamics, which is the expertise that we bring to the table."

The geographical location of a research organisation can also influence access to the necessary skills required. If a research organisation is not based in an area where there is a strong clinical research base, there is a much smaller pool of individuals from within the locality from which to select individuals.

…"It's not just financial; it's also people. If you are in an area like we are here, where there may be a certain skill shortage, then that can be business critical…So we lacked a key member and just couldn't convince anybody to come up here. I think the issue is what we offer at the time would be, essentially, a climate to relocate up here and move your family and you can't relocate, or you would relocate if you were convinced that what you were relocating to was a long-term future, and you are not sure about the long-term future. There is no very long-term future anywhere at the moment, but it's particularly acute in biotech. It's fine if there aren't many companies around, but if there are that many companies around, then people will relocate. I haven't relocated up here; I fly up every week."

In addition, not being located in an area where there is high level of clinical research is also perceived to influence the attractiveness of an organisation to receive financial backing to support development of innovative, but inherently risky products. Often these constitute a major part of the portfolio of a biotech start-up company.

…"It's a geographical thing. There are lots of small biotechs, small pharmaceutical companies like ourselves and some are smaller. We have or had quite a good portfolio, but we have essentially run out of money. The other thing is, if you are in San Diego, for instance, your product would be valued more and be more inclined to throw money in, so, definitely, UK-Europe bioscience is less well funded than it is in the US."

The first phase findings indicated that for smaller commercial organisations, contract services organisations are an extremely valuable option in providing the expertise required for this model of innovative but high-risk research. However, it is important that care is taken when selecting which CRO to work with.

…"We found that one of the problems some of the smaller biotechs had was they were working with very big CROs, and found they were bottom of the list with everything."

It was suggested that for smaller medical devices and biotech companies, selecting a niche organisation to conduct project management needed to be thought through carefully. Suggested features to be considered included using smaller CROs or clinical trials units where the research organisation would be one of relatively fewer clients, or selecting a CRO with specific expertise in a particular intervention, or experience in a particular disease area. This enables the smaller research organisation to access very specific expertise.

…"So there's been a huge shift towards contract research. A lot of the small biotechs are experts at the lab work, particularly in areas like oncology. It isn't really worth their while expanding their companies to include clinical research."

In addition, it was also highlighted that specialisation is one approach which could actually assist contract research organisations in developing particular niches in the market. This strategic approach could help the CRO to maintain and develop a particular skills set that would subsequently allow them to market themselves to all sizes of commercial research organisations.

…"To maintain the kind of expertise and the payroll to conduct a clinical trial is huge. Doing a lung cancer study today and tomorrow a leukemia study, there's a mismatch of expertise there. If pharma have to maintain experts in all of those areas, they aren't working to 100% utilisation, and it's a very expensive thing to do. Hence the whole reason the whole CRO industry was founded. I only need 30% of that person's time to go out to that particular site, so depending on what drug happens to come through, I maintain a group of people in-house that have experience that can conduct

that clinical trial. That's a very expensive thing to do because you're talking about very talented, very well-educated, very experienced people in order to do this for you. So for pharma, they don't have to maintain that payroll, as I'm going to go out and find it in a group of people that are already maintaining it."

Recommendations

i. A dedicated portal for UK Clinical Research should be set up to assist less experienced clinical researchers in acquiring relevant knowledge and expertise. The portal should ideally hold and up-date information about approval requirements, project management support, training provision, contract research services, professional and trade bodies, and charities and patient organisations.

ii. The support provided by recently implemented NIHR Research Design Services should be extended to actively support innovative and atypical research models that do not conform to the RCT approach.

iii. A review of current training and accredited provision should be undertaken.

iv. A UK-wide strategy should be developed that identifies a career trajectory for clinical research. Career profiles of the range of roles engaged in clinical research should be developed.

v. Greater resources should be granted to patient and charity groups to enable these groups to increase the level of active support they can provide to research organisations.

vi. Research organisations should be incentivised to provide accredited training provision.

vii. More flexible forms of employment (for example secondments, positions jointly funded by commercial and non-commercial organisations, or multi-host contracts) should be implemented to promote retention and ease skills shortages experienced by small organisations and groups reliant on fixed-term contracts.

viii. Faster contracting should be a priority to help secure continuity across university and other publicly funded research projects. Bridge funding should be available for research staff experiencing temporary gaps in funding.

5. Networks & Strategy

Clinical research depends on successful working relationships between the focal research organisation and other key stakeholders, including commercial firms, non-commercial and academic scientists, clinicians, the NHS, regulators, government strategists and policy makers, charities, patient groups, professional/trade associations, and funding bodies. Networks – defined as "*inter-organisational interactions of exchange, concerted action, and joint production*" (Alter & Hage, 1993, p.46) – are, therefore, crucial. They affect the ability to attract resources, acquisition of relevant expertise and staff, selection of partners, selection of sites and engagement of clinical and patient groups. Clinical research can be characterised, then, as a 'networked innovation' process - a distinct form of innovation which demands engagement, collaboration and coordinated work across partner organisations (Swan et al, 2007; Swan & Scarbrough, 2005).

Formal network structures include contractual arrangements as well as mandated networks, such as NIHR Clinical Research Networks. However informal networks are equally critical since knowledge shared though informal networks (e.g. word of mouth reputation) often precede the development of more formal, contractual relationships. Different partner organisations involved will also have different strategic/market imperatives, attitudes and expectations. It is important to understand these in order to encourage participation in clinical research and effective working relationships.

5.1 Developing relationships with NHS Trusts & sites

The NHS acts as a major gatekeeper to patient populations and is, therefore, one of the UK's key assets in securing the future for clinical research. However, as seen, contract negotiation with NHS Trusts for clinical research remains problematic. The Department of Health has initiated measures to improve the situation, but the majority of respondents in our study believed that the changes need to be much faster and more dramatic if the UK is to improve its competitive position, particularly in commercial research.

Particular problems centre on:
agreeing resource use; negotiating remuneration levels; negotiating permissions to use clinical sites; and securing engagement of NHS staff, even where contracts have been agreed.

Despite the new Coordinated System for gaining NHS Permission (CSP), each Trust also follows its own unique procedures. This lack of consistency means that the time it will take to negotiate contracts cannot be predicted accurately in advance. This can create large costs in terms of delays in start dates and overruns for research programmes.

…"The bureaucracy in the UK is becoming a serious limitation to running trials here. There is no consistency across hospitals or trusts and the time taken to set up trials is far greater than other EU countries. The vagaries of the R&D committees are a major negative factor."

Researchers recognised that Trusts have a legal responsibility to protect their resources and patients. However, the disparate procedures in place to gain NHS permissions and access to sites were seen as a major impediment to managing trials (see Section 7, Figure 7.1.1). It was also evident that some Trusts were 'known' (informally) to have streamlined the process much more effectively than others, for example, using standardised forms and reducing Trust-specific information requested. Therefore, it was felt that it should not be difficult in legal-terms for other Trusts to follow suit.

…"The research governance framework basically says what you should be doing. It says you need to do research properly. It doesn't say research is a dreadful risky thing and it should be avoided at all costs. I think there are two issues. Is the trust prepared to accept that research is part of normal clinical practice, which it should be? As a trust we should be doing research. It should be part of normal clinical practice, but with some trusts it is some kind of 'out there special thing' that only us doing research can understand. I do think there are people trying to justify their own position by making people do extra bits of paperwork and adding, 'in our trust you have to fill in 65 extra forms.' We just have the standard forms, so if it's a nationally accepted adopted form, we adopt it as a trust."

The findings presented in Section 4 highlighted that localised, tacit knowledge is required to develop an insight about how, practically, to nurture collaborations. The research culture also differs significantly across Trusts and relationships can be difficult to establish where a research

organisation is not familiar with the local culture. For this reason, research organisations will usually choose to work with Trusts that they have worked with reasonably successfully before. By using the same site, researchers already have experience of the local governance procedures and/or have learned how to negotiate contracts. In addition, researchers have an insight about how to work with individuals in Trust departments and who will actually deliver. This can make it difficult for Trusts, and NHS staff, that are not already 'in the loop' to get started as research sites.

Additional challenges emerge from competition between different research groups for use of NHS resources. In particular, as certain Trusts develop their reputation as study sites, this encourages more research to take place at these locations, and the use of resources (including patients) at these sites can become saturated. Consequently, the amount of time and effort that Trusts can put into relationships with each individual research organisation and into recruiting patients becomes strained. However, researcher organisations are reluctant to select sites (such as regional hospitals) with little previous experience. Therefore, it can be difficult for Trusts (both acute and primary care) that do not have a reputation for previous research to become part of the network of relationships that a research organisation works with, even where they a motivation to do so and have large numbers of patients not already involved in studies.

…"The emphasis for UK policy should be to work with the commercial sector (sponsor companies & CROs) to improve the quality of clinical research undertaken across the board, not just to bolster those already doing well and creating centres of excellence - this will simply create an unacceptable level of competition for resources and patients at these sites and overwhelm them, whilst many regional hospitals and GP centres remain participating only in a few trials and not conducting them to an adequate standard."

Those working in pharmaceutical firms also reported experiencing greater difficulty in developing relationships with NHS Trusts than those in non-commercial organisations. In part, this is because more complex financial arrangements need to be agreed. Commercial organisations also felt that some Trust staff were more sceptical about the merits of commercial research and that this made it difficult to move beyond a service-level relationship toward a genuinely collaborative partnership.

These challenges spill over to smaller commercial organisations. In particular, these organisations are typically under acute short-term financial pressures – pressures that are not always recognised by Trusts more used to dealing with large pharmaceutical firms. Even short delays in conducting studies can threaten the survival of these kinds of organisation. The high cost of conducting research projects within the UK means that this group is already strongly incentivised to base clinical sites at non-UK locations. A better awareness of the unique constraints faced by smaller commercial firms might help the development of more successful working relationships between Trusts and this type of industry.

…"UK sites still seem to think that Pharma and Biotech companies have money to burn and that the UK's reputation for high quality work will mean that Sponsors will automatically work in the UK. Sites, administrators and regulators need to accept that work in the developing world is now of high quality and is offered at significantly lower costs. Without this realisation clinical research in the UK will continue to decline. The focus needs to be put on improving patient recruitment and giving value for money. In other words the UK needs to be more commercially aware and ready to compete against other nations."

