White Rose Research Online

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk
Universities of Leeds, Sheffield and York

Deposited via The University of Leeds.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/id/eprint/115734/

Version: Accepted Version

**Article:**
Brown, SR, Sherratt, D, Booth, G et al. (2017) Experiences of Establishing an Academic Early Phase Clinical Trials Unit. Clinical Trials, 14 (4). pp. 349-356. ISSN: 1740-7745

https://doi.org/10.1177/1740774517710250

© The Authors 2017. This is an author produced version of a paper published in Clinical Trials. Uploaded in accordance with the publisher's self-archiving policy.

**Reuse**
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

**Takedown**
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

UNIVERSITY OF LEEDS
University of Sheffield
UNIVERSITY of York

# Experiences of Establishing an Academic Early Phase Clinical Trials Unit

Sarah R Brown[1], Debbie Sherratt[1], Gill Booth[1], Julia Brown[1], Fiona Collinson[1], Walter Gregory[1], Louise Flanagan[1]

Word count: 3979

Running title: Establishing an early phase trials unit

Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK

Corresponding author: Sarah R Brown, LICTR, University of Leeds, Leeds, LS2 9JT

Email: S.Brown@leeds.ac.uk

Tel: +44 (0)113 3431472

The Myeloma UK Clinical Trials Coordinating Office is funded by Myeloma UK

The Yorkshire Cancer Research Centre for Early Phase Clinical Trials is funded by Yorkshire Cancer Research

**Abstract**

Background: Early phase trials are essential in drug development, determining appropriate dose levels and assessing preliminary activity. These trials are undertaken by industry and academia, with increasing collaborations between the two. There is pressure to perform these trials quickly, safely and robustly. However, there are inherent differences between developing and managing early phase, compared to late phase, drug trials. This paper describes an approach to establishing an academically-led early phase trial portfolio, highlighting lessons learned and sharing experiences.

Methods: In 2009 the University of Leeds Clinical Trials Research Unit became the Clinical Trials Coordinating Office for Myeloma UK's phase I and II trials. We embarked on a transition from working extensively in phase III to early phase trials development and conduct. This involved evaluating and revising our well-established standard operating procedures, visiting other academic early phase units, and developing essential new documentation and processes.

Results: A core team of trial and data managers and statisticians was established to facilitate expertise and knowledge retention. A detailed training plan was implemented focusing on essential standard practices for early phase. These included pharmacovigilance, recruitment, trial design and set-up, data and site monitoring, and oversight committees. Training in statistical methods for early phase trials was incorporated.

Conclusion: Initial scoping of early phase trial management and conduct was essential in establishing this early phase portfolio. Many of the processes developed were successful. However, regular review and evaluation were implemented to

enable changes and ensure efficiencies. It is recommended that others embarking on this venture build on the experiences described in this article.

**Keywords:** Early phase; phase I; phase II; cancer trials;

## Introduction

Translation of early (predominantly basic) research to the clinic is a well-recognised challenge in the drug development pathway.[1] Challenges arise in academia with limited relevant funding streams, complexities in designing early phase studies, and the necessary iterative collaboration between laboratory scientists, clinical researchers and industry partners. Early phase drug trials, including phase I and II, are essential steps in the development pathway, delivering research from bench to bedside, and providing proof of concept to move to large scale phase III testing and beyond. There is, however, an inevitable high attrition at these earlier stages, due to emerging safety concerns, changing industry priorities, or withdrawal of drugs from company development pipelines, all adding layers of complexity.

