

Final Report: Efficient / innovative delivery of NIHR research

An International Trials Toolkit for use by NIHR Clinical Trial Researchers to guide set-up and conduct of international surgical trials.

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Abstract

Increasingly clinical trials research needs to adapt to the changing health environment as we move to personalised health approaches, a greater awareness of the need to inform global health and to address generalisability across cultures and health service structures. This leads to the requirement for international collaboration in clinical trial conduct. International trial conduct is however more complex which can cause significant time delays, hinder efficient delivery and hence delay the potential for patient benefit.

The Clinical Trials Research Unit (CTRU) at the University of Leeds, UK, has experience of running a number of international surgical trials, all of which faced varying and complex challenges during set-up and implementation resulting in significant delays to timelines. With these issues in mind, the CTRU successfully bid for funding from a call issued by the UK's National Institute for Clinical Research (NIHR) which focussed on supporting efficient/innovative delivery of clinical trials. The funding enabled the development of an international trials toolkit for use by UK researchers, to guide the efficient set-up and conduct of international surgical trials and therefore improve the delivery of research.

This project was led by the Leeds CTRU, in collaboration with Clinical Trials and Evaluation Unit (CTEU) Bristol and the Birmingham Clinical Trials Unit (BCTU) at the University of Birmingham, and brought together expertise from other UK based clinical trials units with experience of running international surgical trials. The toolkit content is based on the obstacles and successes encountered by these CTUs in coordinating and delivering international trial collaborations from the UK.

The final toolkit can be found at the following webpage: <https://internationaltrialstoolkit.co.uk/> and includes suggested collaborative models for trials running on an international level, case studies, links to existing resources and key areas for considerations. Areas for considerations covers sponsorship, finance, contracts, insurance, research governance, protocol, monitoring, trial supplies, data collection, sample collection, health economics/PROMS and data ownership/publication. Each section also covers different models of working along with key issues and practical advice on how to approach the difficulties that currently hinder the delivery of international surgical trial research.

Introduction

Increasingly clinical trials research needs to adapt to the changing health environment as we move to personalised health approaches, a greater awareness of the need to inform global health and to address generalisability across cultures and health service structures. This leads to the requirement for international collaboration in clinical trial conduct. International trial conduct is however more complex which can cause significant time delays, hinder efficient delivery and hence delay the potential for patient benefit.

Currently in the UK there is limited experience of successfully extending recruitment of trials internationally. In trials where this has been attempted there are often long timelines for set-up and time to first patient recruited from international sites.

The Clinical Trials Research Unit (CTRU) at the University of Leeds, UK, has experience of running a number of international surgical trials, all of which faced varying and complex challenges during set-up and implementation resulting in significant delays to timelines. With these issues in mind, the CTRU successfully bid for funding from a call issued by the UK's National Institute for Clinical Research (NIHR) which focussed on supporting efficient/innovative delivery of clinical trials. The project aimed to unlock the potential of international collaboration to provide efficient, faster delivery of patient benefit by developing an International Trials Toolkit for use by NIHR Clinical Trial Researchers to guide set-up and conduct of international surgical trials.

The International Surgical Trials Toolkit was developed based on the combined experience of successful international trial collaborations (e.g. NIHR ROLARR, NIHR LAVA, NIHR INTACT, Star-trec, Rocs, Basil-2, Foxtrot) and extensive international networks (American College of Surgeons, Australian College of Surgeons, IDEAL Collaboration) within the Royal College of Surgeons Clinical Trials Centres (Leeds, Birmingham, Bristol, Oxford, Liverpool/Manchester, London and York CTUs). The project was led by the Leeds CTRU at the University of Leeds, in collaboration with Clinical Trials and Evaluation Unit (CTEU) Bristol and the Birmingham Clinical Trials Unit (BCTU) at the University of Birmingham.

This toolkit aims to share the lessons learnt from previous trials in order that international trials can be set up and coordinated in a more timely fashion so reducing cost of international trials, reducing delays in delivery and hence enabling results to impact patients in a more timely fashion.