Non-commercial organisations, in contrast, find it somewhat easier to develop working relationships with NHS Trusts and staff. Typically these will already have established relationships with a small number of local NHS Trusts, as this group includes both NHS research groups that stem from particular Trusts, and also university-based research units which are often formally affiliated with University-Hospital NHS Trusts through mutual medical schools. By being co-located, and in many cases sharing governance structures, it can be easier for these organisations to develop the local insight that is necessary to nurture relationships with individuals from Trust governance and contract departments, and staff from clinical departments. This suggests that there may be an advantage in the UK context in promoting more sustainable partnerships between commercial firms and non commercial research organisations (such as university based clinical trials units), which can help to mediate relationships with NHS Trusts and staff.

Patient recruitment is, of course, a key activity in managing clinical research. There are two main issues here. The first is that targets, for various reasons that are hard to predict, are not met. The second is that targets are over-inflated and unrealistic. In most cases those managing trials would

prefer accurate assessments of patient numbers, even if these were low. Large pharmaceutical firms are typically experienced in carrying out feasibility assessments to ensure targets are realistic. However, feasibility assessments are not always conducted in a systematic manner in other kinds of organisation, suggesting a need for greater training in this regard.

In general, different organisations regard similar factors (such as having an experienced research team) as important in influencing patient recruitment. However, compared to commercial organisations, non-commercial groups rated having an interesting research topic, and developing relationships with the Trust R&D departments as particularly helpful in encouraging sites to recruit successfully. For some kinds of research forming ongoing relationships with networks of GPs was also an effective strategy for encouraging recruitment. Non-commercial research units often have to rely on goodwill rather than financial remuneration to incentivise the involvement of key stakeholders. In particular, academic interest can be used strategically to motivate collaboration between themselves and clinical staff.

…"Yeah, it tends to be because we don't pay the centres, or we pay them the minimum amount to do the work, whereas industry will pay them based on ... they may have got rates and paying commissions to do clinical trial work so they will get reimbursed for their time. Whereas we don't have the money to pay consultants or GP's or nurses, so it's goodwill. It's their academic interest."

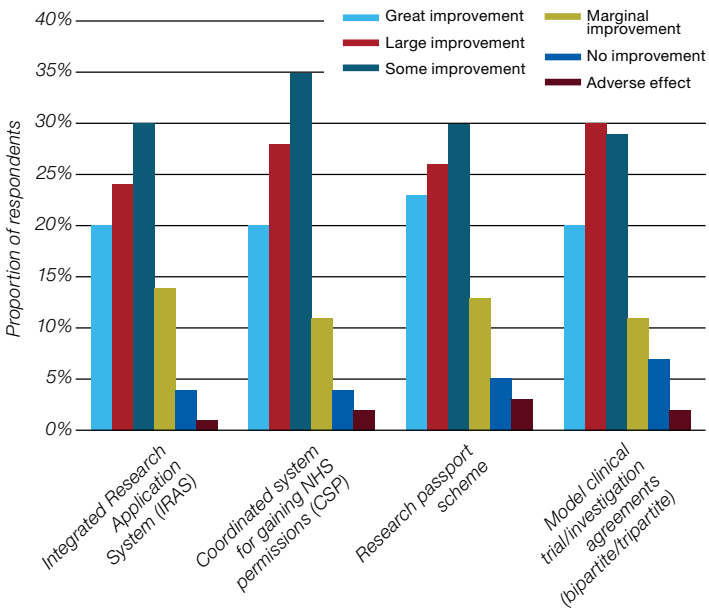
5.2 Policy initiatives aimed at improving collaboration and approvals

Recent NIHR policy initiatives have the potential to support network relationships, providing more structured arrangements to bring together different stakeholder groups. Many of these initiatives are in their relative infancy and their success is yet to be seen. However, it will, no doubt, depend on the perceptions of different groups regarding their value, as these influence whether or not they will engage. For example, some interviewees working in larger commercial firms, whilst positive about the ambitions of NIHR Clinical Research Network scheme, did not see it as offering them any significant advantage over their own site and patient recruitment processes. Indeed some saw it as adding an extra layer of bureaucracy that could further slow contract negotiation.

That said, policy initiatives aimed at streamlining the set-up stage of projects have been positively embraced. In particular, the Integrated Research Application System (IRAS) and Coordinated System for gaining NHS Permissions (CSP) are perceived as having the potential to provide significant improvements to the process (Figure 5.1.1). However a number of interviewees, whilst welcoming the idea of a research passport that would be valid across all Trusts, expressed some scepticism as to its practicability, noting that most Trusts would still require additional local review.

The development of bipartite/tripartite Model Clinical Trial/ Investigation (mCTA/ mCIA) Agreements between the NHS Trusts, Research Organisations and Contract Research Organisations, aimed at smoothing contract negotiations, has also been warmly welcomed (Figure 5.2.1). However, it was stressed that only time would prove the effectiveness of this initiative and, in particular, whether all Trusts would now follow similar practices. Some felt that the time taken to launch the various policy initiatives had been far too long. Consequently, it is important that data about the actual effect of these new initiatives is captured.

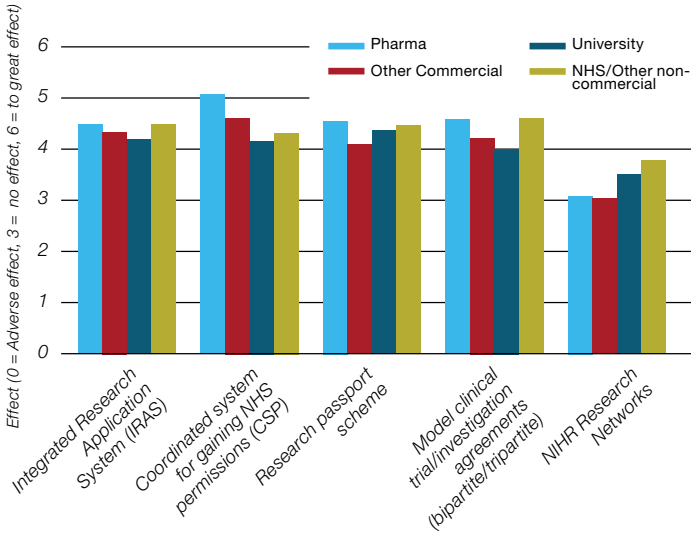
Figure 5.2.1 *Current attitudes towards recent policy initiatives affecting the governance approval process*



Attitudes towards these recent initiatives were similarly positive across different lead organisations (Figure 5.2.2). It is worth noting, however, that attitudes do not reflect actual practice. For example, early figures indicate that only a small proportion (around 10-20%) of pharmaceutical industry regulatory applications are actually using the IRAS system, even though they see it as very positive. This may reflect that the structures found typically in pharmaceutical

firms are inhibiting use of this initiative, as historically these organisations have two separate, non-overlapping departments for the approvals process - one focused solely on regulatory submission and the other focused on ethical review and governance permissions. This highlights that it is important for strategists and policy makers to be informed by empirical data describing actual behaviour, as attitudinal data may not in practice reflect the real experiences of researchers.

Figure 5.2.2. *Current attitudes towards the effect of recent policy initiatives aimed at supporting the management of clinical research: Categorised by respondents' organisation*

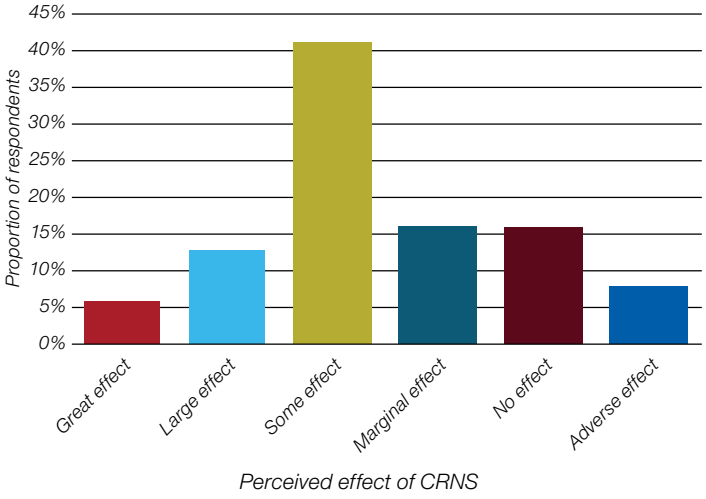


NIHR Clinical Research Networks (CRNs) aim to bring together research organisations with healthcare professionals and their patients from all parts of the country. As a result, the CRNs have the potential to remove barriers to setting-up research within the NHS through promoting relationships between research organisations and clinical sites. The National Cancer Research Network established in 2001 formed the model for the other disease clinical research networks that were created more recently, and is considered to be very effective at supporting clinical research in this disease area. However, reaction to Clinical Research Networks more broadly was more temperate, with respondents perceiving a moderate improvement resulting from this. In particular, whilst the networks work well for the clinical discipline of cancer, it was pointed out that the specific features of other diseases, and the historical underpinning of other clinical specialities, present challenges for adoption of this model across all clinical disciplines. Therefore, it is important to ascertain the features that make the cancer CRN successful, and what is distinctive, in order to inform for the development of other networks.

Whilst welcoming the aspiration of the CRNs to assist with patient recruitment, respondents had mixed feelings about whether, in practice, these networks could adequately accommodate the pace at which industry worked (Figure 5.2.3).

…"We've used the networks to an extent, a couple of networks recently, but every time we've used them we've found we put more resource in than the value we get back. We notice a lot of money going in, but we're not seeing anything back, and I'm not wasting my resources until I've seen something. So it's a catch 22… It's frustrating because I think they need a culture shift. It's been difficult for them because they've had the whole infrastructure to set up, but if you work in pharma you need to just get on and do it. They're doing stuff really well and really nicely and they're quoting metrics that frustrate me because it's all about how much adoption there is, which are input metrics. But as long as you get the outputs that are expected that's absolutely fine by me. So it's that whole project plan and thinking of the end game and working back. Get everything set up quick. They need to be working on the people side of things, training and development, informed consent."

Figure 5.2.3 *Current attitudes towards the effect of the NIHR Clinical Research Networks on improving the ease of managing projects*



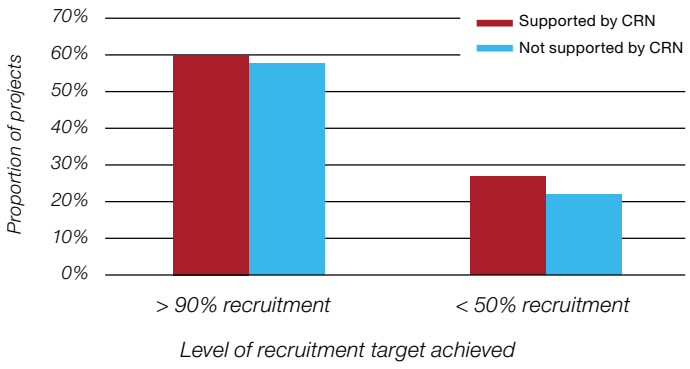
Overall, there was concern from researchers about the extent to which the NHS had actually bought into the aspiration to support clinical research via many of the initiatives developed by the Department of Health (DH). Concerns about the research culture of the NHS and whether *all* Trusts would in practice engage with DH rhetoric and policy in support of clinical research were repeatedly raised by respondents. This was considered

to be an issue that originated at the Board-level of some Trusts, where lack of support manifested in poor engagement of clinical departments and staff with research projects. Some research managers suggested that, in reality, engaging with clinical research was still a low priority for many clinicians.

