UKCRC Registered Clinical Trials Units

UKCRC Registered CTU Network
Report of survey of registered CTUs 2013
Efficient Trial Conduct Task and Finish Group

UK CLINICAL RESEARCH COLLABORATION

igniting our potential

Summary of conclusions and recommendations

- **Despite recent improvements in the research approvals process, there is still room for further improvement in the process for NHS R&D approvals**
  - *Recommend Executive Group consider how best to apply leverage for further improvement and reducing unnecessary bureaucracy*

- **Better training of site staff would help improve study conduct and efficiency**
  - *Concern this may get worse (at least initially) with reconfiguration of the networks*
  - *CTUs should develop ways to share knowledge about sites, and explore better ways of working together to support sites and provide site training*

- **Improve working relationships between CIs and CTUs**
  - *Develop guidance / training on the roles and responsibilities of a CI, the purpose, roles and responsibilities of CTUs, and good working practices between CI and a CTU*
  - *Consider developing a template agreement between CIs and CTUs setting out roles and responsibilities*
  - *Reinforce that realistic recruitment targets are vital for efficient planning and conduct*

- **Close liaison with NIHR Clinical Research Network, particularly with regard to performance management**
  - *Executive Group should review how best to input into setting of the High Level Objectives by NIHR*
  - *High Level Objectives should not just be focussed on recruitment*

- **Sharing good practice across CTUs would improve efficiency across the network**
  - *Systems should be developed to allow sharing knowledge of good / bad practice across CTUs*
  - *Support good practice by developing training across the CTUs network*
- **Better information is needed about how to improve the efficiency and quality of trial conduct**
  - *CTUs should be encouraged to conduct research to evaluate strategies to improve the efficiency of trial conduct*
  - *This would be facilitated by stronger links with the MRC methodology hubs*
  - *The network should consider developing strategies for rapid sharing of knowledge and experience across CTUs, and other key stakeholders*
- **Regular checks of the UKCRC registered CTU email lists would help ensure they are up to date and that all CTUs are represented.**
  - *Recommend review by UKCRC secretariat*

Objectives

The aim of this survey was to identify inefficiencies during the two key stages of the trial conduct life cycle:

(i) from grant award to first patient
(ii) from first patient to publication

Methods

The survey was developed by the Efficient Trial Conduct Task and Finish Group. Following discussion, it was agreed the two key timeframes for inefficiencies were from grant award to recruitment of the first patient, and from recruitment of the first patient to publication of results. The aim was to keep the survey simple and easy to complete, and to seek responses from a wide range of job roles within the network.

The survey was constructed in SurveyMonkey (Annexe 1). Following discussion at the CTU directors meeting, it was agreed to send the survey to all email lists, with the exception of CTU directors as this list was overloaded with surveys at the time. A link to the survey was sent to the following registered CTU email distribution lists on 24 May 2013, with an email reminder after two weeks:

- Quality Assurance
- Information Systems
- Statistics
- Trial Managers
- Pharmacovigilance

Table 1: CTUs with at least one response

- Birmingham Clinical Trials Unit
- Bristol Randomised Trials Collaboration
- Cambridge CTU
- Cancer Research UK Clinical Trials Unit (CRCTU)
- CHaRT, Aberdeen
- CTEU Bristol
- Edinburgh Clinical Trials Unit
- ICR-CTSU
- Intensive Care National Audit & Research Centre
- Keele Primary Care Musculoskeletal Trials Unit
- King's Clinical Trials Unit
- Leeds CTU
- Leicester CTU
- MAHSC CTU
- Newcastle Clinical Trials Unit
- NI Clinical Research Support Centre
- OCTRU cancer stream
- PRIMENT CTU, University College London
- SEWTU
- Sheffield CTRU
- South East Wales Trials Unit
- TCTU
- Wales Cancer Trials Unit
- Warwick
- West Wales Organisation for Rigorous Trials in Health (WWORTH)

Results

Responses were received up to 1 July 2013. Overall, there were 43 respondents from 25 registered CTUs (Table 1). Multiple responses from different respondents within the same CTU were included in the analysis. Respondents were asked their job titles; one third reported being in trial management and a fifth were directors or senior management (Table 2).

Table 2: Job roles for respondents

	n=43	%
Trial Management	14	33%
Director / Senior Management	8	19%
Research / Programme Manager	6	14%
Statistician	5	12%
Quality Assurance	3	7%
IT/Programmer	2	5%
Other	5	12%

Responses to question:

"Between grant award and recruitment of the first patient, what do you think are the top three inefficiencies in trial conduct?"

R&D approvals were reported as a top inefficiency by 23 respondents (19%); contracts by 22 (18%), and other approvals by 13 (11%) (Figure 1). Site selection, feasibility and piloting at sites, and site training were also reported as inefficiencies. Issues at site level, in approvals and in site set up and training, were noted in many comments submitted (Annexe 2).

Responses to question:

"From recruitment of the first patient to publication of the trial results, what do you think are the top three inefficiencies in trial conduct?"

The clear front runner as the top inefficiency for this section was "recruitment targets not met / overestimation of predicted recruitment", reported by 19% of respondents (Figure 2). Data collection (including CRF design) was the next most common (11%), followed by writing up and submission for publication (9%). Delays with approvals remain a problem, as these now apply to new sites. Various aspects of planning were also reported as inefficiencies, including planning the patient pathway, study monitoring, and end of study planning.