With continuing pressure to develop new drugs and novel treatment combinations that offer improved patient outcomes, it is essential that early phase trials are conducted quickly, safely and efficiently. Historically, the majority of early clinical trials have focussed on new drugs and drug combinations using tried and tested trial designs, predominantly undertaken by industry and developed in line with their strategic priorities. There are now more opportunities to develop academically-led early phase trials in the UK in previously under-explored areas, particularly in the field of oncology where early phase trials involve patients and are often conducted differently to other disease areas. Successful initiatives in oncology such as the Experimental Cancer Medicine Centre (ECMC) Combinations Alliance provide a framework to develop such studies using novel drugs made available from a number of industry partners.[2] There are also opportunities to evaluate drug repurposing from one therapeutic area to another, allowing knowledge transfer. For successful

delivery, it is essential that investigators are supported by academic clinical trials units (CTUs) with expertise in developing and managing early phase trials within the regulatory framework. While there are currently 49 UK Clinical Research Collaboration registered CTUs in the UK,[3] there are notable differences between developing and managing small, often safety-driven, early phase trials, as compared to large-scale multi-centre phase III trials. However, the current registration system assesses only expertise and experience associated with the latter. CTU expertise in early phase trials is scarce, with only 13/49 registered CTUs having expertise in phase I trial design and delivery.[4] Across Europe, approximately one third of European Clinical Research Infrastructure Network centres conduct phase I trials, compared to 85% conducting phase III.[5]

The University of Leeds Clinical Trials Research Unit (CTRU) is a UK Clinical Research Collaboration registered unit and one of 15 members of the National Cancer Research Institute Cancer Clinical Trials Units Group. The CTRU has an international record in late phase trials across cancer and other disease areas, undertaking associated methodological research. In 2009 Myeloma UK set out an innovative research model to rapidly and systematically address the challenges that slow down research and the development and access to new drugs for myeloma patients. Part of this model was to establish a clinical trials network to deliver prioritised phase I and II trials. Leeds CTRU was successfully awarded a grant to become the Clinical Trials Coordinating Office for the Myeloma UK Clinical Trials Network, providing infrastructure funding to lead the design, central coordination, data management and analysis of the Network's trial portfolio. Since then, a portfolio of 6 phase I and 7 phase II protocols have been developed through the Network,[6-8]

funded through industry partnerships and Myeloma UK, and the CTRU has expanded its early phase research into other disease areas, including the initiation of the Yorkshire Cancer Research Centre for Early Phase Clinical Trials.

The aim of this paper is to describe the approach to establishing an academically-led early phase drug trial portfolio at the CTRU, highlighting the key processes developed, lessons learned, and providing recommendations to enable others to develop similar trials infrastructure to share in our experience.

**Initial scoping**

Building on existing links with national and international academic trials units already running phase I and II trials, the senior management team, consisting of clinical, statistical, trial management, data management and operational staff, visited two academic units and Cancer Research UK's (then) Drug Development Office to learn from their experiences. This was essential in gaining an understanding of key processes for managing early phase trials and how they differ to later phase studies. This information was used to develop a framework of standard operating procedures and guidelines for phase I and II trials, and an associated training program for staff. In addition, key guidance on best practice in early phase trials was reviewed and incorporated.[9] The studies undertaken by CTRU were carefully selected on the basis of a full internal risk assessment, and discussion with the trials' Sponsor (University of Leeds). It is important to note, however, that the phase I trials undertaken at

CTRU were not first in human studies. Guidance and best practice relating to these studies was, however, adopted where appropriate.[10]

## Key considerations and recommendations

### Establishing a core team

Table 1 summarises the key recommendations for establishing a core team. The CTRU initiated a strategy to transfer existing late phase trial skills to the early phase setting. The first action was to establish a dedicated core team of researchers including clinicians, trialists and statisticians, working towards facilitating knowledge development, retention and specialisation. The CTRU team was headed by the co-Director of the cancer division with significant experience in myeloma trials, a lead statistician with phase II methodological expertise, and a lead trial manager. An independent advisory committee was established comprising clinicians with phase I and II trials expertise. It was necessary to appoint staff with a high level of experience and expertise to conduct the projects.