…"NIHR network infrastructure is in place and I as a researcher welcome it, but it is hindered by clinician attitudes and insufficient drive for delivery."

37 of the projects in our survey sample had been supported by the NIHR CRN. These projects showed little difference in the levels of recruitment achieved compared with projects that had not been supported by a CRN in the same time period (Figure 5.2.4). However, this finding needs to be considered in conjunction with the fact that the success of the CRNs will depend, at least in part, on the implementation of initiatives, such as the Integrated Research Application Scheme (IRAS), the Research Passport Scheme and Coordinated System for gaining NHS Permissions (CSP). These had not been implemented at the time that these projects were being set up, and so the data provided is not necessarily indicative of the future integrated system of support that the networks will be founded upon.

Figure 5.2.4 *Patient recruitment achieved: Comparison of project supported or not by the NIHR Clinical Research Networks*



5.3 Relationships with UK intermediary groups

Clinical research organisations could engage with a variety of intermediary bodies - including professional & trade groups, patient groups, charities and regulators - to gain the knowledge required to successfully manage a project. Networks with such organisations provide a useful source of local knowledge and experience. In our study, contact with professional and trade groups were valued as a useful source of advice and information and also as a route to access other relevant stakeholder groups.

Patient groups and charities are, similarly, considered to be extremely useful in helping clinical researchers to identify potential practical issues associated with project design and protocols (see Figure 4.2.1). Patient groups, for example, can give practical advice on methods of obtaining informed consent or on the timing and location of trials to attract patients. Patients may also approach these groups when considering participation in a clinical research project. However, in practice, contact with these groups by clinical researchers is quite infrequent. This suggests a need to encourage closer working relationships between clinical research managers, patient groups and charities.

…"Charities are a gatekeeper, but they can't open the gate; that's the problem. They have lots of pools, but it's quite difficult for them to know quite where to point these people, either in terms of a named person or a website, very basic to more complicated."

The NIHR CRN actively encourages the involvement of patient representation within clinical research projects through the patient public involvement (PPI) infrastructure. This is providing a more structured arrangement to support partnerships between researchers and these patient groups. Engagement with charities is one approach to access patient representation.

…"One of the ways that charities can get involved with the clinical research network PPI [patient public involvement]infrastructure is to fund that person or work or whatever system they created because one network might have an actual PPI group and another might just decide to have a person. There are lots of different ways of doing it. I suppose networks will see a large part of their patient engagement as being the relevant charities."

Support from INVOLVE - the NIHR-funded national advisory group for promoting public involvement in the NHS - was perceived as a useful bridge for developing connections between the public and researchers within the research process, specifically for non-commercial research groups. However, it is also stressed that challenges exists with ensuring that collaboration goes deeper than just providing 'token public representation' on advisory boards. Only when research organisations seriously value the contribution that patients can bring to a study, can a proper working partnership be developed.

…"Inevitably some researchers have patient representation just to tick the right boxes, so it's difficult

to know how much people are doing it because they're being told, or because it's a good idea. But when people start to do it in a small way, maybe they don't involve people in the right way. But if they really are doing it just because the funder is telling them to, the researchers will go, "the public representative didn't contribute anyway at the meeting". Then the public representative says "I wasn't comfortable about contributing, the way it was set up didn't work, or the building wasn't even accessible". There's all sorts of barriers on both sides, because they haven't thought it through. "

5.4 Balancing Strategic Interests

Clinical research led by large pharmaceutical firms is naturally under the strongest direct commercial pressure to be streamlined and efficient - the aim is to minimise the time taken to get a product to market in order to maximise the time within patent. These demands influence the structure of the research, such that the typical aim is to produce straightforward, and uncomplicated, RCT project designs. This model of research is less likely to focus on diseases areas or topics where patient recruitment is problematic.

…"With drug trials it is all about speed. Every day that you slow down in getting it to market you lose, I think the latest figures are 2.1 million dollars per day is lost for every day you delay in getting it to market."

However, industry is under increasing pressure to demonstrate cost-effectiveness in the UK market. Drugs that are not considered cost effective will not be recommended for use by the NHS. If the UK is an important market, commercial organisations must, then, try to predict future demands from bodies such as the UK's National Institute for Health & Clinical Excellence (NICE) early in the development process. This is having an effect on the focus of research projects, with an increasing pressure to design studies in such a way as to demonstrate economic value for the NHS.

…"There seems to be a realisation in the UK that industry has to do trials to help NICE make a good decision. So, they're (policy makers) starting to look beyond just looking at doing studies that get past the MHRA for regulatory approval and to actually do studies to show that the treatment effect is worthwhile. That's probably good as it means they're starting to think about cost-effectiveness and the size of the treatment benefit...and that may improve trials."

…"It's a complete package, what we can look at is not just how to get your drug to market, but how the whole marketplace looks and what other things you may need to take into consideration, which helps you as you're designing your clinical trial, to make sure you've got that full picture. Because more and more, people like NICE and related bodies around the world want to know what they're getting for their money in getting this drug, and what else is it going to impact, so the healthcare economics part of it too. So we need data to say, yes, this may be a very expensive drug for rheumatoid arthritis; however, in terms of physio appointments, medical aids, occupational therapy, those bills would come down, so you can start to put the cost/benefit in place for that."

On the other hand, pharmaceutical firms also need to balance the UK's influence in how they develop and position a research project, with their global networks and market aspirations. The UK's National Health Service (NHS) has unique market features. There is also increasing recognition that over the next few years there will be increasing market pressures resulting from the 'pipeline problem', as Wall Street growth expectations suggest that the number of new chemical entities that are developed needs to be doubled to maintain profitability within the industry (Hooper, 2005).

…"I'm thinking now of a DTI document looking at the ratio between investment in research and new US patents. The pharmaceutical sector has a very poor return on investments, in terms of new discovery, and it has had for quite some time now. First of all, the market in which they sell their products is not a true market. There are various deals like the pharmaceutical pricing and regulation scheme, PPRS, in this country, but also other sorts of things as well. It doesn't act like a true market, so drugs don't find, if you like, their true place."

Unlike much of the non-commercial research conducted in the UK, for large pharmaceutical firms, the UK constitutes only one geographical location where clinical research sites are located. Therefore, if the UK's regulatory, governance and approvals framework is perceived to be too arduous and uncertain, this can act as a disincentive for commercial research to be conducted within the UK context.

…"Most people try to go through the FDA for advice and input because that's probably the biggest regulator. They do enter dialogue with the MHRA if it's specific. Obviously, if it's a UK-only study, it would

be the MHRA. A lot of companies are wanting to look at global markets, so they'll look at negotiations with the FDA instead, what it is the FDA are looking for in the program, to make sure that when they get to the end point where they've got the results and they've gotten to the FDA, the FDA are saying, 'that's nice, but it would have been better if…' And then they have to go away and do another two or three years work, so I like to do that discussion up front, right through to data services, producing the final package, so the whole range of services."

Academic research groups, in contrast, experience pressure from the need to demonstrate scientific excellence to ensure continuity in public research funding. Many non-commercial research groups are modelled in such a way as to fit in with government funding priorities, such as for essential medicines which are not the focus of commercial industry. In particular, for this type of research organisation, scientific reputation is crucial to secure continuous funding. It is paramount, then, that these groups develop quality working relationships with different funding bodies. However, they also face financial challenges related to changes in UK priorities and the strategy behind the UK funding of this type of research.

…"It's all but impossible to get research funding at full economic cost.... the NIHR funding stream are not allowing FEC increasingly. The HTA is the main one that does, but many of the other schemes - research design services, academic health centres for the future - a lot of these other things don't do FEC."

The predominantly public healthcare system in the UK means that developing relationships that span commercial and non-commercial organisation is crucial to the success of clinical research. Indeed, one of the biggest potential advantages of the UK in terms of attracting commercial investment is its National Health Service. However, our research suggests that often the development of productive working relationships between commercial and non-commercial organisations is left to chance. Existing networks tend not to cross commercial and non-commercial boundaries and there can be rather low tolerance of the very real pressures that different partners face.

Recommendations

i. Further support is required to strengthen relationships between research organisations and the NHS.
ii. NIHR initiatives to support the development of good relationships between the NHS and commercial research organisations are welcomed, and should be further reinforced and monitored as to their effects.
iii. Transparent information on NHS Trusts' clinical research governance processes should be easily available.
iv. Information on NHS Trusts' approval times and site-level recruitment and completion figures should be publically available.
v. There should be an evaluation of what makes effective clinical research networks, such as the Cancer CRN, to support the development of networks in other areas.
vi. Involvement with patient and charity groups should be promoted. There should be provision to cost charitable donations into publically funded research.
vii. All research organisations should be encouraged to work with NICE to ensure that research findings are tailored to the NHS context.
viii. A 'community of practice' for UK clinical research managers and research nurses should be fostered, in order to support the sharing of knowledge and expertise and build a strong identity and job market around UK clinical research.

6. Incentives & Drivers

The development of productive relationships between research organisations and other stakeholder groups is influenced by the different drivers that promote involvement in a project. Research organisations need insight into how different organisations, communities and individuals are incentivised, which may in practice require balancing dissimilar or even antagonistic actions. This section highlights the different drivers promoting organisations and groups to engage in clinical research, which require tailored support to be provided from UK strategists and policy makers.