Figure 1: Inefficiencies between grant award and recruitment of the first patient

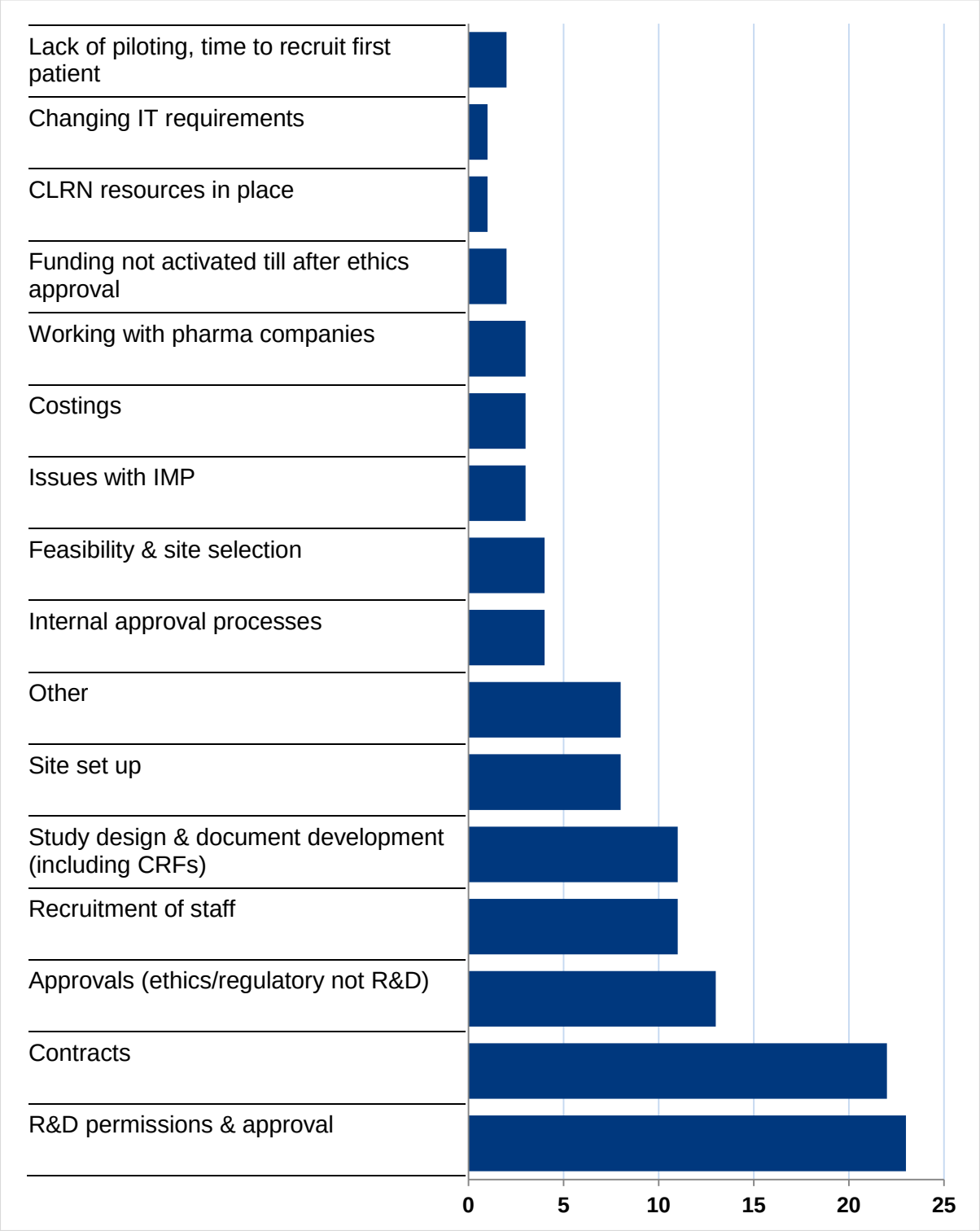
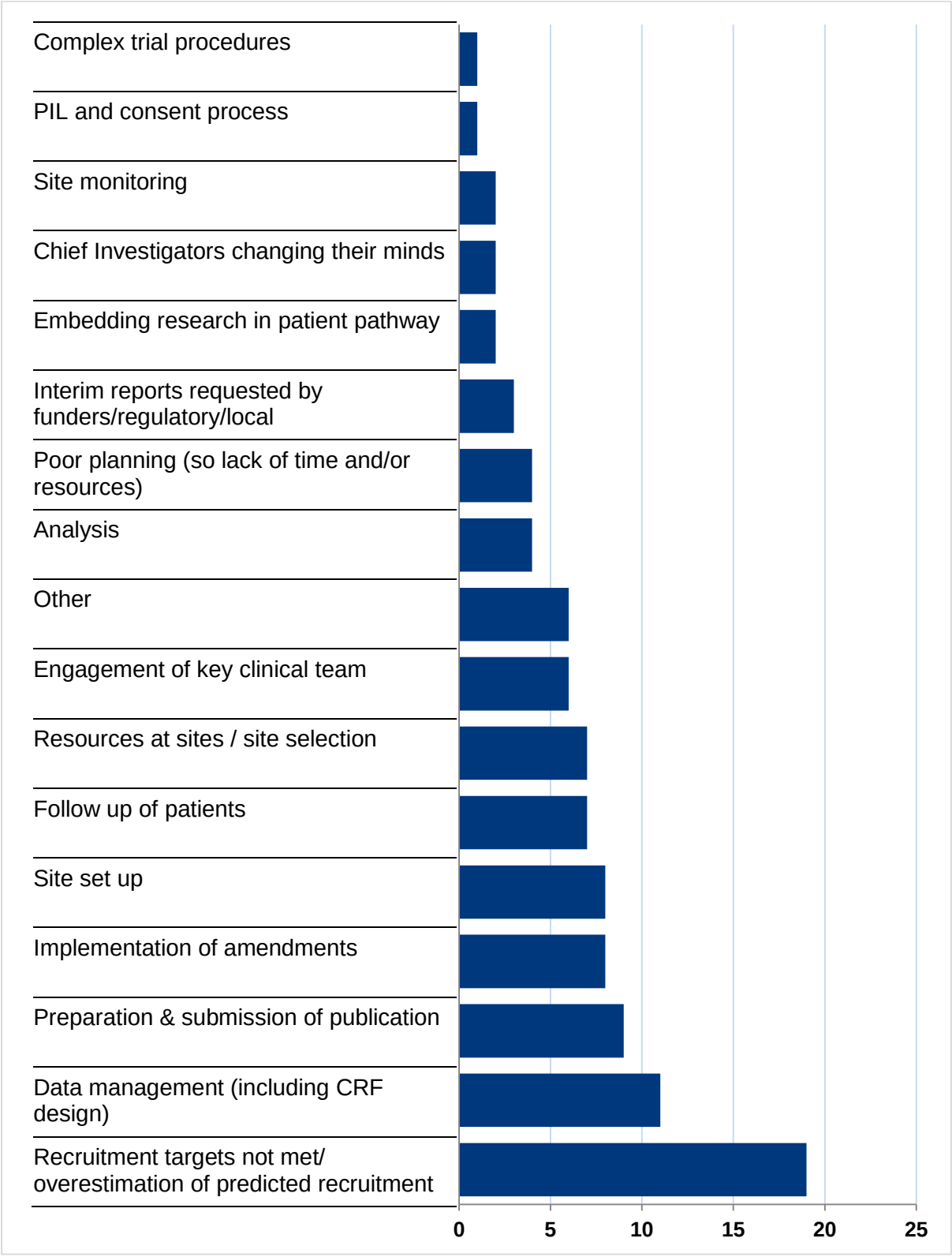


