Gaining approval for clinical research

Set-up and delivery of a clinical research project can be complicated and difficult. This article introduces the regulatory processes involved in gaining approval for clinical research and discusses the obstacles that may be encountered.

This article introduces key processes involved in gaining approval for clinical research and describes some important obstacles faced by researchers. It should be noted that regulatory requirements depend upon both the specifications of the project and local policies. England and the devolved administrations within the UK have different operating practices.

A number of significant changes to research regulation are being implemented as part of a drive to streamline and improve the set-up and delivery of clinical research studies.

The basics

It is important not to underestimate the amount of preparatory work, time and support needed to undertake a clinical research project. Significant groundwork is needed even before a study is ready for research approval application.

The basic initial requirements include a research protocol, secured funding, sponsorship (*Figure 1*) and adequate indemnity arrangements. In addition, the specific approval requirements of the research project need to be established early on, as the approvals processes can be complicated and longwinded. Applications to most regulatory bodies are made through the Integrated Research Application System, the national online research approvals and permissions application system.

The typical applicant requires both ethical approval and NHS site approval ('NHS permission' or 'research and development approval') for his/her study. Ethical approval is obtained through the Research Ethics Service for all studies involving NHS patients or NHS property. The ethics review process is performed by research ethics committees. Where studies are led from England, both ethical and NHS site approval are arranged through a single system called 'Health Research Authority approval'. Devolved administrations have alternative applications arrangements in place.

Certain studies require approval from the Medicines and Healthcare products Regulatory Agency, an agency within the Department of Health. Clinical trial authorization is issued by the Medicines and Healthcare products Regulatory Agency for clinical trials of medicinal products, and clinical investigations of non-CE marked medical devices also require Medicines and Healthcare products Regulatory Agency review (Medicines and Healthcare products Regulatory Agency, 2016). Other regulatory bodies issue approvals in specialized circumstances such as the Human Tissue Authority, Human Fertilisation and Embryology Authority and the Gene Therapy Advisory Committee, which acts as the research ethics committee for gene therapy clinical research.

Supporting documents are submitted with applications and include participant information sheets and consent forms. Guidance for preparing these forms can be found at www.hra.nhs.uk.

The project will be scrutinized by a number of bodies to ensure that the study design is ethically and scientifically sound, there has been adequate resource planning, the burdens and costs are appropriate and accurately

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Figure 1. Sponsorship.

Sponsorship is required for all clinical research studies. The sponsor ensures that there are adequate resources and arrangements in place to support the study. The role of the sponsor is defined by the UK Clinical Trial Regulations as 'an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial' (www.mrc.ac.uk/research/policies-and-resources-for-mrc-researchers/clinical-research-governance/clinical-trials-regulations/). For studies within the NHS, the sponsor may be a commercial company, the NHS trust or the university with which a clinical academic holds a contract.

The sponsor provides indemnity for the investigators in a clinical trial. If the sponsor is an NHS trust, indemnity cover is for negligent harm but not for non-negligent harm. Insurance for non-negligent harm can be provided if the sponsor is the university.

represented, and research governance standards are followed. The current Research Governance Framework (Department of Health, 2005) (*Figure 2*) provides good practice guidance to researchers. This will be replaced in due course by a new UK-wide framework for health and social care research.

The Health Research Authority

The Health Research Authority is an NHS body, launched in December 2011 to improve and streamline health research regulation while promoting and protecting the interests of patients and the public (www.hra.nhs.uk). It was set up following commitments made in the government's 'Plan for Growth' (Department for Business Innovation and Skills, 2011) to tackle failings in the initiation and delivery of health research in the UK. This came in response to a government-commissioned report by the Academy of Medical Sciences (2011) 'A new pathway for the regulation and governance of health research' which proposed, among other measures, creation of a new health research regulatory agency.

The Health Research Authority oversees the Research Ethics Service, which manages ethical review for clinical research in the UK. The functions of the Research Ethics Service are to 'protect the rights, safety, dignity and well-being of research participants' and 'facilitate and promote ethical research that is of potential benefit to participants, science and society'. Since its inception the Health Research Authority has also taken over provision of the Integrated Research Application System and has combined ethics committee with research and development approvals into a single Health Research Authority assessment called 'Health Research Authority Approval'. This applies to studies led from England only, but the Health Research Authority works closely with devolved administrations to harmonise operating practices within the UK.

The Health Research Authority has produced a draft UK-wide Policy Framework for Health and Social Care Research to replace the current Research Governance Framework. At the time of writing, this has been through a public consultation period and is expected to come into force, after revisions, sometime in 2016.