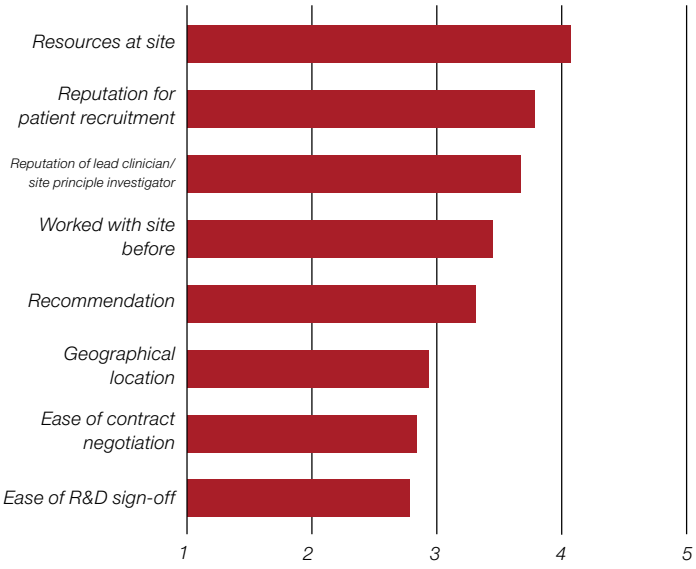
6.1 Enrolling NHS clinical sites and clinicians

Enrolling NHS sites necessitates skilful balancing of incentives at the organisational level when setting up contracts and obtaining permissions from R&D offices. Attention also needs to be given to individual incentives in order to enlist clinicians to become site investigators and to commit clinical departments to recruit patients. The time taken for these negotiations, and the cost, can be difficult to predict accurately in advance and the analysis of survey data highlighted that there was significant variation in ease of contract negotiation and approvals. NHS Trusts appear to employ different policies as to whether financial remuneration and other non-financial recompense are directly provided to the collaborating department or centre, or retained by the institution as a whole, such that the participating clinical department and their staff perceive few tangible rewards for engaging in clinical research.

Contract negotiation was perceived as one of the greatest impediments to managing a clinical research project (see section 2.4). In addition, the time taken to obtain NHS research governance approval was considerably higher than for gaining other approvals, and was viewed as a much greater impediment for project management (see section 3.1). It was felt that the variation across NHS Trusts made planning difficult and could result in the entire project running over time.

Distinct features of NHS Trusts act as incentives for research organisations to select particular recruitment sites. The findings highlight that the resources provided by a site, and the reputation of a Trust for patient recruitment, together with the reputation of the lead clinician, were important aspects which influenced the selection of sites for the projects reported (Figure 6.1.1). It is perhaps surprising, given that ease of contract negotiation and R&D sign-off are viewed as particularly notable challenges for project management, that these aspects are not more influential when selecting sites. In practice however, researchers do not have access to information about the actual time a Trust typically takes to provide permissions, and so in general are not able to utilise a 'local' nuanced knowledge to inform their selection for the majority of sites. However, researchers will use a site that has previously been successfully used by the research group, and further information about a site may also be obtained from recommendations given by other contacts.

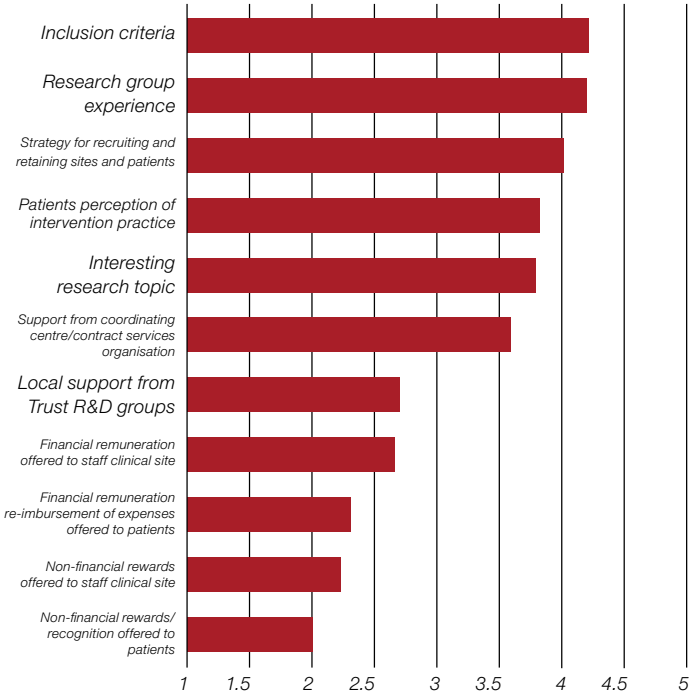
Figure 6.1.1 *Features influencing the choice of recruitment sites for use by the projects*



Scale: 1 = Not at all important 5 = extremely important

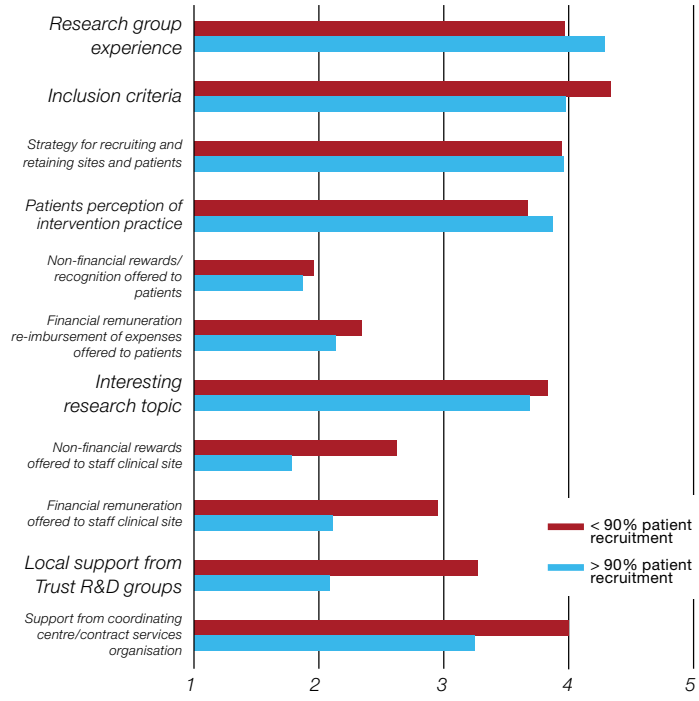
Certain aspects of project design are perceived to affect the level of recruitment at sites. The findings indicate that respondents believed that expertise in planning and designing the project, such as inclusion criteria & recruitment strategy and presenting an interesting topic, were more important factors for recruitment than explicit incentivisation through the provision of rewards, such as financial and non-financial remuneration (Figure 6.1.2). However, for those projects which experienced problems with recruitment, it was perceived that low levels of financial remuneration and non-financial rewards, together with low levels of support from Trust R&D departments, did adversely influence a site's ability to recruit (Figure 6.1.3).

Figure 6.1.2 *Importance of support mechanisms in influencing the ability of sites to recruit*



Scale: 1 = Not at all important 5 = extremely important

Figure 6.1.3 *Aspects influencing the ability of sites to recruit: Projects which successfully recruit compared with projects which experienced greater challenges with recruitment*

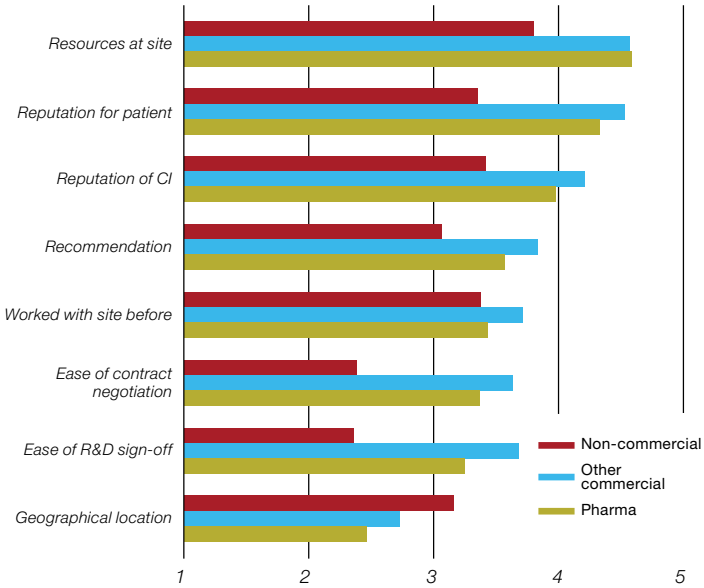


Scale: 1 = Not at all important 5 = extremely important

Different types of research organisation had particular priorities which influenced their selection of sites, which again reflected their overall motivations to be engaged in clinical research. Non-commercial organisations place a higher priority on the geographical location of sites (Figure 6.1.4). Typically these will already have established relationships with a small number of local NHS sites, as this particular group of organisations includes both NHS research groups that stem from particular Trusts, and also university research units which have formal University-Hospital associations.

Commercial groups place more importance on the resources, reputation for patient recruitment, the ease of contract negotiation and ease of R&D sign-off when selecting sites (Figure 6.1.4). This reflects perhaps more priority on set-up efficiency. Pharmaceutical companies also placed more reliance on recommendation of sites compared with non-commercial groups, which may indicate that this type of organisation have more networks that they can access that can be used to inform their selection.

Figure 6.1.4 *Features influencing the choice of recruitment sites for use by the projects: Categorised by organisation*



Scale: 1 = Not at all important 5 = extremely important

The process of engaging NHS Trusts and staff to become involved in a research project is complex and requires skilled negotiation by the research organisation. Challenges for project management may emerge when balancing the incentivisation of NHS sites at the Trust level, with motivating individual clinicians and clinical departments to collaborate. Indeed, balancing remuneration at the Trust level with the rewards and benefits that a clinical member

of staff will see manifest within their own department, can be a difficult to achieve in practice. This in turn can make it difficult to incentivise involvement at the departmental and individual level.

In particular, it was felt that changes to the Consultant Contract through the 2002 framework (Department of Health, 2002) and its subsequent amendments resulted in a change of emphasis on NHS Consultants' participation in clinical research. Whilst the changes to the rewards system ultimately increased overall pay, it was felt that this contract gave less prominence to rewarding clinicians to participate in research. It is believed that more recent changes to the merit system may address this issue. However, changes to the registrar training scheme are also perceived to have not necessarily incentivised clinicians to conduct clinical research. Overall, the merit system has altered the motivation for clinicians to become involved as investigators for projects, and thus changed the context of collaboration between NHS Consultants, other clinical staff and external research groups.

…"To be honest, I don't know why the medics do it. The money that goes in goes into the Trust, they used to get all of that. Now they don't, they get a small proportion of it back and that gets shaved off for R&D, which adds burden with no benefit. They're not seeing much gain. It's usually down to passion for the subject. To be fair, some of the Trusts, some of the hospitals get it, and they understand that they can bring money in if they get themselves organised. They've got a business focus, so they treat the trials as a business and they do have sufficient churn that it pays for their staff and it provides some extra income. But that has to get to the place where the impact on 'what's in it for me' is going to actually hit."