Methods

Design and Development

A working group was established comprising of key members of UK based surgical trials units and clinicians with experience of running international trials. The toolkit content is based on the obstacles and successes encountered by these surgical trials units in coordinating and delivering international trial collaborations from the UK (including both surgical and non-surgical clinical trials. This working group met face to face at three meetings and developed ideas for subjects to include within the website. A smaller more focused core working group, comprised of members from the Leeds CTRU at the University of Leeds, the Clinical Trials and Evaluation Unit (CTEU) Bristol and the Birmingham Clinical Trials Unit (BCTU) at the University of Birmingham, were responsible for developing the content for each section, drawing upon previous experience, and utilising the knowledge of local contacts with relevant expertise e.g health economists, insurance brokers, sponsor representatives. The core working group had regular meetings and teleconferences to keep each member updated with timelines and to obtain additional input/feedback as required. The Information Systems team at the CTRU at the University of Leeds were responsible for the technical development of the webpage.

Review

The initial draft of the toolkit was initially presented the Royal College of Surgeons Surgical Trials Centre Directors meeting on 27th November 2018 which is attended by key members of each Royal College of Surgeons Surgical Trials Centres (Leeds, Birmingham, Bristol, Oxford, Liverpool/Manchester, London and York) as well as surgical speciality leads and associate surgical speciality leads. The toolkit was well received and resulted in feedback and additional content identified. The toolkit underwent amendments based on this feedback and was circulated to key stakeholders e.g. the wider working group and local groups with expertise e.g Leeds Surgical Trials Centre Steering Group for consultation at the beginning of 2019 resulting in further amendments. The finalised toolkit was presented again at the following Royal College of Surgeons Surgical Trials Centre Directors meeting on 13th March 2019.

Content

The toolkit is comprised of 5 sections:

- 1) Collaboration models
- 2) Considerations
- 3) Case Studies
- 4) Resources
- 5) Feedback

Figure 1 shows the homepage of the International Surgical Trials Toolkit. All sections can be accessed from the dropdown menu at the top of the screen, with the three

main areas (collaboration models, considerations, case studies) having additional buttons linking to these sections.

➤ *Collaboration models*

Three main models of working for surgical trials involving international recruitment are included:

- Model 1: One host institution/sponsor within the UK responsible for co-ordinating the trial and co-ordinating both UK and international research sites
- Model 2: One host institution/sponsor within the UK responsible for co-ordinating the trial and co-ordinating UK sites only. Use of a local spoke/CRO/lead site to co-ordinate international sites.
- Model 3: The same or very similar protocols. Two or more host institutions each responsible for co-ordinating the trial and sites locally, feeding into a single trial analysis

The collaboration model section of the International Surgical Trials Toolkit (figure 2) acts as an overview of the models of working, the advantages and disadvantages of each and key points for considerations with links to the relevant sections of the website.

➤ *Considerations*

The working group identified 12 key areas that were felt to require thorough consideration when designing and implementing a surgical clinical trial involving international recruitment. These 12 key areas relate to areas felt to be integral to the successful delivery of trial (e.g. protocol, data collection), areas likely to cause delays to timelines (e.g. contracts, establishing adequate insurance arrangements) and areas which may require different arrangements as compared to a trial recruiting solely in the UK (e.g. research governance, finance). Each of the 12 key areas also covers different models of working along with key issues and practical advice on how to approach the difficulties that currently hinder the delivery of international surgical trial research. The 12 key areas of considerations can be accessed from the dropdown menu at the top of the page, or on the Consideration page which has quick click icons for each area (figure 3). To break up the amount of information included on the website, and to make this more user friendly, each section makes use of diagrams, tabs, and drop down menus (figures 4&5).

➤ *Case studies*

Case studies of surgical clinical trials being led from the UK that involved international recruitment are included on the website (figure 6).

Each case study contains the following information:

- Summary of the trial
- Reason international recruitment was required
- Countries involved
- Arrangements for each of the 12 key areas for considerations
- Obstacles encountered

An example of a case study is shown in figure 7.

➤ *Resources*

Links to existing relevant resources have been included on the website e.g. information relating to country specific research governance, legislation and guidance for planning projects

➤ *Feedback*

The feedback section enables website users to submit any feedback or suggestions, which can then be used to update the website.