In line with its objectives, the Health Research Authority has close links with other bodies involved in research regulation and promotion such as the Medicines and Healthcare products Regulatory Agency and the National Institute for Health Research.

The Integrated Research Application System

The Integrated Research Application System (www.myresearchproject.org.uk) is a freely accessible online system that is used to prepare and submit applications for health-care research approval. An Integrated Research Application System account is simple to set up with an email address and chosen password. Multiple projects can be entered within a single account.

Resources available to guide researchers within the Integrated Research Application System include an e-learning module and help page. Green icons attached to questions within the forms provide question-specific guidance. A telephone contact number and email address is also available for technical support and other queries.

When a new project is created, it opens to a navigation page. On the left side of the page is an access panel for all the forms that can be captured in the Integrated Research Application System. For each project, information entered into the 'Integrated Dataset' of the Integrated Research Application System allows easy population of other forms within the Integrated Research Application System and avoids the need to enter duplicate information for different approvals.

The Integrated Research Application System is designed to tailor further questions according to the responses given, so care is needed when answering questions in the project filters. An incorrect answer can mean that the subsequently generated questions are not appropriate for the study.

Responses to the project data questions in the Integrated Research Application System should be carefully considered before project submission for regulatory approval. Typical project data question topics are shown in *Figure 3* (World Health Organization, 2010; Department of Health, 2012).

Figure 2. Clinical research governance.

The Research Governance Framework for Health and Social Care (Department of Health, 2005) is a Department of Health publication that guides best practice for all research performed in the NHS and social care organizations in the UK. This will be replaced by a UK Policy Framework for Health and Social Care Research, which is the result of collaboration between the Health Research Authority and devolved administrations. The deadline for public consultation responses to the draft document has now closed and a revised document is expected to be published later in 2016. Researchers should continue to refer to the current framework guidelines until they are replaced.

Current guidance is in five main areas: ethics, science, information, health, safety and employment, finance and intellectual property. The following standards are included:

- Protection of the wellbeing and rights of the participants in a study is of greatest importance in clinical research
- Ethical approval is required to formally safeguard ethical standards of practice
- It is considered unethical to unnecessarily duplicate research or produce research of poor quality
- All research proposals should be independently peer reviewed for scientific quality. Further ethical and scientific safeguards exist in the form of various regulatory bodies that must issue approval before a study can start
- Research should follow the principles of Good Clinical Practice
- Research data must be retained for an appropriate period after the study ends. This allows further analysis and review by regulatory bodies
- The results of the research should undergo critical peer review and be made available to the public, research participants and those who could benefit from the findings.
- It is good practice to register clinical trials on a publicly accessible register
- Health and safety regulations must be adhered to for the protection of participants, researchers and all other staff
- Public funds should be used correctly and with transparency
- Intellectual property rights should be protected
- Provision must be made for compensation to participants in the event of harm.

Figure 3. The Integrated Research Application System integrated dataset.

The integrated dataset contains four sections:

Part A: Core study information

Part B: Additional information for specific applications – this section applies in specialized circumstances such as exposure to ionizing radiation, use of human tissue, adults unable to consent for themselves, children, trials of investigational medicinal products and medical devices

Part C: List of research sites

Part D: Declarations – this section is for electronic authorizations

Core study information

This includes administrative details and questions regarding the scientific design and conduct of the study, recruitment of research participants, care and protection of research participants and data protection measures in place. Typical project data question topics include:

- Study design and methodology
- Burdens or risks placed on the research participants
- Criteria for study termination or early withdrawal of a research patient
- Provisions in place for monitoring the research
- Adequacy of research site to fulfil its role: infrastructure, facilities and expertise of staff
- Plans for reporting and disseminating the results of the research
- Choice of population from which the subjects will be recruited
- Inclusion and exclusion criteria
- Methods that will be used for participant recruitment
- Information provided to research participants
- Details of the consent process
- Risks of any proposed intervention
- Any deviation from standard therapy and whether this can be justified
- Care provided to the patient during the study and after it ends
- Costs to patients and whether they will be reimbursed
- Qualifications and expertise of staff
- Insurance and indemnity arrangements in the event of harm to a research participant
- Data protection measures including long-term storage arrangements.

Ethical review

Applications for ethical approval are submitted in the Integrated Research Application System and are reviewed by research ethics committees. Each research ethics committee consists of lay members and people with particular expertise including health-care professionals and academics.