In practice, the drivers for individuals to get involved in any role within a clinical research project vary. To successfully recruit and retain team members and collaborate with other key stakeholder groups, (such as clinicians based at clinical sites), requires skilled use of different forms of incentivisation. However, in practice identifying the appropriate incentivisation is based on a local insight into what drives different people to participate. This understanding is developed again through experience. For example, such as when a skilled project manager develops an appreciation of the practical level of involvement clinicians from sites actually want to have.

…"Motivation varies. You get some surgeons who are highly motivated by doing it. They want to fill the CRFs out themselves and usually with everything are very particular. You get other centres where the guy just wants to do the surgery and then have the research staff follow them up, which is also fine, providing the resource is there. But for lots of our studies we have to provide research nurses, research physios to do the follow-up because if we didn't the hospital has no resource. I know that the clinical research networks are looking to address that, which is a welcome development, and also to train more people in GCP."

…"I think different things drive different people. The clinical research fellows come in with a clinical background, and I think many of them are asking 'does this do any good?' And so they already have questions about their practice... the investigators, the consultants, if you go to them with everything organised, everything easy, then they will do anything for you. If you don't have everything in place, they can't, they don't have the capacity. You only want them to do the minimal extra to their day-to-day work… There is a massive incentive for the consultant in the NHS is a merit system, which determines pay, and one of the big things is being a principal, the chief investigator. This has come in relatively recently."

In addition, even when appropriate incentives for stakeholder groups to become involved in projects exist, it can be difficult for research groups to find routes to communicate these clearly, so that the levels of involvement expected and the potential benefits can be fully understood. Engagement of the primary care sector in clinical research is particularly difficult, as typically quite significant numbers of GPs need to be involved. These often have little direct on-site support available from R&D services, or little previous involvement with clinical research. Thus, research organisations need to commit proportionally large levels of resources (time and money) in order to negotiate with and motivate individual sites (in this example GP Practices). In addition, there was concern that it was difficult to provide the necessary incentives for this type of NHS site to participate in external research projects.

…"Most of the people I've talked about are academic and it's part and parcel with their job. The difficulty that might be to them is to get ordinary GP's or other service practitioners to get involved. What's in it for them? There's nothing in it for them, actually, except we might pay them for their time. They've just got to

recognise that. If we're going to practice everything they mention, where's the evidence coming from? The evidence comes from research, and they can help do that research to take care of their patients."

6.2 The drivers for research

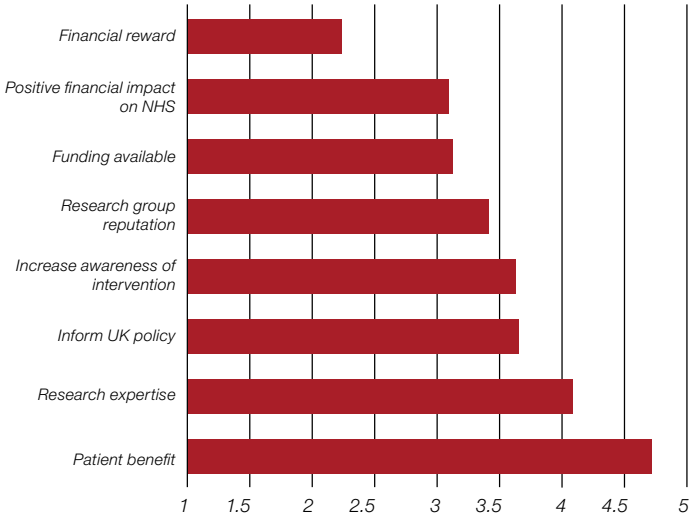
The findings presented within this report highlight various challenges that influence the ease of managing clinical research in the UK. Therefore, it is important for government strategists to recognise why particular types of research organisation choose to conduct clinical research projects within the UK. In particular, only by recognising that different research organisations have different drivers, can policy be developed to meet the needs of these groups. Commercial research constitutes a very valuable component of the UK economy. In order to make a profit these types of organisations must maximise the time they market a product within patent, and thus are under pressure to complete clinical research projects speedily and efficiently. The research conducted by non-commercial organisations is equally valuable in supporting the specific health needs in the UK. Whilst this model of research does not necessarily experience the same time pressures, overall the findings suggest that non-commercial research faces greater challenges in terms of the ease of managing projects.

…"The higher order question is what are the motivations for doing research at all? Clearly industry, it has to do research that it thinks is going to contribute to its profitability. That's totally different from the objectives of other people involved in research, who aren't even assessing commodities. They might be assessing physiotherapy, which can't be packaged and sold with surpluses passed on to shareholders. That's the bigger question, and it's reflected in the fact that the European clinical trial directive was under the EC industry directive and not the public health one"

The survey findings indicate that there are many different drivers which promote clinical research in the UK (Figure 6.2.1). Unsurprisingly, patient benefit is of high importance to all groups. In addition, further developing an existing area of expertise was rated highly. This illustrates that organisations value the experience that team members have previously acquired and by conducting further clinical research in an existing area, the research organisation can subsequently leverage existing networks of relationships and expertise.

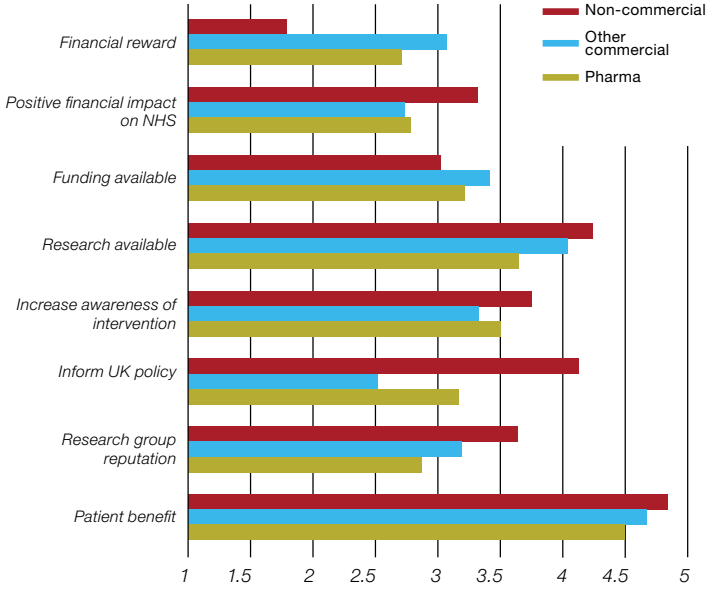
Research organisations have different priorities when conducting clinical research (Figure 6.2.2). Financial reward was obviously important for commercial groups. Enhancing a particular research group's reputation and informing UK policy were more important motivators for non-commercial research teams. This reflects the importance to these groups of building a reputation for producing good quality research findings, in order to increase the likelihood of further funding.

Figure 6.2.1 *Drivers for developing a research project*



Scale: 1 = Not at all important 5 = extremely important

Figure 6.2.2 *Drivers for developing a research project categorised by different organisation types*



Scale: 1 = Not at all important 5 = extremely important

The different drivers for conducting research reflect the various models of research and require specific policy support.

Commercial organisations clearly need to generate profit and the UK represents just one geographical location in

which to conduct clinical research. These organisations are adept at conducting highly efficient research through the adoption of the RCT model with a straightforward design. In general commercial organisations are less likely to conduct research with features which present challenges for project management (e.g. prevention trials that are problematic in terms of recruitment), as this increases the risk of delay in reaching the market. In general therefore, researchers from commercial organisations consider the UK a good place to conduct clinical research projects that adopt the RCT model, as there are robust patient populations that will ultimately constitute a target market. The NHS as a potential market continues to be highly valued, such that often clinical research projects for late phase or marketed innovations will be framed specifically with the UK context in mind. The UK also provides high levels of clinical expertise and access to highly qualified individuals.

Smaller biotech and start-up organisations however do experience difficulties. In general, this type of organisation is founded on developing a single or small number of clinical innovations which often carry a greater risk of failure. Whilst still aiming to generate profit, these smaller organisations do not have the same level of available resources and often experience skills shortages and lack expertise in project and business management.

…"The challenges are very different in small pharma, but it's ultimately the same thing you are trying to achieve, so you still have your hurdles and put up with all that. People aren't necessarily nicer to you because you are a smaller company struggling. They perhaps would give you a less aggressive time, but they will still expect the targets and hurdles to be met in the same way that you would if a large pharma. When you go to phase III, they think you are on the road to greater finances, they tend to treat you in the same way. The only other difference is you don't have the resources to survive big gaps, so we don't have a reserve."

Medical devices companies operate a different commercial model. They do not have the same type of patent cover as medicines so it is much easier to make amendments to the innovation. This can lead to different types of competition issues and time-pressures compared with medicines research, as there is less incentive to achieve a 'first-to-market' product. However, once marketing approval is received, these organisations are under increased pressure to continuously develop modifications and improvements to the product.

…"Medical devices companies don't have these protections in place that drug companies have when it comes off patent in so many years. They've got the market, the drug companies, for a lot of years. They can make a lot of money and rake it back. It's not the same with the device industry. After that, the copies, it's very easy to work your way around a patent for a device. The lifetime of a product is very, very short or the ability to rake back. What you would do is watch somebody else develop a device, slightly modify it, and ride on the back of that. It costs you less. You don't have to do the studies; they can. They get all the costs and then you put it on the market as well. You can't do that in the drug industry. The first movers spend a lot of money, so if somebody else is right on the back of that, not spending that money. Intellectual property is a more complex area."

The different drivers thus influence the type of research that takes place. Moreover, the support offered by UK strategists and policy makers can also influence what types of clinical research are conducted. If research is likely to be problematic to practically undertake because it does not necessarily conform to a standardised RCT model then policy support needs to be developed to ease the management of these types of projects.

Many non-commercial research groups develop a research stream that is actively shaped by government funding priorities, such as the development of essential medicines which are not necessarily the focus of the commercial sector. These groups must develop expertise in managing projects that are typically more complicated and non-standard. For example, research into rare diseases and acute diseases present inherent challenges for project management as there is generally a smaller patient population from which to recruit. The findings demonstrate that these types of projects achieve lower levels of recruitment (Figures 6.2.3 & 6.2.4). As this type of research does not necessarily conform to the RCT model, policy support and development would be welcomed to further promote this particularly valuable clinical research.

When comparing the recruitment rates for acute diseases with those for chronic conditions, as would be expected, the former experience greater difficulty reaching anticipated recruitment levels (Figure 6.2.3) as patients often cannot be identified in advance. In particular, in the UK healthcare context, conditions such as asthma, diabetes and hypertension are already medically controlled. Consequently, for many disease areas, there are much lower numbers of patients who could potentially be recruited to test interventions designed to treat an acute situation. Projects around rare diseases also experience

greater recruitment difficulties given the smaller patient population from which to recruit (Figure 6.2.4).