Results and Conclusion

The toolkit, which can be found at <https://internationaltrialstoolkit.co.uk/>, provides an accessible, coherent and comprehensive source of information and guidance for the set-up and delivery of international surgery trials. This is a much needed resource for UK surgical investigators needing to navigate options and processes for setting up international studies. In the long term, this will also provide a more streamlined and efficient approach to delivering international surgical trials for funders.

Dissemination

The International Surgical Trials Toolkit can be accessed at the following webpage address: <https://internationaltrialstoolkit.co.uk/>

The International Surgical Trials Toolkit webpage was made live on 20th May 2019 to coincide with International Clinical Trials Day and promoted via news pages and Twitter accounts of involved clinical trial units. Information relating to the toolkit has been sent to the Royal College of Surgeons Surgical Trials Centre network and the MRC Regulatory Support Centre for further dissemination.

The International Surgical Trials Toolkit was presented at the Society of Clinical Trials Annual Meeting in New Orleans (20th-22nd May 2019), with a plan for further presentation at the International Clinical Trials Methodology Conference in October 2019 and the IDEAL (Idea, Development, Exploration, Assessment, long-term Follow-up, Improving the Quality of Research in Surgery) Conference early 2020.

Future dissemination plans include a paper in a clinical trials journal, additional presentations and sharing of this resource with the Australian and American Colleges of Surgery are being discussed with the working group and the Royal College of Surgeons Surgical Trials Centre network.

Acknowledgements

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Contribution of Authors

Julie Croft, Head of Trial Management (with experience in the design and implementation of international surgical trials), acted as the main project manager and responsible for overall co-ordination of the project in addition to writing and review of the content for the website.

Helen Howard, Head of Trial Management (with expertise in surgical clinical trials management) was a member of the core working group and reviewed content for the website.

Lucy Culliford, Research Fellow (with expertise in surgical and international clinical trials), was a member of the core working group and developed and reviewed content for the website.

Laura Magill, Senior Lecturer in Clinical Trials (with expertise in surgical and international clinical trials management), was a member of the core working group and both developed and reviewed content for the website.

Dmitri Nepogodiev, Doctoral Research Fellow (with expertise in surgical and international clinical trials), was a member of the core working group and both developed and reviewed content for the website.

Deborah Stocken, Divisional Director (with expertise in medical statistics in clinical trial design), input into the design of the toolkit and reviewed content for the website.

Vicky Napp, Operations Director (with expertise in clinical trial management), input into the design of the toolkit and reviewed content for the website.

Gill Booth, Operations Director (with expertise in quality assurance and clinical trial management), input into the design of the toolkit and reviewed content for the website.

Julia Brown, Director of the Clinical Trials Research Unit (with expertise in medical statistics in clinical trials), input into the design of the toolkit and reviewed content for the website.