Figure 2: Inefficiencies between recruitment of the first patient and publication of trial results



Discussion

The response rate for the survey was lower than expected. Despite being circulated to several email lists thought to have a representative from each registered CTU, some CTUs appear not to have received notification of the survey (personal communication). Nevertheless, despite this low response rate, responses were received from a wide range of job roles.

The top reported inefficiencies present no surprises; time to gain approvals, contract negotiations and poor recruitment. These are all well recognised as challenges to conducting trials efficiently. Some issues reported are outside the control of either individual CTUs or the CTUs network, such as delays with approvals and contracts, CLRN resources being in place, and funding not being activated until after ethics approval. Other issues that emerged offer some insight into a range of problems facing CTUs. Many concerns identified relate to planning (such as piloting, feasibility, site selection, site set up, and planning of recruitment and study conduct), whilst other relate to study design, both in study set up and delivery (such as document development, complex trial procedures, patient information and consent process, and embedding research in the patient pathway).

Time to gain NHS R&D approvals

Despite recent improvements in the research approvals processes with the implementation of IRAS and CSP, delays during set up and recruitment phases remain a problem. The frustration for CTUs is that the issues leading to delays at sites are usually beyond their control. Continuing to push for improvements in the NHS R&D approvals process should be a priority for the network, as this is likely to have more influence than any individual CTU. The Executive Group could consider how best to apply leverage for further improvement, potentially through developing stronger links with the Health Research Authority.

Time to complete contract negotiations

Delays in contract negotiation are also often outside the influence of an individual CTU. The delays include contracts between funder and sponsor, contract with the CTU, and subcontracting by the sponsor.

Poor recruitment

Meeting recruitment targets is a key challenge for all trials. Responses in this survey offer some insights into the wide range of factors that can contribute to poor recruitment, and to their potential solutions. For example: setting realistic targets for sites using information from the site and/or network, collecting appropriate feasibility data on the target population, making better informed decisions about site selection, checking for competing trials, and better engagement by the Chief Investigator. Prompt recognition of problems with recruitment will facilitate planning and prompt remedial action.

Other issues

Once approvals are in place, delays across a range of other activities are reported; these include developing the supporting documents, such as CRFs, and the database. Working with pharmaceutical companies and issues around the IMP were also reported as inefficiencies during set-up; although these were not reported by large numbers of respondents some CTUs do not take on CT-IMPS. Recruitment of staff both at the CTU and at sites is also an issue, although for some responses it is unclear which is being referred to. For those CTUs with little or no core support, any delay in recruitment of CTU staff after funding is approved is even more critical.

Some comments suggest poor communication and tension between the investigators and the CTU, and that these issues can lead to problems throughout the trial. For example, lack of appropriate feasibility, unrealistic recruitment targets, multiple changes to the CRF which then delays the database, lack of engagement leading to delays in site set up and responding to problems with recruitment, and delays in the final report writing and submission for publication.

Conclusions and recommendations for action

- **Despite recent improvements in the research approvals process, there is still room for further improvement in the process for NHS R&D approvals**
  - *Recommend Executive Group consider how best to apply leverage for further improvement and reducing unnecessary bureaucracy*
- **Better training of site staff would help improve study conduct and efficiency**
  - *Concern this may get worse (at least initially) with reconfiguration of the networks*
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- **Regular checks of the UKCRC registered CTU email lists would help ensure they are up to date and that all CTUs are represented.**
  - *Recommend review by UKCRC secretariat*

Acknowledgements

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Annexe 1: Survey

UKCRC Registered Clinical Trials Units

Efficient Trial Conduct Task and Finish Group

Survey of CTUs

The UKCRC Registered CTU Network would like to understand more about how to improve efficiency in trial conduct. To reduce inefficiency we need to know what the key inefficiencies are.

This survey is to ask CTU staff what they think are the top inefficiencies. The survey should take no more than 3-5 minutes to complete. Thank you for your help.

***1. CTU Name:**

***2. Your job title:**

3. Between grant award and recruitment of the first patient, what do you think are the top three inefficiencies in trial conduct?

1

2

3

4. If you would like to, please explain why you think these are so important?

5. From recruitment of the first patient to publication of the trial results, what do you think are the top three inefficiencies in trial conduct?

1

2

3

6. If you would like to, please explain why you think these are so important?

Thank you for your help.

Results of this survey will be circulated to registered CTUs.

Done

Annex 2: Inefficiencies between grant award and recruitment of the first patient

Original text	Coded category
Under-estimation of getting approvals in place (MHRA, Ethics and R&D)	Approvals (ethics/regulatory not R&D)
Time taken to obtain ethics and R&D approval	Approvals (ethics/regulatory not R&D)
Any internal approval	Approvals (ethics/regulatory not R&D)
Ethics review and approval	Approvals (ethics/regulatory not R&D)
Ethics review. There is a mix of people on ethics committees, some are highly experienced in research, some much less so. While this appears to tick the box on paper, it can in reality be highly inefficient. There have been cases where researchers need to explain why basic trial design elements such as a control group is being included, only to be given an unfavourable outcome due to including a control arm! Training for lay members is a need, and training to other non-research active members too.	Approvals (ethics/regulatory not R&D)
Regulatory approvals and frequent changes in processes	Approvals (ethics/regulatory not R&D)
gaining approvals Ethics & R&D - management of the process	Approvals (ethics/regulatory not R&D)
Gaining Ethics and R&D approvals	Approvals (ethics/regulatory not R&D)
getting approvals in place	Approvals (ethics/regulatory not R&D)
Getting approvals in place	Approvals (ethics/regulatory not R&D)
REC approval	Approvals (ethics/regulatory not R&D)
IRMER (where required)	Approvals (ethics/regulatory not R&D)
Local approvals	Approvals (ethics/regulatory not R&D)
Changing scope of IT requirements	Changing IT requirements
CLRN resources being in place	CLRN resources in place
Length of contract negotiations to activate award and be able to employ the necessary trial specific staff to set up trial	Contracts
Agreements between Sponsor and Site	Contracts
Contractual arrangements	Contracts
Contractual arrangements	Contracts
Contract agreements	Contracts