Most research ethics committee applications in the UK are processed through a new central booking service, which replaces the central allocation system, local allocation system and proportionate review allocation system*. It is still possible to apply to a specific research ethics committee of choice using the new service.

*Proportionate review was introduced to speed up processing of applications that are thought to pose low risks to participants. Guidelines for eligibility are available on the HRA website, using the No Material Ethical Issue Tool.

The application for research ethics committee review is booked by telephone. Contact details are available on the Health Research Authority website (www.hra.nhs.uk). Electronic submission of all necessary documents through the Integrated Research Application System is required on the same day as booking. Before booking it is therefore important to have all supporting documentation ready and ensure that appropriate authorizations have been made. Mandatory electronic authorizations have been introduced, meaning that all required signatures must be performed electronically through the Integrated Research Application System and therefore all signatories will need to have their own Integrated Research Application System account in order to authorize. All required authorizations must be made before the application is submitted.

It is recommended that applicants attend the research ethics committee meeting as it allows committee members to address queries directly with the researcher.

With few exceptions, the research ethics committee must provide an opinion within 60 days of receipt of a valid application. Aside from a 'favourable' or 'unfavourable' opinion, a 'favourable with additional conditions' response may be issued. Alternatively the opinion can be provisional, pending further information or advice from a specialist referee. 'No opinion' may arise in a proportionate review case, with a recommendation for referral to a full meeting.

NHS permission

Research taking place within an NHS organization must be approved by the host NHS organization before it starts. Until recently, separate NHS permissions for each site were requested using site-specific information forms generated through the Integrated Research Application System. Applications in England are still made through the Integrated Research Application System but coordinated through the Health Research Authority. Separate coordinated system arrangements have been developed for each devolved administration in the UK.

In England, each site is now asked to make a local 'capacity and capability' assessment. If its involvement in the study is then jointly agreed, arrangements are put in place to fulfil its requirements. The final step is confirmation that it can proceed. For non-commercial studies, the Health Research Authority is trialling 'schedule of events' and 'statement of activities' template documents for submission through the Integrated Research Application System, which are intended to clarify the resource requirements and cost implications for each site. Costs for activities are recorded in line with the Department of Health attributing the costs of health and social care research and development (AcoRD) guidelines (*Figure 4*).

Before the introduction of the Health Research Authority Approval system it was possible for certain studies in England to request NHS permission through the National Institute for Health Research Coordinated System for gaining NHS permission. This service was provided by the National Institute for Health Research Clinical

Research Network, as part of its remit to support high quality research studies (www.crn.nihr.ac.uk). This role has been taken over by the Health Research Authority, but those studies adopted by the Clinical Research Network continue to be eligible for extra practical support through the National Institute for Health Research (*Figure 5*).

Obstacles to approval

The UK has become a less attractive location for conducting clinical research, with evidence of a significant fall in the number of clinical trials undertaken. This has been largely attributed to difficulties in navigating processes for regulatory approvals (Department for Business Innovation and Skills, 2011). Excessively complex legislation, over-stringent and inconsistent interpretation of regulations and inadequate support of research are among the key obstacles identified. In response to these concerns, changes in regulatory mechanisms are being implemented.

Obtaining NHS permission

It is widely agreed that obtaining NHS permission has been one of the greatest obstacles to conducting a clinical trial in the UK (House of Commons Science and Technology Committee, 2013), and widely reported as an important source of delay for multicentre study set-up (Al-Shahi, 2005; Mallick and O'Callaghan, 2009; Rees and Wells, 2010; Thompson and France, 2010; Snooks et al, 2012). This is partly attributed to a cumbersome system of duplicate applications to every participating site, each with its own internal arrangements for approving research. The requirements are not always transparent and applications can take a significant length of time to process.

England, Scotland, Wales and Northern Ireland have developed separate coordinated systems designed to improve the process of gaining NHS permission, especially across multiple sites. In England, the Health Research Authority has taken on the responsibility of providing a single sign-off for NHS centres participating in health research studies.

The National Institute for Health Research now publishes outcome data for clinical trials, which include a 70-day timeline from receipt of a valid research application to recruitment of the first patient.

Research culture within the NHS

Clinical research in the UK would benefit from a culture change, ensuring research is treated as a 'core activity' within the NHS (Cancer Research UK, 2010). Resistance and apathy towards research in the NHS can jeopardize the entire research process from project approvals to study completion. Obstacles can arise in many areas including concerns about research costs or cost recovery and diversion of resources and staff time. Other factors include a lack of understanding of research processes and benefits, mistrust of research, with a paternalistic approach discouraging patient involvement, and simply lack of incentive to support research projects. Some researchers also struggle with lack of expertise and inadequate training in navigating the approval process, further compounding problems achieving project sign-off.