References

n/a

Appendices

Figure 1: Homepage of the International Surgical Trials Toolkit

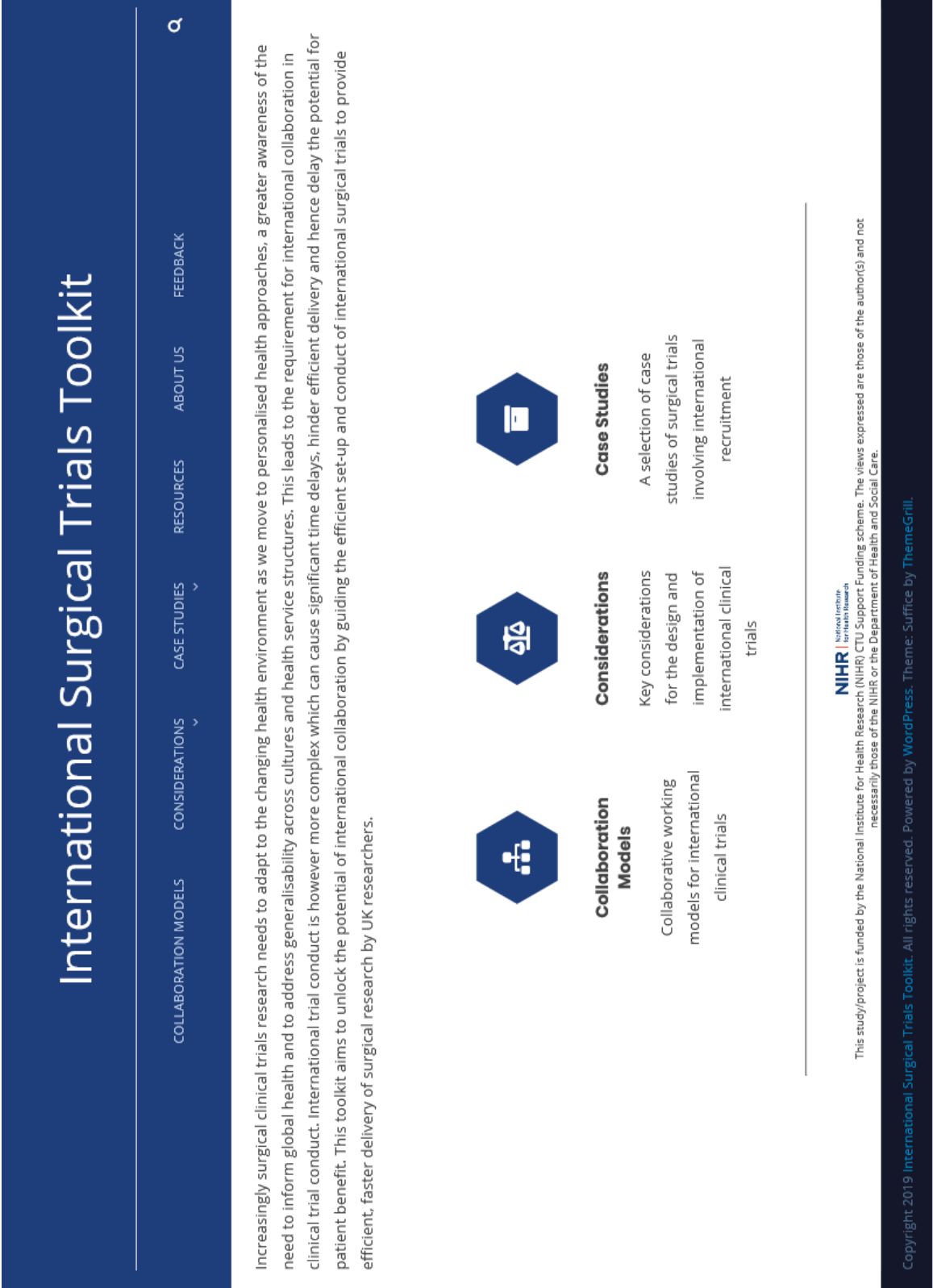


Figure 2: Collaboration section of the International Surgical Trials Toolkit

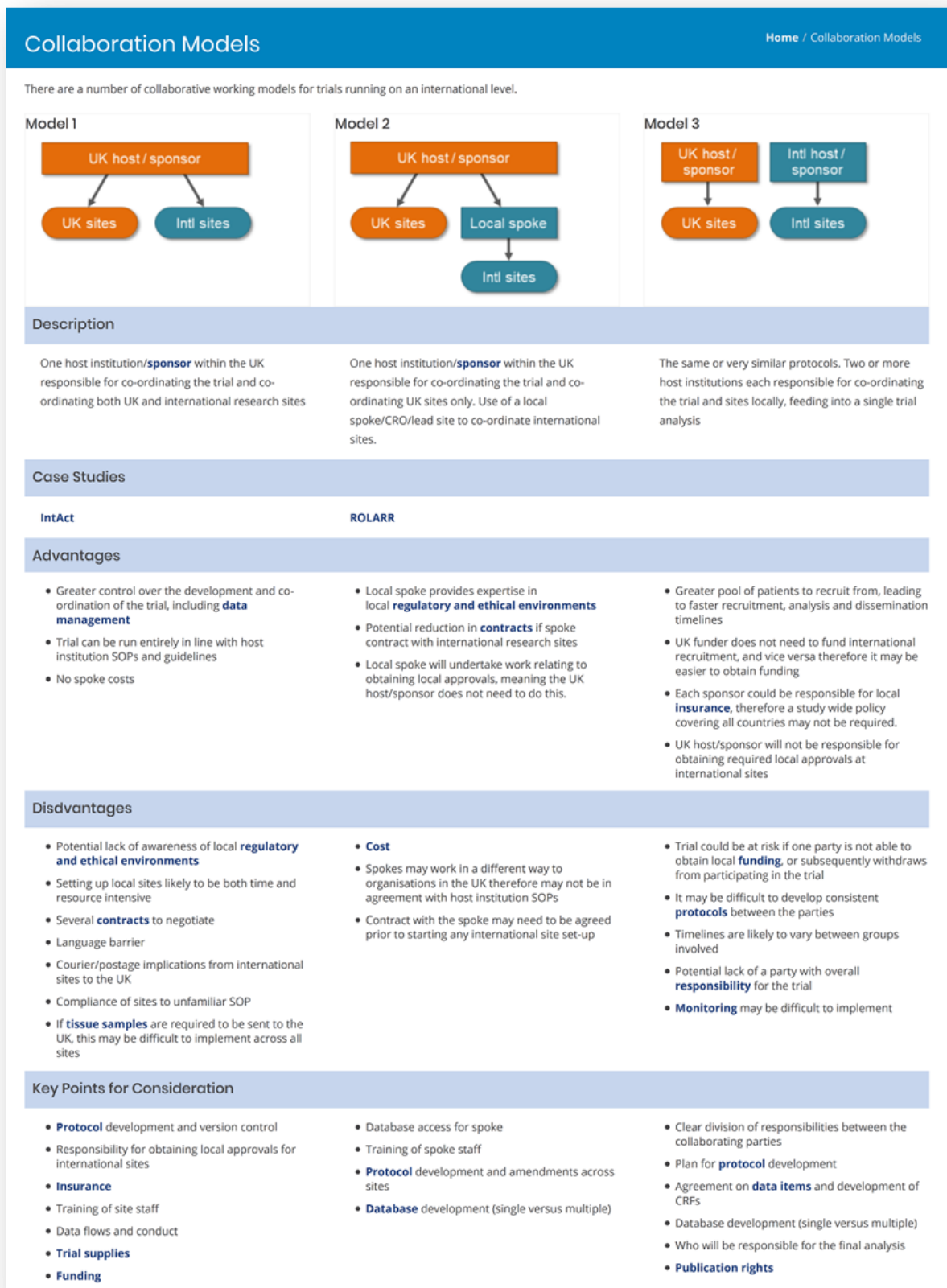


Figure 3: Key consideration icons

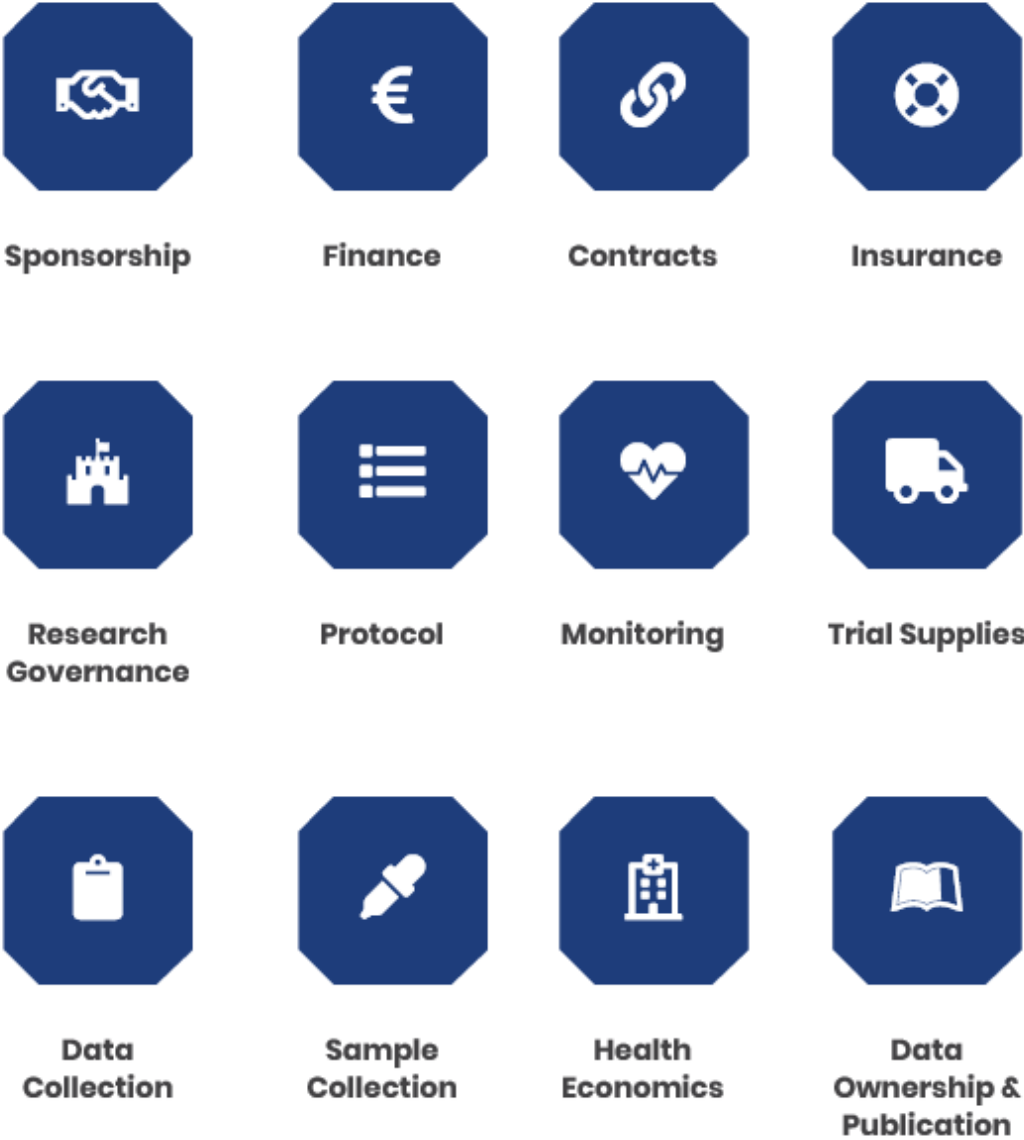


Figure 4: Layout of the Contracts section as one of the 12 key areas of considerations.

Contracts
Home / Considerations / Contracts

Unlike in the UK, where there is a standard model non-commercial agreement (mNCA) that can be used between non-commercial sponsors and participating NHS sites, a research agreement will need to be developed to put in place between the sponsor and participating international sites. Differing healthcare systems, national & local legislation and organisational arrangements can lead to long periods of contract negotiation which can adversely affect trial timelines. Different time zones and potentially language barriers can mean that even simple queries can take a while to resolve. Sponsors may choose to contract directly with all research sites, or may choose to sub-contract this responsibility to a spoke/lead site.