Original text	Coded category
Contract delays	Contracts
Contract negotiation	Contracts
Contract negotiations especially around the IP section	Contracts
Contracting between funders, lead institutions and CTUs	Contracts
Contracting with partners and suppliers for IMP study	Contracts
Contracts	Contracts
contracts	Contracts
Contracts	Contracts
Contracts	
Time taken to draw up contracts with sponsor	Contracts
Setting up sub-contracts/ external finincial contracts	Contracts
Site agreements (contract agreement and signatures)	Contracts
Contracts (lack of use of model contracts)	Contracts
Contracts and subcontracts	Contracts
Delays in contracts.	Contracts
Getting contracts in place	Contracts
Contracts taking excessive time to agree between funders/sponsor, and sponsor/subcontractors	Contracts
formal agreement from clinical sites	Contracts
Securing Excess Treatment Costs and Service Support Costs	Costings
Agreeing attribution of costs and clrn support	Costings
Duplicated NHS cost applications (SSCs and ETCs), each area has different processes and local requirements creating lots of unnecessary effort	Costings
Poor assessment of feasibility by participating sites (including potential evaluable patients)	Feasibility & site selection
Site selection, training and initiation - availability of essential documentation	Feasibility & site selection
Robust feasibility of deliverability	Feasibility & site selection
Recruiting GP Practices to identify and recruit patients to a study	Feasibility & site selection
The NIHR making you apply for seed corn funding to	Funding not activated till after ethics

Original text	Coded category
get protcol and CRF development, done pre-ethics (again - pre-award because of the way they make us work - contra MRC and charities)	approval
Funding not activated until Ethics/MHRA approval	Funding not activated till after ethics approval
pharma companies	Issues with IMP / working with pharma
Pharma company completion	Issues with IMP / working with pharma
Pharmaceutical manufacturing	Issues with IMP / working with pharma
Compliant IMP development	Issues with IMP / working with pharma
Delays caused by Pharma not providing required docs	Issues with IMP / working with pharma
Unforeseen issues with IMP sourcing (for CTIMPs)	Issues with IMP / working with pharma
Chasing signatories for service level agreements, SSI and R&D forms in an ever changing NHS management structure	Internal approval processes
Gaining approval from support departments (at this site)	Internal approval processes
MPE assessment delays	Internal approval processes
No piloting	Lack of piloting
r & d process	R&D permissions & approval
R&D	R&D permissions & approval
R&D (incl. approval, site agreements & research passport approval	R&D permissions & approval
R&D approval	R&D permissions & approval
R&D approval	R&D permissions & approval
R&D approval (including site agreements)	R&D permissions & approval
R&D approval delays	R&D permissions & approval
R&D approval process (at other sites) and delayed initiation	R&D permissions & approval
R&D approval/ signed CTSA delays	R&D permissions & approval
R&D approvals	R&D permissions & approval
R&D approvals process not being harmonised across the UK	R&D permissions & approval
R&D approvals. No one believes its getting better - the trusts are clearly gaming it by starting and stopping the clock when they feel like it.	R&D permissions & approval
R&D delays	R&D permissions & approval

Original text	Coded category
R&D hold ups	R&D permissions & approval
R&Ds individual requirements for what should by a standardised process for R&D approval	R&D permissions & approval
Gaining NHS R&D permissions	R&D permissions & approval
Access to trial documentation through CSP	R&D permissions & approval
Gaining r&d permissions	R&D permissions & approval
site approvals	R&D permissions & approval
Time taken to gain R+D approval	R&D permissions & approval
Research Governance Approval	R&D permissions & approval
Research governance approvals	R&D permissions & approval
NHS R&D Permissions/approvals	R&D permissions & approval
Getting staff in place	Recruitment of staff
Lack of support for getting trial underway as no staff yet	Recruitment of staff
recruitment of staff	Recruitment of staff
Resultant delays in staff recruitment	Recruitment of staff
Delays in recruiting staff due to not receiving award prior to ethics approvals.	Recruitment of staff
Time taken to recruit trial staff	Recruitment of staff
staff recruitment - slow process	Recruitment of staff
Staffing (employing study staff & gaining RN support)	Recruitment of staff
Time taken to appoint staff onto the grant	Recruitment of staff
Timely appointment of excellent staff (as work is delayed without them)	Recruitment of staff
Unavailability of staff due to competing priorities	Recruitment of staff
Opening sites	Site set up
organising training (GCP and study specific)	Site set up
Take taken for site set-up	Site set up
Setting up new centres	Site set up
Training Clinical staff	Site set up
Time taken to train study staff in psychological interventions	Site set up
Time to set-up Centres can vary considerably between Trusts.	Site set up

Original text	Coded category
Having to explain over and over the same issues to new investigators and trial staff	Site set up
In multi-centre studies - agreement on data to be collected	Study design & document development (including CRFs)
Design of a robust CRF with adequate PI/nurse input	Study design & document development (including CRFs)
The NIHR not responding expeditiously when we respond to changes they demand to the design and costs, after conditionally awarding the grant subject to changes (I know - it's technically pre-award)	Study design & document development (including CRFs)
Documents being drafted quickly to get approvals, only to be amended later as not thought through fully	Study design & document development (including CRFs)
Creation of documentation for the study including CRFs.	Study design & document development (including CRFs)
User Acceptance of the eCRF	Study design & document development (including CRFs)
Writing of actual trial/study protocol for REC/MHRA- too many people involved and disagreements between investigators about the design etc..	Study design & document development (including CRFs)
Agreed & finalised paperwork, correct versions at all sites etc	Study design & document development (including CRFs)
Operationalising the protocol written to receive the grant award	Study design & document development (including CRFs)
Agreement on CRF	Study design & document development (including CRFs)
Getting the investigators to decide the real detail of exactly what they are doing	Study design & document development (including CRFs)
Time it takes to get first patient in study	Time to recruit first patient
Responsible staff allocation at sites for the study data	Other
Majority of tasks undertaken by the study coordinator	Other
Manual administrative tasks	Other
Non cohesive team	Other
Chief Investigators not allocating sufficient time and focus on trial	Other
Trial supplies (WRT to delay &/or obtaining, & availability	Other
No being prepared for a positive response (award of grant)	Other
Highly paid staff undertaking non-specialist tasks	Other