The data demonstrates that research about disease areas achieve different levels of patient recruitment (Figure 6.2.5). Although a large number of cancer research projects are completed having reached anticipated recruitment, a notable proportion have considerable recruitment difficulty. This reflects the fact that whilst some cancers have larger groups from which to recruit, rare cancers will inherently have greater recruitment challenges. However, commercial groups are more likely to conduct research into these rarer types of cancer, with the smaller patient numbers presenting greater challenges for project management. Projects focusing on respiratory, cardiovascular, stroke and diabetes conditions (RCSD), achieve a lower proportion of projects which reach recruitment targets compared to cancer projects. However the RCSD group have a low proportion of projects that only achieved less than 50% of the recruitment target.

Figure 6.2.3 *Recruitment achieved during project: Categorised by acute compared with chronic diseases*

Figure 6.2.4 *Recruitment achieved during project: Categorised by rare compared with common diseases*

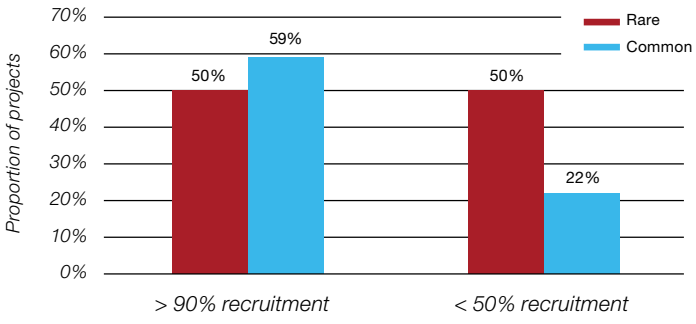


Figure 6.2.5 *Recruitment achieved during project: Categorised by disease area*

Recommendations

i. NHS Trusts need to be flexible in how they negotiate contracts and permissions with different types of research organisation which reflect the different incentives that need to be offered. In particular, Trusts should recognise the specific financial and resource constraints experienced by smaller commercial organisations.

ii. Incentives to encourage greater NHS involvement in clinical research need to be targeted at different levels of the NHS: the organisational-level, site-level and individual-level.
   - All Trusts should be strongly encouraged to 'buy into' initiatives to develop a streamlined consistent system of approval and access.
   - Trusts should promote participation of clinical departments in clinical research, and ensure that benefits are directly received from this involvement.
   - Greater attention should be given to encouraging the active involvement of clinicians as lead investigators in clinical research projects.
   - Research conducted by pharmaceutical organisations can be supported through policy initiatives that encourage approval bodies and NHS Trusts to participate in a generic and streamlined procedure for the set-up of projects, and for clinical sites to increase the efficiency with which they recruit patients.

iii. Smaller commercial organisations can be supported through the development of a national network of support organisations that could provide expertise in areas such as project management, legal and regulatory issues and business management, which these organisations typically lack.

iv. Research conducted by the non-commercial sector needs to be incentivised through the availability of public funding that supports projects which support the UK's healthcare needs. These research groups require more flexible forms of employment to retain existing contract research staff.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7. Conclusions and Recommendations

This report has presented findings which highlight that there are many challenges associated with managing different types of clinical research projects within the UK. In the following sub-section we present respondents' perceptions of the major impediments to conducting clinical research. However, it needs to be recognised that perceptions about impediments do not necessarily reflect the real experience of managing a project as a number of major findings have demonstrated throughout this report. In order to summarise the major findings we believe it is constructive to consider macro-level issues that influence the overall operations of a research organisation, and how these can create challenges in the day-to-day management of clinical research projects. Throughout this report, it has been highlighted that there are a whole host of different types of research organisation which engage in various models of research. The major findings suggest that the current system is a 'one size fits all model' where what is perceived as 'good research' is informed by the RCT model. In practice strategists and policy makers need to consider and engage with all research models in order to strengthen the clinical research sector in the UK.

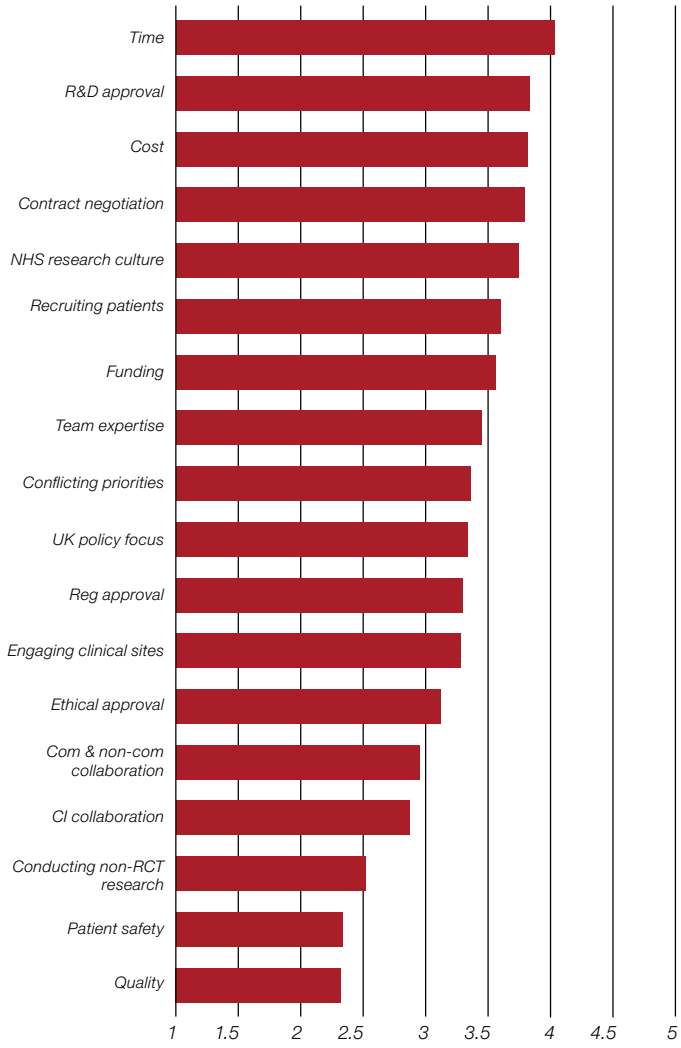
7.1 Impediments to managing clinical research in the UK

In terms of perceptions, all respondents believed that the time taken to conduct clinical research in the UK, obtaining R&D approval, the cost of conducting clinical research, contract negotiation with NHS sites and the NHS research culture were the greatest impediments to conducting clinical research (Figure 7.1.1). Aspects relating to the quality of research, adhering to requirements to ensure patient safety, and conducting non-RCT research were viewed as lesser impediments.

Whilst conducting non-RCT research was perceived as a minor impediment, it should be noted that respondents' perceptions do not necessarily reflect the actual experiences of managing clinical research. In particular, the findings from this project overall highlight that many of the challenges are related to conducting atypical research that does not conform to a RCT model.

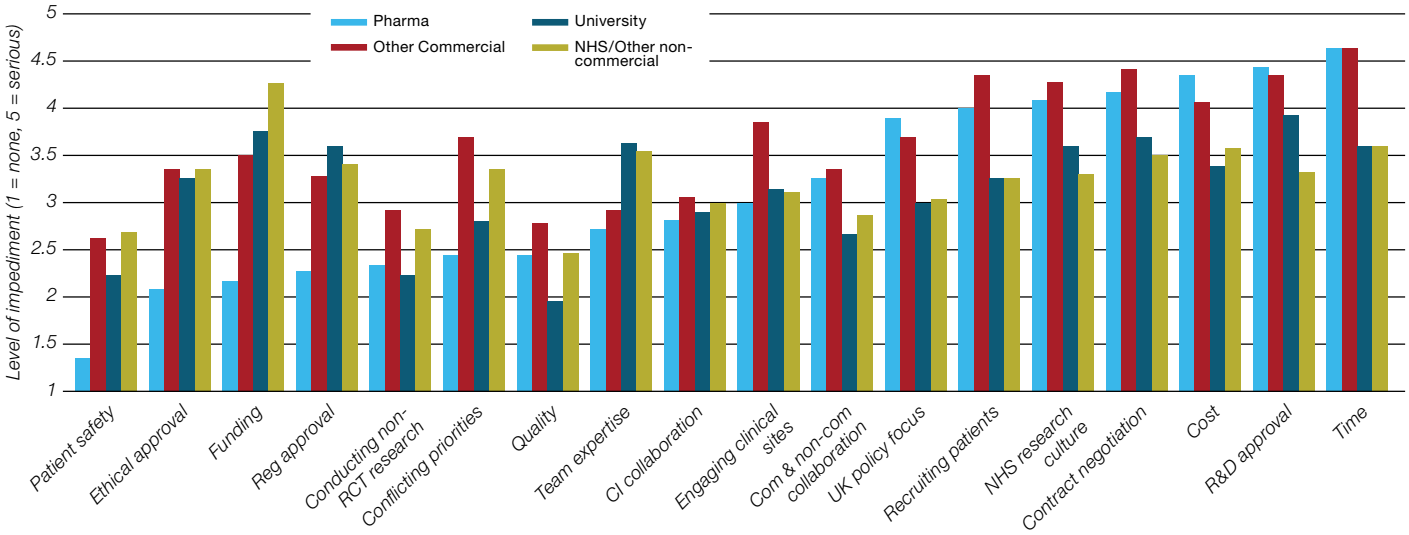
It is also important to note that respondents from different

Figure 7.1.1 *Current perceptions about the impediments to managing clinical research in the UK*



types of organisations had differing opinions about the current impediments that influence the management of clinical research in the UK (Figure 7.1.2). Respondents from pharmaceutical organisations in particular perceive aspects such as patient safety, obtaining funding and obtaining ethical approval as not being an impediment to their research management. Whilst time and cost issues were viewed as important by researchers from all organisations, they were perceived as particularly important by respondents from pharmaceutical and other commercial organisations. Whilst respondents from all organisations

Figure 7.1.2 *Current perceptions about the impediments to managing clinical research in the UK: Categorised by type of organisation of respondent*



perceived obtaining R&D approval as a great impediment, this was particularly marked for pharmaceutical, other commercial and university/ academic research groups. The respondents from university and other non-commercial organisations rated funding as a particularly significant impediment, which reflects their reliance on external finance for projects.

Respondents from commercial organisations identified time and cost, and other aspects that reflect efficiency concerns such as R&D approval and contract negotiation as significant impediments. However, relative to other research organisations, pharmaceutical companies experience less difficulty with completing projects on time. Nevertheless this group are most directly influenced by global pressures. It should therefore be recognised that comparisons with their experiences of managing projects should not necessarily be made with other UK research organisations, but rather with other global enterprises.