Sponsor ↔ Site
Sponsor ↔ Spoke ↔ Site

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graph TD
    A[UK host / sponsor] --> B[UK sites]
    A --> C[Intl sites]
    
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The host institution/sponsor contracts with all international research sites.

Advantages

An advantage of the sponsor contracting with each research site is that there is greater control over the content of the individual research agreements, and to an extent, the time taken for these contracts to be reviewed. There also wouldn't be the need to finalise a spoke contract prior to starting contracting with individual research sites.

Disadvantages

Negotiation of research agreements for international sites has a significant impact on staff resource required to manage this in comparison to a trial being run in the UK alone, not only in time required but also level of seniority of staff to conduct these negotiations. This is particularly an issue when there are a number of international sites involved in the trial. It is recommended that this is taken into account when [costing a trial grant](#) to ensure appropriate staffing and timelines in relation to the number of contracts involved.

Legislation ▾

Template Contracts ▾

Key Areas for Disputes ▾

Financial Payments ▾

Figure 5: The Insurance section as one of the 12 key areas of considerations showing the use of banners and dropdown boxes.

Definitions Considerations Recommendations

Period of Insurance ^

The active insurance period will cover any events and consequent claims that occur within that period. The overall period of insurance cover required will depend on the nature of the trial e.g. if the trial is felt to be low risk, and the trial intervention is delivered soon after entry into the trial and the trial has a long follow-up period, active insurance cover may not be required for the full duration of trial follow-up. If an insurer is willing to link to period of active insurance cover to recruitment, this may provide some protection against future insurance costs should there be a need to extend the trial.