Annexe 3: Comments on the top three inefficiencies between grant award and recruiting the first patient

[inefficiencies listed in the survey quoted in square brackets]

Contractual arrangements " negotiating the main funding contract, sub-contracts with collaborators, site agreements etc. Agreeing across the NHS, HEIs and NIHR has been very time consuming, especially since the NIHR/DH changed the terms of their standard contracts regarding Intellectual Property. Securing Excess Treatment Costs and Service Support Costs. A recent ETC application took more than 6 months to confirm funding, largely due to DH subvention negotiations between PCTs & DH. Regarding SSCs, there have been regional differences in interpretation of the SSC costing guidance, and the principle that SSCs approved by the lead CLRN will also be approved by CLRNs for other collaborating centres does not seem to operate in practice, leading to multiple negotiations across the country before sites can open. Gaining R&D permissions (especially in primary care). IRAS no longer allows duplication of SSI forms so, individual SSI forms must be created and populated (using cut and paste) with material duplicated in other SSI forms; and each separate SSI requires its own checklist. Following NHS reforms in 2013, CCGs or organisations hosting research in primary care have been given little guidance as to interpretation of responsibilities of research governance. Other factors mentioned include: sponsor organisations becoming more risk-averse and introducing greater checks and more resource-intensive processes; and the delay before funds are released by the funder until ethics and MHRA approvals are in place. [Contractual arrangements, Securing excess treatment costs, Gaining NHS R&D permissions]
Senior staff voted on what they considered to be the hold up in setting up their trials. Experienced staff recruitment and retention also an issue within our trials unit. [R&D delays, MPE assessment delays, Delays caused by Pharma not providing required docs]
Despite the mCTA site R&D offices still request changes to these and other contracts such as Material Transfer Agreements and if separate Financial Agreements - there is often delays with the review of these documents. Site initiation and training can be difficult as often site staff are not available and/or are lacking GCP training which causes delays to issuing start certificates. Once sent to the CLRN, sites are supposed to be able to access trial documentation on CSP. Sites often inform us that they can not access this and information needs to be sent out from the CTU which is duplication and takes up a lot of time and effort, if the purpose of CSP was to streamline the process. [Contract negotiation, Site selection, training and initiation - availability of essential documentation, Access to trial documentation through CSP]
This whole area has undergone a lot of improvement recently. Locally, the time taken for R&D approval has been dramatically reduced. However, getting approvals from the relevant support departments prior to submitting the R&D application can be a very frustrating process. Often the people responsible for signing the form have a clinical role and very little or no time for admin or paperwork. Departmental managers also tend to look at the inconvenience or cost of the trial to their department without weighing up any benefits against them and resulting negotiations to get their approval can be time consuming. It is well documented that R&D approval at sites can be very variable, but also sites aren't often ready to start even when they have got R&D approval. Hopefully the new NIHR 70 day

target will help with this. Many trusts have now adopted the model non-commercial agreement, but sometimes the nature of the study or relationship means this is not appropriate, subsequent contract negotiations are often very lengthy. [Gaining approval from support departments (at this site), R&D approval process (at other sites) and delayed initiation, Contract agreements]
Piloting essential to prevent issues cropping up at a later stage. [Non cohesive team, Agreed & finalised paperwork, correct versions at all sites etc, No piloting]
Unnecessary and complex bureaucracy slows things down without good reason [Gaining R&D permissions, Agreeing attribution of costs and CLRN support, Contracts and subcontracts]
I feel the main inefficiencies are the time taken at local sites to ensure that they are set up and in a position to recruit patients in a timely manner. There are often large delays in ensuring that the relevant approvals are in place and that the infrastructure is set-up prior to starting to enable recruitment. [CLRN resources being in place, R&D approval/ signed CTSA delays, Local infrastructure in place (set-up and training)]
Getting contracts arranged and signed off at Universities and Trust R&D departments is difficult. We had delays in sites putting in their SSIs due to new DoH metrics, this caused a backlog and delay in the way we work at the trials unit. [Contracts, Opening sites]
Our staff are grant funded so we often need to recruit to a new grant [Recruitment of staff]
Variations in time to set-up Centres may influence trial management plan. Some centres reset R&D approval clock so review time can be longer than guideline and target suggests. Trials unit work hard to work with Centres to ensure they are approved and recruiting to plan. [Time to set-up Centres can vary considerably between Trusts.]
I'm not sure why you are asking why they are important - that would seem obvious. [Poor assessment of feasibility by participating sites (including potential evaluable patients), Ethics review and approval, R&D approval (including site agreements)]
People are reluctant to put too many hours into a project until they know that it is being funded. You may have confirmation of a site PI's involvement but they do don't have data collection staff on board or sometimes not in post. If a CRF is not practical to use at site then staff are reluctant to complete but don't give their input before the final version is approved. [Time it takes to get first patient in study, Responsible staff allocation at sites for the study data, Design of a robust CRF with adequate PI/nurse input]