7.2 Interdependency of macro- & micro-level issues influencing the management of clinical research projects

This study was conducted in the context of considerable changes to the UK system within which clinical research is organised and managed. Major alterations to the regulatory & governance approval process have occurred, and considerable attention from UK strategists and policy makers has resulted in the implementation of numerous initiatives that ultimately aim to improve the UK environment within which clinical research is conducted. Our findings suggest that it is constructive to consider the relationship between macro-level issues that possibly generate operational and management challenges for the research organisation, and issues experienced with the day-to-day management of clinical research projects. This distinction can be an important aid for policy review in terms of how to respond to the different types of issues that exist, as the first group reflects issues that stem from beyond the research organisation and influence the overall research environment, whilst micro-level issues reflect challenges that are generated at the project-level and influence the management of research at a day-to-day level.

A systematic literature review was used initially as a tool to identify the types of challenges that influence the management and organisation of clinical research. A synthesis of the literature supported the development of a two-tier model categorising macro-level and micro-level issues that affect the management of clinical research within the UK (Table 7.2.1). This classification can be a useful aid to support critical appraisal of the types of areas that UK strategists and policy makers should consider.

Macro-level issues highlight the challenges experienced by research organisations in managing and conducting research within the UK institutional context. As these types of issues are encountered at the organisational level, to successfully conduct clinical research within the UK a research group must successfully manage these challenges by developing an appropriate organisational strategy and overall research focus. Practically this means

that research organisations need to 'fit' their particular model or models of research within what is generally interpreted to constitute 'good research'. Accordingly, a research project needs to be designed and presented to the various approval and regulatory bodies as adhering to acceptable ethical principles and regulatory and governance standards. This was shown to be a major challenge for research that did not conform to the standard RCT model of research. In addition, strategically, policy makers aim to promote clinical research in the UK by introducing a variety of initiatives and schemes which balance the dual concerns of increasing the economic value of the UK clinical research sector, with promoting clinical research that addresses UK healthcare priorities. However, as there are numerous different types of clinical research taking place within the UK, which are grounded in various research models, UK policy initiatives can sometimes generate differential, contradictory and unforeseen consequences, particularly affecting the ease with which different types of research project can be conducted.

Micro-level issues relate to the challenges that are experienced during the day-to-day management of research projects. Although these are directly affected by the response of the research organisation to managing the macro-level challenges which frame the environment within which research is conducted, micro-level issues describe the barriers and enablers that are experienced typically by individual managers and researchers at the project level. As such, these types of issues relate to aspects such as overall coordination of projects to ensure successful set-up and recruitment, through obtaining necessary approvals, to ensuring that the necessary skills and expertise are available to successfully run a project through to completion. Successful project management is dependent on the creation of a network of other stakeholder groups, upon whom there is a degree of dependency around expertise and resources, including access to patients. The majority of research projects conducted within the UK are dependent on the NHS for patients, but challenges can be experienced with contract negotiation, obtaining governance permissions, and with engaging clinical staff. Further challenges arise in terms of motivating investigators, nurses etc. to participate in projects. Obviously financial constraints that are often experienced by smaller commercial and non-commercial organisations also have an impact on what resources are available for day-to-day project management, since this affects the level of incentivisation that can be offered to team members and other collaborators, such as clinical sites. As different research organisations have different strategies and occupy various niches within the sector, there are considerable variations in the specific barriers and enablers to clinical research according to the type of research being conducted.

Table 7.2.1 *Categorisation model of issues affecting the management of clinical research projects in the UK*

Theme
Macro-level: Institutional challenges
Competitive innovation market pressures
UK strategy & policy
Ethical principles
Regulatory, legal & governance framework
Micro-level: Project management challenges
Day-to-day coordination of a project – Project set-up & recruitment
Establishing a network - Collaboration, alliances & outsourcing
Managing expertise & incentivising a project team
Set-up & management of clinical sites – Working with the NHS
Recruiting & motivating participants
Financial constraints

7.3 Balancing the support required for different models of clinical research: Recommendations & areas for policy attention

Legislation at the European level, together with extensive changes to the regulatory, ethical & governance framework, and the implementation of numerous strategic and policy initiatives to support clinical research have changed the context within which research is organised and managed within the UK.

This report has highlighted numerous challenges that influence the successful management of clinical research projects within the UK. It has been emphasised that the policy response to these challenges needs to recognise and support *all* the research groups that constitute the clinical research sector within the UK, in order to promote 'UK PLC'. Clinical research is a knowledge-intensive industry and its future is reliant on developing and nurturing the expertise that this sector relies upon.

…"I think what you have here is an industry that they want to see maintained here, perhaps grown here as much as makes sensibly possible on the world stage, given limitations. I don't think anyone would disagree. Population is a limitation. The way the health system is structured, there are limitations that you have to work within. But this is an industry, the development of drugs

and the conduct of clinical trials, that we as a country need to keep in-house and not outsource. This is certainly not the automobile industry or the ship-building industry. And we have our own dynamics and economic factors that makes us an industry which I hope people would want to keep in the country, because if you think about it, what natural resources are left in the UK? Expertise is the greatest resource that we have because there's a limited number of things here that we can say are exclusively our natural resources which we can exploit. Knowledge is one of them."

The findings underline the fact that many of the challenges of conducting clinical research are compounded because of the complex array of different stakeholder groups involved and the different models of research that are being conducted. This presents challenges for policy makers in balancing the support required for different types of research organisation, whilst more generally promoting the clinical research sector within the UK.

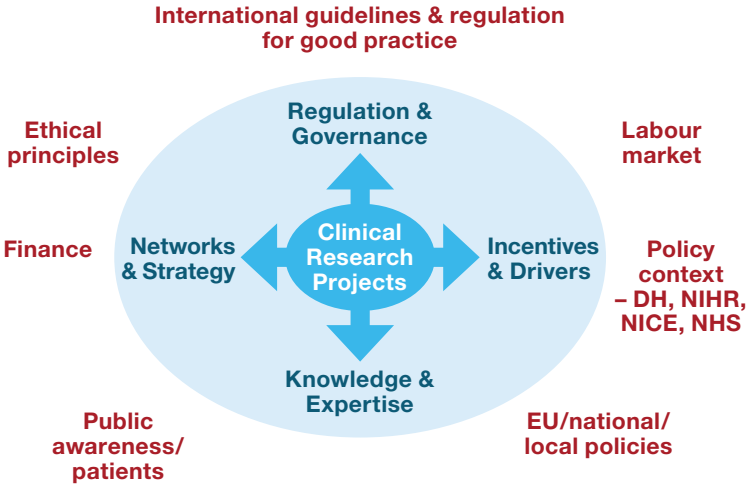
At best the system is a 'one size fits all model', where what is perceived as good research is framed by a standard RCT model. Other models of research experience considerable challenges. This has the potential to discourage research groups from developing innovative approaches to clinical research which are based on atypical features that might differ considerably from a standard RCT. That is not to say, however, that large commercial groups do not experience challenges as they experience the greatest pressures from the global context in which they operate, and often feel marginalised by other groups within the healthcare sector. Policy makers should recognise that different clinical groups require different levels and types of support, and should also be aware that strategic changes to the UK environment may inadvertently create additional challenges for the organisation and management of particular types of research.

Naturally, perceptions regarding the most important types of clinical research for a UK policy focus are related to the type of organisation that a respondent represents. Respondents from commercial organisations perceive that policy should support the needs of their model of research where time is of the essence. Respondents from non-commercial research organisations suggest that greater policy attention should focus on providing funding for research areas deemed to be of most importance in the UK health service context.

The findings presented in this report provide particularly valuable insight into how certain groups view particular aspects of the process of managing clinical research projects. Other stakeholder groups, including policy makers and the regulatory & governance approval groups should recognise that these attitudes exist, even if they debate the legitimacy of these views from the context of their own remit and the actions that they have taken. This is important because attitudes shape whether people become involved in research. In short, if researchers see the UK context as too challenging, then they may chose to conduct projects elsewhere, or cease to engage in clinical research. However, it also needs to be recognised that attitudes and perceptions of the effects of very recent initiatives, such as the introduction of the UKCRN, are not reflective of actual behaviours at a project level, and in-depth research should be undertaken to explore their actual impact on the successful management of clinical research projects. It is vital that research is undertaken to generate in-depth findings regarding the actual experiences of managing clinical research within the UK, which survey data, however detailed cannot adequately capture.

This report has explored the challenges experienced when managing clinical research projects under four themes. These themes are interlinked and the issues that have been highlighted over-lap these areas. For example, challenges related to a lack of expertise are also inherently linked to the incentives to recruit and retain project team members. Nevertheless, it is important to re-iterate that it is the macro-level context, including global and market pressures, the UK strategic emphasis and policy initiatives, ethical principles and the regulatory & governance framework, that influence how the challenges associated with these four themes are experienced in the day-to-day management of projects.

Figure 7.3.1 *Schematic model depicting the UK clinical research system*



From the findings of this research, we summarise our overall recommendations:

Regulation & Governance

i. The process for obtaining R&D approval from NHS Research Governance offices should be streamlined and made transparent.
ii. Performance data on R&D approval times for different NHS Trusts should be publically available for comparison
iii. Standard documentation and information should be used across all NHS Trusts, with a guaranteed turn-around for decisions.
iv. Information on how to obtain approvals (including regulatory, ethics and R&D) should be provided in the form of a 'one-stop-shop', with clearly signposted pathways for different models of research. Applicants should demonstrate they have consulted this information.
v. Examples of completed documentation (such as the 'mock forms' for a medicines and biotechnology product which are provided by the MHRA) should be provided by approval bodies for different models of research.
vi. The regulatory & governance system needs to reflect the particular ***risks*** and endemic features of different models of research. Training for committee members should include greater detail about how to assess the risks of different models of research.
vii. The system of 'flagged' ethics committees for medical devices should be further extended with dedicated ethics committees being set up for other different models of research.
viii. The regulatory & governance system should actively encourage the inclusion of innovative forms of research. There should be different routes provided through forms, and greater flexibility to include novel approaches.
ix. Members of approval bodies should receive training in how to assess novel approaches for research design to ensure that assessment of non-standard research features accurately assesses the risk.