Figure 4. Attributing the costs of health and social care research and development (AcoRD).

The AcoRD guidance 'provides a framework for the NHS and its partners to identify, attribute and recover the various costs of research in the NHS'. It applies only to England.

NHS costs for clinical studies are divided into research, support and treatment costs. Details are in the AcoRD document published by the Department of Health. This can be found at www.gov.uk/government/publications/guidance-on-attributing-the-costs-of-health-and-social-care-research

Figure 5. The National Institute for Health Research Clinical Research Network.

A study must be 'adopted' by the National Institute for Health Research Clinical Research Network Portfolio to be eligible for support. Researchers complete a Portfolio Adoption Form via the Integrated Research Application System for the study to be considered for adoption. Both commercial and non-commercial clinical research studies in England can apply for network support. Commercial studies apply through the 'Industry Application Gateway'.

Portfolio studies benefit from help in set-up and delivery of the study. This includes access to practical expertise, help with site identification and engagement, funding for research support posts and cover for other costs. Non-commercial studies receive financial support for NHS support costs.

Eligibility criteria for National Institute for Health Research Clinical Research Network support are published on the National Institute for Health Research website at www.crn.nihr.ac.uk

The Secretary of State, clinical commissioning groups and NHS England are required under the Health and Social Care Act 2012 to promote research and the use of research evidence. NHS England's draft document: Research and Development Strategy 2013–2018 (NHS England, 2013) sets out aims and objectives to help achieve this. It is not entirely clear how the ambition to embed research into the health system will be realized and there is no quick fix. Addressing the bureaucratic obstacles, providing education and training, creating incentives to engage with research and encouraging involvement of patients and the public with research are important steps in the right direction.

The European Clinical Trials Directive

Introduction of the Directive 2001/20/EC (European Commission, 2001) for clinical trials of investigational medicinal products has compromised clinical research activity in the UK by increasing costs and administration and extending the time required for launching new trials (Science and Technology Committee, 2013). This has been exacerbated by gold plating of EU legislation in the UK. The directive, drafted by the European Commission and enforced in the UK from 2004, aimed to improve regulation across the European Union and is acknowledged to have had favourable impact on the ethical regulation of trials in Europe. The Clinical Trials Directive has since been revised in response to calls for more proportionate regulation, with largely positive reception.

KEY POINTS

- Significant preparation, time and support are required to set up a clinical research project.
- Overly complex processes for gaining research approval are compromising clinical research in the UK.
- Regulation should be proportionate to risk so that streamlining the approval process does not compromise ethical standards.
- Along with regulatory reforms, a culture change towards research and a greater understanding of research processes and benefits are required.

Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use (European Parliament and Council of the European Union, 2014) now replaces Directive 2001/20/EC. It includes the provision of a new EU portal and clinical trials database. The regulation will not be applied until the portal and database are independently assessed as being fully functional. At the time of writing this is predicted to be by the end of October 2018.

Conclusions

Health-care research regulation and governance in the UK is overly bureaucratic, complicated and confusing. These difficulties are recognized and there are ongoing efforts to streamline approval applications and improve support so that good clinical research can continue. Some progress has already been made, in particular for ethics approval application, which was once considered a significant bureaucratic stumbling block. Measures introduced in recent years include the introduction of 'multicentre' research ethics committees, removing the need for multiple duplicate applications, clear timelines for provision of a research ethics committee opinion, and introduction of the Integrated Research Application System. It is hoped that new measures such as the Health Research Authority Approval system will similarly improve the process of gaining NHS permission. It is clear that further work is needed. The various approvals processes should run in parallel and be overseen by suitably qualified and trained authorities who have an understanding of the regulatory, legal and technical aspects of the project. This would ensure greater consistency in approach, reduce unnecessary bureaucracy and help guide rather than hinder the researcher.

Checks and controls must exist in research but it is important to ensure that regulatory scrutiny is proportionate to risk. The challenge is to ensure that the protection of the rights of trial participants is prioritized while avoiding excessive bureaucracy. However, the drive to improve efficiency should enhance rather than compromise ethical standards. Patients and the public are let down by missed opportunities to participate in good research. It is also unethical to squander research funding, waste research time and ultimately fail to answer important clinical questions because of red tape and unnecessary constraints.

In addition to addressing excessive bureaucracy at national and local levels, a new culture in the NHS must be fostered that treats research as a core responsibility rather than simply a danger or a nuisance. **BJHM**

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