1. Investigators are very good at big ideas and big picture issues, but generally terrible when you get to the level of detail required to create a database, set up appropriate queries, write the SAP, create the data collection forms, etc etc. Without the detail, you can end up with trials that aren't actually measuring the primary outcome, and many other fundamental errors. 2. There is too much red tape in setting up new centres, particularly in other countries 3. I seem to spend a lot of my life explaining that patients should be followed up regardless of compliance, and other issues. It's a shame everyone isn't taught the basics of trial methods at university. [Getting the investigators to decide the real detail of exactly what they are doing, Setting up new centres, Having to explain over and over the same issues to new investigators and trial staff]
The time between submission of the grant and the response is often substantial (a few months), but they may pass quite quickly. At least some steps (in particular: invitation to trial initiation meeting, planning of data base & CRF initiation, planning the schedule of initiation of centres) should be taken during the waiting time. These activities could often be cancelled much easier in case of a negative response that set-up late following a positive response. [Not being prepared for a positive response (award of grant)]
The writing process to obtain the grant award does not always consider the difficulties associated with operationalising the study, and hence time taken with setting-up the site, not to mention obtaining ethics and R&D approval. [Operationalising the protocol written to receive the grant award, Time taken to obtain ethics and R&D approval, Take taken for site set-up]
Contracting is a major issue as each organisation is different and the template agreements do not reduce risk or lock agreements down enough. R&D approvals are devolved and all work differently between England, Scotland and Wales. This means you never know what to expect in way of response to any R&D approvals. Some R&D offices take longer to respond whilst they wait for more established R&D offices to respond first. Other R&D offices require far too much information and walking through each item submitted. Some R&D offices undertake their own Risk Assessment meetings even for non-substantial notifications. [Contracting with partners and suppliers for IMP study, R&D approvals process not being harmonised across the UK, Creation of documentation for the study including CRFs.]
Substantial work ideally involving the Trial coordinator needs to be done prior to ethical approval - when the funding is contingent on having that approval, appointing staff is an issue as they are needed 2-3 months prior to ethics and may not be in post until 3 - 6 months after approval has been given. [Delays in recruiting staff due to not receiving award prior to ethics approvals., R&Ds individual requirements for what should by a standardised proccess for R&D approval, Delays in contracts.]
All of these are rate-limiting factors and delay trial set-up. [Robust feasibility of deliverability, Under-estimation of getting approvals in place (MHRA, Ethics and R&D), Chief Investigators not allocating sufficient time and focus on trial]
I hope this is anonymous! The barriers the NIHR themselves put up to efficient research

creates a constant sense of financial uncertainty and crisis in our unit, which receives very little core funding and wastes a lot of time on what should be unnecessary paperwork and admin. The NIHR frequently blame us for not making progress "pre-award" when actually it's their staff that are failing to get back to us expeditiously when the ball's in their court. However, the NIHR are like cows in India. You can't criticise what is clearly a ludicrous system compared to the MRC, which adds unnecessary work from the "War and Peace" outline application form through the comabative conditional award period though to the need for seedcorn funding to do tasks every study requires. Clearly, seedcorn funding is better than having to subsidise the activity from another project budget or CTU support funding, but the idea that doing the pre-ethics work should be subject to a separate application is insane. The R&D approvals - I don't need to explain do I? The R&D office staff have a tedious and miserable job, which they're rarely resourced or incentivised to do well. There is rarely continuity of care, if the person is part time (which they always are), on holiday (frequent) or sick (likely) you're application is stuck. As a result, recruitment is delayed, making the failure of the trial more likely as multiple "lessons learned" publications detail. [The NIHR not responding expeditiously when we respond to changes they demand to the design and costs, after conditionally awarding the grant subject to changes (I know - it's technically pre-award), The NIHR making you apply for seed corn funding to get protcol and CRF development, done pre-ethics (again - pre-award because of the way they make us work - contra MRC and charities), R&D approvals. No one believes its getting better - the trusts are clearly gaming it by starting and stopping the clock when they feel like it.]
In my experience these always delay trial start date [gaining approvals Ethics & R&D - management of the process, staff recruitment - slow process]
They delay the trial in general [Contract delays, R&D approval delays, Training Clinical staff]
Issue when no core funding is in place to provide some core staff who can start projects before the trial specific coordinators or trial managers are in post, funded by the actual grant. I would not divide the trial life cycle in these two sections; I would take 3 sections: say from is grant is active to FPFV; and then from FPFV to Last Patient very last visit as actual end of trial; and then from end of trial to publication. [Length of contract negotiations to activate award and be able to employ the necessary trial specific staff to set up trial, Writing of actual trial/study protocol for REC/MHRA- too many people involved and disagreements between investigators about the design etc.., Unforeseen issues with IMP sourcing (for CTIMPs)]

Annexe 4: Inefficiencies between recruitment of the first patient and publication of trial results

Original text	Coded category
Data collation and merging the various elements of the trial	Analysis
Analysis takes longer than predicted	Analysis
Not enough time given for robust analysis within timelines	Analysis
Analysis and discussions around this	Analysis
Trial procedures too complex/ inadequate training	Complex trial procedures
Having to correct CRFs and check missing data	Data management
Poor timing of data collection	Data management
Data query resolution after Last Patient Last Observed Value, before data lock	Data management
Missing or incorrect data - strategies for managing this efficiently throughout trial	Data management
Data input and data cleaning to ensure top quality data output	Data management
Paper-based data collection methodologies	Data management
Final clean data set for analysis: Data queries are not resolved in a timely manner from sites	Data management
Delays in data entry and cleaning prior to analysis	Data management
Timely data flow (related to site staff availability/turnover)	Data management
Data handling - very time consuming and reporting to various bodies takes even more resource.	Data management
Chasing of missing data at sites	Data management
problems with or changes in NHS patients pathway	Embedding research in patient pathway
Research not embedded into clinical practice	Embedding research in patient pathway
Minimal communication between clinicians, trial managers and statisticians during trial conduct	Engagement of key clinical team
Chief Investigators not allocating sufficient time and focus on trial	Engagement of key clinical team
PI not fully engaged	Engagement of key clinical team
Lost motivation from clinical staff	Engagement of key clinical team
keeping research staff engaged for long duration trials	Engagement of key clinical team