Due to the early nature of these trials alternative approaches were required compared to the phase III setting, with a higher degree of monitoring, increased site visits, intensive source data verification, closer and more intensive data management and statistical input and tracking of safety and risk profile. At the time of initiating the early phase portfolio, electronic data capture (EDC) was not used within CTRU., with data return via paper-based case report forms (CRFs). The key difference compared with high-risk phase III trials was therefore the short time frames in which CRF return, data entry and validation needs to occur.

CTRU staff managing late phase clinical trials specialised in either trial or data management. Due to the small scale nature of phase I trials it was more efficient to amalgamate roles, with a trial manager taking on data management responsibilities including data validation and data querying. Database development and maintenance was provided by the CTRU IS department. The combined role ensured knowledge of the trial and trial patients was strengthened in a smaller, core team including a senior trial manager operating across a number of early phase trials, ensuring day to day oversight of the portfolio and providing appropriate cover where necessary, and a data management assistant providing data entry and querying support. The combined role, requiring the core competencies of both trial and data management, ensured the person responsible had in depth knowledge of the whole trial protocol including treatment schedules, safety monitoring requirements, and follow-up schedules. This enabled efficient monitoring of recruitment, data return and safety data closely and effectively. Safety data was then reviewed more widely by the chief investigator and safety review committee.

Phase II trials are typically larger than for phase I, impacting the number of sites recruiting and amount of data collected. Acknowledging the higher risk relative to phase III it was found that the phase III model of both a trial manager and a data manager, working together to ensure effective delivery, worked adequately for these trials.

A team of two statisticians was established initially to focus solely on phase I and II trials and the associated statistical methodology. This enabled expertise to be

developed in a number of early phase designs. These include phase I algorithm-based designs such as the 3+3 approach, which provide a pre-specified set of rules to determine dose escalation according to the number of dose limiting toxicity (DLT) events observed within an individual dose cohort, and model-based designs such as the continuous reassessment method which apply a statistical model to the DLT events observed across all cohorts in order to make dose escalation recommendations based on a pre-specified target toxicity rate.[11-13] For phase II this includes multi-outcome designs,[14] which enable decisions regarding trial continuation to be made on a number of intermediate outcomes. Typically, the investment of statistical time for these trials is in design evaluation. Core infrastructure support from MUK enabled statisticians to commit time to identification, development and evaluation of appropriate statistical designs up-front. This was essential to ensure that the most appropriate and reliable designs were used.

*Table 1 Recommendations for establishing a core trial team*

- Identify core trial and data managers and statisticians to work wholly on phase I and II trials, to ensure coherent and well trained team.
- Combine trial and data management roles in phase I trials.
- Allow statisticians to develop methodological knowledge and provide dedicated time to design trials.

**Establishing standard practices**

Table 2 summarises key recommendations for establishing standard practices.

*Pharmacovigilance*

As is standard across all drug trials, there is a requirement to report any safety concerns to the relevant competent authority in Europe and the FDA in the USA. Pharmacovigilance processes were already well established within CTRU for later phase trials and required little adaptation for the handling of Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions in the phase I and II setting. The speed for reporting safety events to CTRU was considered acceptable for the higher risk of the trials (within 24 hours of event occurring) as was the time to process these in-house and react to any issues. For later phase trials run through the CTRU, the Principal Investigator at site assigns causality and expectedness of a Serious Adverse Event. This may not be overruled by the Chief Investigator unless the Principal Investigator felt appropriate. However, for early phase trials, participating sites typically have limited experience of the drug. The Chief Investigator is therefore permitted to overrule local assignment and re-assess based on their experience with the drug, following discussion with the Principal Investigator. This approach is different to that in the USA where the trial Sponsor assesses causality and where adverse reactions are a subset of all suspected adverse reactions.

The main difference for phase I trials was the requirement for sites to report dose limiting toxicities (DLTs). The need for rapid reporting (within 24 hours of occurrence) and urgency of processing a DLT was incorporated as a pharmacovigilance task in line with existing processes for Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions. This approach also ensured rapid Chief Investigator review to allow any necessary action to be expedited.