Extended reporting period

Claims can be made during the period of active insurance cover. An extended reporting period means claims can be brought for a set amount of time after the active cover has expired, providing the event occurred within the active reporting period. This can sometimes be provided at no additional cost, or may incur a small additional premium. This can be decided up front whether to take this out, or it may be that this is decided upon at the end of a trial using a risk based approach depending on the number of safety events observed within the trial.

Policy Options v

Evidence of Site Insurance ^

The requirement for local site insurance should be clearly detailed within the contract with international research sites. Will any further evidence of local site insurance be required in addition to this? If insurance policy documents are to be collected in, these will most likely be in a different language and therefore may require translating. Other options include creating an insurance declaration proforma to be completed by the local site in English confirming what level of insurance is in place, along with limits if required.


Funding of Trial Insurance v

Patient Information Sheets v

Figure 6: Case studies section of the International Surgical Trials Toolkit

Case Studies Home / Case Studies


A selection of case studies of surgical trials that have involved successful international trial collaborations/networks.



ROLARR

ROLARR
Robotic versus laparoscopic surgery for rectal cancer surgery.


A multi-centre trial comparing laparoscopic surgery against robotic-assisted laparoscopic surgery for rectal cancer, co-ordinated from the Clinical Trials Research Unit at the University of Leeds.



GLiSten
Intraoperative lymph node staging for stratified colon cancer surgery

GLiSten
Next Generation intraoperative Lymph node staging for Stratified colon cancer surgery – Developmental phase


A multi-centre CTIMP (Clinical Trial of an Investigational Medicinal Product) aiming to optimise the dose, and then evaluate, oral 5-ALA administration for intra-operative fluorescence diagnosis of metastatic lymph nodes in colon cancer, co-ordinated from the Clinical Trials Research Unit at the University of Leeds



LAVA
Liver resection surgery vs. thermal Ablation for colorectal liver metastases

LAVA
Next Generation intraoperative Lymph node staging for Stratified colon cancer surgery – Developmental phase


A multi-centre trial comparing the effectiveness and cost-effectiveness of thermal ablation versus liver resection surgery in high risk patients eligible for liver resection, co-ordinated from the Clinical Trials Research Unit at the University of Leeds with University College London as Sponsor.



IntAct
IFA to Prevent Anastomotic Leak in Rectal Cancer Surgery

IntAct
Intraoperative Fluorescence Angiography to Prevent Anastomotic Leak in Rectal Cancer Surgery


A non-CTIMP multicentre randomized controlled trial comparing surgery with IFA (intra-operative fluorescence angiography) against standard care (surgery with no IFA) to determine the effect on anastomotic leak in patients undergoing elective anterior resection for rectal cancer.



COMICS

COMICS
Conventional versus Minimally Invasive extra-corporeal circulation in patients undergoing Cardiac Surgery: a randomised controlled trial


A non-CTIMP multicentre randomised controlled trial comparing conventional heart-lung machines with miniaturised heart-lung machines in cardiac surgery.



VerDiCT

VerDiCT
Preoperative Volume Replacement vs. usual care in Diabetic patients having CABG surgery: a randomised controlled Trial


A CTIMP RCT that was running as a single centre in the UK, and due to logistical reasons was not recruiting to time and target.



FALCON
an RCT by the World Clinical Health Research Unit on Global Surgery

FALCON

A pragmatic multicentre factorial randomised controlled trial testing measures to reduce surgical site infection in low and middle income countries (LMICs).



UNIVERSITY OF BIRMINGHAM


BCTU
Birmingham Clinical Trials Unit

STAR-TREC


An international multicentre randomised, feasibility study comprising a 1:1:1 randomisation for eligible subjects with a small, clinically localised rectal cancer between; (a) conventional TME Surgery, (b) organ saving with Chemoradiotherapy ± transanal microsurgery and (b) Short course preoperative radiotherapy ± transanal microsurgery.