Original text	Coded category
Lack of engagement of key study team members	Engagement of key clinical team
Keeping up recruitment & follow up.	Follow up of patients
Inadequate patient follow up processes	Follow up of patients
Recruitment and retention	Follow up of patients
Mechanisms of following up participants e.g. questionnaires	Follow up of patients
Reducing attrition.	Follow up of patients
Participant retention - harder for longer term follow up, especially with only short-term treatment	Follow up of patients
Maintaining the importance of follow-up with patients	Follow up of patients
Number of Substantial Amendments	Implementation of amendments
Research Governance Approval (amendments)	Implementation of amendments
NHS R&D approval of amendments	Implementation of amendments
Making amendments	Implementation of amendments
Protocol amendments - implementation at sites	Implementation of amendments
Any internal approvals (amendments)	Implementation of amendments
Amendment times	Implementation of amendments
Time to approve and implement amendments to the protocol	Implementation of amendments
Interim reports for funders	Interim reports requested by funders/regulatory/local
reporting of similar information to different bodies at different times	Interim reports requested by funders/regulatory/local
Multiple reports to different agencies (ethics, RG, funders, sponsors etc),	Interim reports requested by funders/regulatory/local
Investigators changing their minds in what to collect	Investigators changing their minds
Investigators changing their minds in the detail of what is to be analysed	Investigators changing their minds
Excessive sponsor 'oversight' or local R&D input to CTIMPs, implementing processes which achieve little	Other
Change in staffing (staff turnover)	Other
Over officious R&D departments requiring information outside of their scope	Other
PI's persisting on publishing premature data	Other
Additional funding requirements	Other

Original text	Coded category
Maintaining experienced site staff and need for retraining of sites, including maintenance of essential documentation.	Other
PIS burden. I agree that patients need to be informed, but the level of detail required by ethics committees often seems overly burdensome as compared to usual practice of consenting to treatments - e.g. the information required to be shown before patient data is used by a researcher vs the information shown before invasive brain surgery as treatment. Needs a more reasonable take on proportional	PIL and consent process)
Not planning the end-of-trial phase or planning most tasks for the time when the last patient completed the trial (no front-loading)	Poor planning
not having clear guidelines how all trial functions need to interact during the time after "last patient last visit"	Poor planning
Ramifications of poor planning at grant application stage can result in drug supply issues/increased costs/interruptions to IMP supply, changes to eCRF system after study start, under-recruitment etc	Poor planning
Insufficient resource allocated to trial management/marketing of the trial	Poor planning
Finalising reporting of findings through peer review and editorial processes after trial funding has finished	Preparation & submission of publication
Finalising papers for publication in scientific journals	Preparation & submission of publication
journal reviewing time	Preparation & submission of publication
permissions from NIHR to submit paper for publication	Preparation & submission of publication
Publication bias- negative findings not published.	Preparation & submission of publication
Time/resource allocated to produce publication (which is after grant end)	Preparation & submission of publication
Writing up	Preparation & submission of publication
Writing the paper - getting everyone on board with this	Preparation & submission of publication
Grant had finished before trial has been completed and named Research Assistant/ or PostDoc not in place anymore to write paper- CI is last so to speak "last man standing"	Preparation & submission of publication
sample size miscalculation - leads to insufficient recruitment	Recruitment targets not met

Original text	Coded category
Recruitment rate lower than predicted	Recruitment targets not met/ overestimation of predicted recruitment
Poor recruitment	Recruitment targets not met/ overestimation of predicted recruitment
slow recruitment rates	Recruitment targets not met/ overestimation of predicted recruitment
recruitment over optimism	Recruitment targets not met/ overestimation of predicted recruitment
Over estimation of recruitment potential	Recruitment targets not met/ overestimation of predicted recruitment
Poor recruitment at sites (usually due to over estimation of number of evaluable patients by site PI)	Recruitment targets not met/ overestimation of predicted recruitment
slow recruitment issues	Recruitment targets not met/ overestimation of predicted recruitment
Inaccurate estimations of likely number of eligible patients per site	Recruitment targets not met/ overestimation of predicted recruitment
Time taken to recruit all participants	Recruitment targets not met/ overestimation of predicted recruitment
Recruitment methods - harder when only opportunistic	Recruitment targets not met/ overestimation of predicted recruitment
Failure to recruit - often because eligibility criteria are too tight and have to be widened	Recruitment targets not met/ overestimation of predicted recruitment
Recruitment target is usually too ambitious	Recruitment targets not met/ overestimation of predicted recruitment
Recruitment problems overall - delay in target time lines to complete recruitment	Recruitment targets not met/ overestimation of predicted recruitment
delays in recruitment	Recruitment targets not met/ overestimation of predicted recruitment
Centres not recruiting as expected	Recruitment targets not met/ overestimation of predicted recruitment

Original text	Coded category
Sites wildy over-estimating suitable patient availability.	Recruitment targets not met/ overestimation of predicted recruitment
Sites not delivering on their target recruitment	Recruitment targets not met/ overestimation of predicted recruitment
Accrual at sites	Recruitment targets not met/ overestimation of predicted recruitment
CLRN resources in place throughout the trial	Resources at sites
limited resource for recruitment at trial sites	Resources at sites
Clinicians not having time or adequate support	Resources at sites
Lack of research nurse time to identify patients.	Resources at sites
Under resourced trials. There is a pressure from funders to keep the costs down, which means in effect that trials are often run under resourced which limits staff time, and NHS staff input for recruitment activities	Resources at sites
Lack of staff resources	Resources at sites
Excessive site monitoring and too little implementation of statistical monitoring techniques	Site monitoring
Sponsors insisting on on-site monitoring	Site monitoring
Wasted efforts with poorly recruiting sites	Site selection, poorly performing sites)
Starting recruitment	Site set up
Research governance in adding new sites	Site set up
Site set up	Site set up
Delays in site set-up	Site set up
Obtaining study documentation from trial sites	Site set up
Sites not being set up on time leading to missed patients, particularly in studies into rare disease	Site set up
Getting contracts and approvals in place for new sites	Site set up
Setting up and obtaining approvals for new sites when recruitment is poor.	Site set up

Annex 5: Comments on the top three inefficiencies between recruiting the first patient and publication

[inefficiencies listed in the survey quoted in square brackets]