Knowledge & Expertise

i. A dedicated portal for UK Clinical Research should be set up to assist less experienced clinical researchers in acquiring relevant knowledge and expertise. The portal should ideally hold and up-date information about approval requirements, project management support, training provision, contract research services, professional and trade bodies, and charities and patient organisations.
ii. The support provided by recently implemented NIHR Research Design Services should be extended to actively support innovative and atypical research models that do not conform to the RCT approach.
iii. A review of current training and accredited provision should be undertaken.
iv. A UK-wide strategy should be developed that identifies a career trajectory for clinical research. Career profiles of the range of roles engaged in clinical research should be developed.
v. Greater resources should be granted to patient and charity groups to enable these groups to increase the level of active support they can provide to research organisations.
vi. Research organisations should be incentivised to provide accredited training provision.
vii. More flexible forms of employment (for example secondments, positions jointly funded by commercial and non-commercial organisations, or multi-host contracts) should be implemented to promote retention and ease skills shortages experienced by small organisations and groups reliant on fixed-term contracts.
viii. Faster contracting should be a priority to help secure continuity across university and other publicly funded research projects. Bridge funding should be available for research staff experiencing temporary gaps in funding.

Networks & Strategy

i. Further support is required to strengthen relationships between research organisations and the NHS.
ii. NIHR initiatives to support the development of good relationships between the NHS and commercial research organisations are welcomed, and should be further reinforced and monitored as to their effects.
iii. Transparent information on NHS Trusts' clinical research governance processes should be easily available.
iv. Information on NHS Trusts' approval times and site-level recruitment and completion figures should be publically available.
v. There should be an evaluation of what makes effective clinical research networks, such as the Cancer CRN, to support the development of networks in other areas.
vi. Involvement with patient and charity groups should be promoted. There should be provision to cost charitable donations into publically funded research.

vii. All research organisations should be encouraged to work with NICE to ensure that research findings are tailored to the NHS context.
viii. A 'community of practice' for UK clinical research managers and research nurses should be fostered, in order to support the sharing of knowledge and expertise and build a strong identity and job market around UK clinical research.

Incentives & Drivers

i. NHS Trusts need to be flexible in how they negotiate contracts and permissions with different types of research organisation which reflect the different incentives that need to be offered. In particular, Trusts should recognise the specific financial and resource constraints experienced by smaller commercial organisations.
ii. Incentives to encourage greater NHS involvement in clinical research need to be targeted at different levels of the NHS: the organisational-level, site-level and individual-level.
    - All Trusts should be strongly encouraged to 'buy into' initiatives to develop a streamlined consistent system of approval and access.
    - Trusts should promote participation of clinical departments in clinical research, and ensure that benefits are directly received from this involvement.
    - Greater attention should be given to encouraging the active involvement of clinicians as lead investigators in clinical research projects.
iii. Research conducted by pharmaceutical organisations can be supported through policy initiatives that encourage approval bodies and NHS Trusts to participate in a generic and streamlined procedure for the set-up of projects, and for clinical sites to increase the efficiency with which they recruit patients.
iv. Smaller commercial organisations can be supported through the development of a national network of support organisations that could provide expertise in areas such as project management, legal and regulatory issues and business management, which these organisations typically lack.
v. Research conducted by the non-commercial sector needs to be incentivised through the availability of public funding that supports projects which support the UK's healthcare needs. These research groups require more flexible forms of employment to retain existing contract research staff.

Appendix 1: Specialist Scientific Advisory Board Members

We would like to express our thanks to members of the Specialist Scientific Advisory Board who have provided us with guidance throughout this project.[2]

- Sallie Lamb, Professor of Rehabilitation and Director of Warwick Clinical Trials Unit, University of Warwick
- Sarah Duggan, Manager of Warwick Clinical Trials Unit, University of Warwick
- Sue Ollier, Director of QED Partnership & Chair of the Institute of Clinical Research
- David Gillen, Head of Primary Care Medical Teams (Europe Canada, Australia & New Zealand), Pfizer
- Maire Smith, *Executive director of technology and product innovation at the NHS Institute for Innovation and Improvement*
- Richard Tiner, Medical Director, Association of the British Pharmaceutical Industry
- Barbara Blaney, Director of BioIndustry Scotland
- Tom Walley, Professor of Clinical Pharmacololgy at the University of Liverpool & Director of the HTA Programme
- Nick Edwards, Chairman of Kinapse Ltd. & Chairman of MedInnovate Ltd.

We would also like to thank those who have provided us with support at the September 2009 event presentation of this project's results:

- John Gribben, Professor of Experimental Cancer Medicine at Queen Mary University of London, and Head of R&D for Barts and The London School NHS Trust
- Janette Benaddi, CEO Medvance Clinical Research, and Chair of the Institute of Clinical Research
- John Hladkiwskyj, Vice-President CCA 2000 Contract Research Organisation

2 Positions stated are those held at the time of the research.

Appendix 2: References

Academy of Medical Sciences (2003) *Strengthening Clinical Research: A Report by the Academy of Medical Sciences (AMS)*. Published, October 2003. London: AMS

Alter, C. & Hage, J. (1993) Organizations Working Together. London: Sage.

Association of British Pharmaceutical Industry (ABPI) (2008) *Skills Needs for Biomedical Research: Creating the Pools of Talent Needed to Win the Innovation Race*. London: ABPI.

Darzi A. (2007) *Our NHS, Our Future. NHS next stage review - interim report for the Department of Health*. Published, October 2007. London: The Stationary Office.

Department of Health (2006) *Best Research for Best Health: A New National Health Research Strategy*. Published, January 2006. London: The Stationary Office.

Department of Health (2005) *Research Governance Framework for England*. Second Edition. London: The Stationary Office.

Department of Health (2001) *Research Governance Framework for England*. London: The Stationary Office.

Department of Health (2002) *Consultant Contract Framework*. London: The Stationary Office.

Duley, L., Antman, K. & Arena, J. et al (2008) Barriers to the conduct of randomized trials. *Clinical Trials*, vol. 5, pp. 40-48.

European Union (2008) *Regulation (EC) No 2936/2008/EC (Amendment) of the European parliament and of the Council on Medical Devices Directive,* Official Journal of the European Union.

European Union (2002) *Regulation (EC) No 618/2002 (Amendment) of the European parliament and of the Council on Medical Devices Directive and amending Regulations 2003 No. 1697 and 2007 No. 400*, Official Journal of the European Union.

European Union (2001) *Regulation (EC) No 2001/20/EC of the European Parliament and of the Council of 4th April 2001 on medicinal products "The Clinical Trials Directive".* Official Journal of the European Union, 01.05.2001:L121/34-44.

European Forum for Good Clinical Practice (EFGCP) (2009) Impact of Clinical Research of European Legislation (ICREL): Final Report. Published February 2009. European Commission, Directorate Research.

Groves T. (2009) Senior UK Researchers Campaign for Sensible Guidelines on Regulating Trials. *British Medical Journal, vol 339, pp. 3671*

Healthcare Industries Task Force (HITF) (2007) *Innovation for Health: Making a Difference. Report of the Strategic Implementation Group (SIG)*. Published March 2007.

Hooper, J. (2005) Challenges and Trends in Clinical Research. *European Pharmaceutical Contractor*, SPRING, pp 34-38.

Kinapse (2008*) Commercial Clinical Research in the UK: A Report for the Ministerial Industry Strategy Group (MISG) Clinical Research Working Group*. Published, November 2008. London: Kinapse.

McKinsey & Company (2005) *Clinical Research in the UK: Towards a Single System that Reliably Delivers Distinctive Quality and Rapid Access at Reasonable Cost "The McKinsey Report"*. Published, August 2005.

Medicines & Healthcare Regulatory Agency (MHRA) (2009) UK Clinical Trial Authorisation Assessment Performance. Accessed online, 16th November 2009, Available at: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/UKclinicaltrialauthorisationassessmentperformance/index.htm

National Research Ethics Service (NRES) (2009) National Patient Safety Agency NRES Activity Data October 2009. Accessed online, 16th November 2009, Available at: http://www.nres.npsa.nhs.uk/news-and-publications/publications/general-publications/

Office for Life Sciences (OLS) (2009) *Life Sciences Blueprint: A Statement from the Office for Life Sciences*. Published July 2009

Saunders, M., Lewis, P. & Thornhill, A. (2000) *Research Methods for Business Students*. Prentice Hall: FT.

Swan, J., Newell, S., Robertson, M., Goussevskaia, A. & Bresnen, M. (2007) The Role of Institutional Differences in Biomedical Innovation Processes: A Comparison of the UK and US. *Int J Healthcare Technology & Management*, vol. 8, no. 3-4, pp. 333-353.

Swan, J. & Scarbrough H. (2005) The Politics of Networked Innovation. *Human Relations*, vol. 58, no. 7, pp.913-943.

Yusuf, S., Bosch, J., Devereaux, P. et al (2008) Sensible guidelines for the conduct of large randomized trials. *Clinical Trials*, vol. 5, pp. 38-39.

Appendix 3: Abbreviations & glossary of terms

Many definitions of clinical research exist. For the purpose of this report, we have used the following definitions:

Clinical Research: This is a branch of medical science that determines the safety and effectiveness of medications, devices, diagnostic products and treatment and service delivery regimes intended for human use. These may be used for prevention, treatment, diagnosis or general management of a disease.

Clinical Research Project: Any research project that recruits human subjects for the purpose of studying a medical intervention or healthcare evaluation. This includes drugs, surgical procedures, devices, behavioural treatments, process of care changes, healthcare & service delivery, and the like.

Clinical Trial: A research project conducted for the investigation of medicinal products

ABHI Association of British Healthcare Industries
ABPI Association of the British Pharmaceutical Industry
BIA BioIndustry Association
CRNs Clinical Research Networks
CRO Contract Research Industry
CSP Coordinated System for gaining NHS Permission
DH Department of Health
EPSRC Engineering and Physical Sciences Research Council
FDA Food and Drug Administration
HTA Health Technology Assessment
IRAS Integrated Research Application System
mCIA (bipartite) Model Clinical Investigation Agreement (between NHS Trusts and medical devices companies)
mCIA (tripartite) Model Clinical Investigation Agreement (between NHS Trusts and medical devices companies and CROs)
mCTA (bipartite) Model Clinical Trial Agreement (between NHS Trusts and pharmaceutical companies)
mCTA (tripartite) Model Clinical Trial Agreement (between NHS Trusts and pharmaceutical companies and CROs)
MHRA Medicines and Healthcare Products Regulatory Agency
NHS National Health Service (UK)
NICE National Institute for Health & Clinical Excellence
NIHR National Institute for Health Research
R&D Research & Development
RCT Randomised Controlled Trial
UKCRC United Kingdom Clinical Research Collaboration
NIHR CRN National Institute for Health Research Clinical Research Network (formally UKCRN)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ISBN 978-0-902683-97-6
Designed by warwickdesign, www.designatwarwick.com