Figure 7: An example case study

ROLARR



A multi-centre trial comparing laparoscopic surgery against robotic-assisted laparoscopic surgery for rectal cancer. International sites were required as only a limited number of UK sites were able to perform robotic assisted laparoscopic surgery at the time of set-up.



Countries: Australia, Denmark, Finland, France, Germany, Italy, Singapore, South Korea, the United Kingdom and the United States

Sponsorship

The University of Leeds acted as sponsor for the trial, with co-ordination of the trial delegated to the Clinical Trials Research Unit at the University of Leeds.

Finance

The University of Leeds obtained funding for the trial as the host organisation. This included payments to facilitate delivery of the research at both UK and international sites, in addition to funding for a spoke units in the United States and Singapore

Contracts

The University of Leeds contracted with each participating research site, and with the spoke unit in the United States. Initially, it had been planned that the US spoke unit would contract with participating sites in the United States, however this was not possible due to delays in getting the US spoke unit contract signed off.

Insurance

The University of Leeds put in place insurance to legal liability for claims for injury arising from the Trial and where the University of Leeds was at fault e.g. due to an error in the protocol. International sites were responsible for ensuring appropriate insurance or indemnity for clinical negligence was in place in their respective country and in relation to their clinical activities related to the trial.

Research Governance

Participating international sites were contractually required to obtain required local approvals as per local regulations. Evidence of local approvals were collected prior to the site being opened to recruitment. International sites were responsible for local safety reporting as per local regulations.

Protocol

One single protocol was used for both UK and international sites. Pragmatic trial design, operative specifics were at the discretion of the operating surgeon.

Monitoring

No trial specific monitoring was planned for the trial given the pragmatic nature of the trial however the sponsor reserved the right to conduct triggered site monitoring visits should any concerns have arisen as a result of central monitoring processes.

Distribution of Trial Supplies

Participating sites had to have the ability to perform both trial interventions in order to be eligible to take part in the trial therefore no surgical equipment was provided for trial purposes. Electronic Investigator Site Files (ISF) were sent to international sites.

Data Collection

International sites, not including sites in the United States, sent completed Case Report Forms (CRF) directly to the Clinical Trials Research Unit at the University of Leeds. This data was then entered onto the trial database by dedicated data entry staff. Sites in the United States sent their completed Case Report Forms (CRF) to the US spoke unit. The co-ordinator at the US spoke unit then entered the data from US sites onto the trial database which was accessed over the internet.

Sample Collection

To enable a central pathological review, sites were required to send glass tissue slides or high quality digital slides scans to Leeds. If it was locally acceptable, patients were invited to donate additional tissue blocks for future research as an optional component of the trial. The trial budget covered shipping of tissue from sites to Leeds, and back to sites if they required the glass tissue slides to be returned.

Health Economics/PROMS

Validated translations of patient completed quality of life questionnaires were used where available and combined into a booklet for each required time point, along with translated instructions for completion. The questionnaires used numerical scales and tick boxes (rather than free text fields) and the translated questionnaire booklets were laid out in an identical manner to the UK to facilitate data entry at the Clinical Trials Research Unit. The health economic analysis was performed with a UK NHS perspective, using data collected from UK and US patients.

Data Ownership & Publication

All trial data was owned by the University of Leeds as host institution. Sites were not permitted to publish concerning their patients which was directly relevant to the questions posed in the trial until the first publication of the primary endpoint analysis. All collaborators were listed as contributors, with top recruiting investigators named as authors (subject to journal requirements).

Obstacles encountered

Significant unanticipated delays were experienced in set-up due to the wide variations in national and local legislation, and procedures at participating centres. This in turn had a negative effect on recruitment which ultimately led to a revised timelines and a funding extension application. Two key causes of these delays were difficulties in establishing appropriate insurance arrangements, and in finalising contracts with participating centres with differing health care systems and organisational arrangements. Obstacles also arose in obtaining translations, variance in local research support, the language barrier, time differences, transferring trial data/samples, unexpected centre costs, and changes in collaborating CTU arrangements. Various strategies to overcome these challenges including implementing a risk based process to check that sufficient resources and robust systems were in place to offer adequate participant compensation at centres where insurance arrangements were non-standard.

Conflict of interest declaration

No conflicts of interest to declare.