1. Revisions to the protocol requiring Substantial Amendments to ethics and MHRA for approval, possibly related to the difficulties in appointing a Trial Manager for the period of initial REC and MHRA submissions when the funds had yet to be released (therefore rushing to get a protocol approved so funds can be released, knowing it will need revision) 2. Interim reports to funders, especially when trials have pilot phase, can often be required frequently, and often very little information will have changed and uses valuable trial team resources. 3. Securing additional funding from other sources can be time consuming, or have limited opportunity e.g. nested studies, extra resource for studies [Number of Substantial Amendments, Interim reports for funders, Additional funding requirements]
As above. Clinician input into publications also an issue. [Recruitment rate lower than predicted, Delays in site set-up, Analysis takes longer than predicted]
We focus on surgical trials, and are unable to deviate from the standard NHS patient pathway. This means that any changes can alter how we recruit patients and our ability to do so, and who we can recruit. It can also impact on our ability to deliver the intervention. For instance, our Trust recently implemented a day of surgery admission policy - reducing the time we have to obtain informed consent and perform baseline measures, and preventing interventions that require an overnight stay prior to the operation. We are also hit my cancellations and patients being swapped to different surgeons when there are problems such as reduced bed capacity. Concerning point 2 - data such as recruitment has to be reported to our Trust, the NIHR portfolio and funding bodies. We also have to prepare regular reports through the year to different organisations such as REC, MHRA, and funders. Often the data required is similar but not the same. Point 3 - despite the MHRA's adoption of risk adapted trial management, some Sponsors will only accept on-site monitoring even if the trial concerned could be managed by central monitoring. [problems with or changes in NHS patients pathway, reporting of similar information to different bodies at different times, Sponsors insisting on on-site monitoring]
Negative findings harder to publish, less likely to be cited, therefore unnecessary studies are repeated, wasting more Â£, time, energy etc. [Keeping up recruitment & follow up., Reducing attrition., Publication bias- negative findings not published.]
The main inefficiencies that I see are around slow patient recruitment. The points around CLRN resources and research not being embedded into the clinical practice are especially an issue for us as we work in emergency care trials and having 24/7 screening is paramount to success as patients can come in at any time of day. Often sites are reliant upon a research nurse who is only available during office hours. We have also had a number of times when we have had to suspend sites who could not recruit patients when no research nurse was in place (moved jobs) and it may have taken 8-9 months to replace the nurse. [CLRN resources in place throughout the trial, CLRN resources in place throughout the trial, Time to

approve and implement amendments to the protocol]
Unless data collection is timely and accurate it makes for inefficient analysis. Increased pressure form funding bodies for annual reports etc. and timelines for interim and final reports and the added regulations on the processes required for data management have squeezed and squeezed the amount of time it is expected for statisticians to produce results of study. [Poor timing of data collection, PI's persisting on publishing premature data, Not enough time given for robust analysis within timelines]
1. This causes everyone time in re-programming and re-checking, and then the trial is a nightmare to analyse at the end. 2. Centres always overestimate what they can do. So you have to get extra centres, which is time-consuming. 3. Even if you have a detailed SAP, you frequently end up being asked for a lot of additional work at the analysis stage. And it all has to be done by tomorrow! [Investigators changing their minds in what to collect, Centres not recruiting as expected, Investigators changing their minds in the detail of what is to be analysed]
Again, planning ahead appears to be crucial to have the capacities available at the time when they are needed. This might be more difficult in trials which are driven by "time-to-event" trials, as the end date might have substantial variability. Therefore, regular trial meetings should be performed involving clinicians, trial managers and statisticians to understand the trial progress and any anomalies in the data. The statisticians should be given time to program analyses a few month before the end of the trial, and these (blinded) outputs should be reviewed thoroughly to clarify whether they meet the trial objectives and the expectations of the clinicians for publishing the results. It appears that most UK CTUs do not have a SOP for "data base lock", simply because the UKCRC registration does not require it. There are often function specific guidelines (e.g. site closure for trial management, data quality checks for data managers etc), while there is no SOP that details the interaction of all trial functions (the "big picture") at the end of the trial. An SOP would provide dedicated guidance, including check lists for a final team meeting and subsequent tasks (on all aspects like check of blinding, check of data completeness for primary data, patient allocation to ITT and per protocol populations, review of SAP and available result outputs, agreement on timelines for data base lock, review of unblinded results, drafting and finalisation of reports and publication and program validation steps etc) and would also help to manage expectations on the time point for the availability of the results. In a recent trial it was very helpful that the clinician had drafted a conference abstract before the data base was locked - this helped to prioritise the analyses steps and allowed to submit the abstract within less than two weeks after unblinding. [Minimal communication between clinicians, trial managers and statisticians during trial conduct, Not planning the end-of-trial phase or planning most tasks for the time when the last patient completed the trial (no front-loading), not having clear guidelines how all trial functions need to interact during the time after "last patient last visit"]
Sometimes the time taken to recruit all participants is incorrectly estimated, which has knock-on effects with regards to drift of study-timeline and hence to the publication of results. [Time taken to recruit all participants, Data input and data cleaning to ensure top quality data output, Analysis and discussions around this]

This is the main thing I have noticed, can't think of others [Failure to recruit - often because eligibility criteria are too tight and have to be widened]
Marketing of a clinical trial, once it is set up, is extremely important and this requires time and effort on behalf of the CI and TM team. Often the TM team has insufficient funding to allow time to do this and the CI is 'too busy'. [Chief Investigators not allocating sufficient time and focus on trial, Sites not delivering on their target recruitment, Insufficient resource allocated to trial management/marketing of the trial]
Obviously, if you fail to plan ahead - you delay the analysis and give less time for the report writing. Glad to be blaming ourselves rather than someone else for this one. We've realised that we can cut down the time for data cleaning after follow-up is complete - to allow speedy transfer of data to analysts - if we step up the process of query resolution from 6m before LPLOV and get statisticians, health economists and DM looking at blinded sample data to anticipate where the problems will be early. We've put a lot of work into trying to make this bit of the trial more efficient recently. The C.I. sometimes gets in the way, but mostly they're pleased and impressed that we're thinking ahead like that. [Data query resolution after Last Patient Last Observed Value, before data lock]
All the above are issues when a Chief Investigator is not involving a CTU with the entire trial conduct - including publications- so they are keeping analysis and publications under their umbrella; CTUs have then no influence at all; [Recruitment problems overall - delay in target time lines to complete recruitment, Final clean data set for analysis: Data queries are not resolved in a timely manner from sites, Grant had finished before trial has been completed and named Research Assistant/ or PostDoc not in place anymore to write paper- CI is last so to speak "last man standing"]