*Trial Design and Set Up*

Although early phase trials may be smaller than phase III trials, the time required to develop their design and set them up is typically no different, and in some instances can be longer. It is essential that the most appropriate designs are considered for both phase I and II. Typically, for phase I trials, patients are recruited in cohorts of 2-3 patients at a time to the same dose level, with dose escalation only permitted once safety evaluation of the current dose level has been undertaken and escalation deemed safe. Consideration should be given to alternative methods to the 3+3 design for dose escalation to ensure robust and reliable results are generated to inform future research.[15, 16] The 3+3 design uses a pre-specified standard set of rules to determine dose escalation/de-escalation according to the number of DLT events observed at each individual dose level, escalating if 0/3 events are observed, increasing the cohort size if 1/3 DLTs are observed, and de-escalating or declaring a dose too toxic if ≥2/3 DLTs observed. While this may be the default approach for many studies, an investment of time to develop expertise in alternative methodology is a crucial element of establishing an early phase trials unit. Within CTRU the first 2 phase I trials developed used the 3+3 design to enable us to learn about real-life practicalities of running these trials. However, later trials have adopted model-based approaches, as described earlier, as we have built our knowledge in this area. Thus, the design stage requires intensive input from the statistician, often involving extensive simulations, ongoing discussions with the clinical team and write up of design documentation. This time is, however, often countered by the somewhat decreased time required for analysis, as compared with large scale phase III trials.

Furthermore, it is essential that decision-making criteria for dose-escalation in phase I and interim and final analyses in phase II are fully specified at the start of the trial.

These should be fully transparent in the protocol and the statistical analysis plan, which, as for phase III trials, should ideally be drafted prior to opening to recruitment.

A lengthy development and set-up period impacts the overall timelines, and the resources needed to complete these trials. Although many phase I and II trials require a relatively small number of participants, this is not always reflected in their cost and duration.

*Patient recruitment*

Due to the nature of phase I trials, a restrictive recruitment procedure was implemented to limit the number of patients treated at each dose level as per the underlying dose escalation design, and recruitment was monitored closely. For the initial Myeloma UK phase I trials, only three patients at a time were recruited to each cohort, with a gap between the 1st and 2nd patient at the first dose level to reflect best practice. Only three or four centres were open to recruitment at any time to allow easy tracking of potential patients. Centres were selected on the basis of having a track record in recruiting into and delivering high quality drug trials in myeloma, and good standards in collecting and reporting data. It was also critical that sites had early phase trials experience, with many centres being Experimental Cancer Medicine Centres (centres with world-leading expertise in early phase research).[17] Regular and active communication with centres was essential in order to track patients closely. Processes for monitoring treatment compliance for patients on trial treatment were also developed to ensure patients received sufficient treatment to be evaluated for safety and to highlight any dosing errors. Knowing where patients were in the trial pathway was essential, as was keeping sites informed, to aid recruiting in

a timely manner. Being able to respond quickly to replace patients who withdrew from trial for any reason prevented hold-ups in recruitment and facilitated steady recruitment. Accounting for patient attrition due to non-eligibility or non-evaluability was also essential to ensure the correct number of patients are recruited, treated and have data available for analysis. A two-stage process to log patients approached about the trial and given a patient information sheet, and those subsequently consenting and assessed for eligibility was implemented, helping to prevent over recruitment. This enabled valuable assessment of patterns of recruitment and, in the case of slower than anticipated recruitment, an in-depth evaluation of potential barriers.

*Central and site data monitoring*

It became clear from discussions with other early phase units that more intensive monitoring of trial data was required than for some of the late phase trials due to their higher safety risk. CTRU's phase III process for risk assessment and monitoring plans were adapted for the early phase setting. Fast data turnaround from sites was stipulated for critical data items, ensuring safety review of laboratory parameters and eligibility criteria. Return of data within 48 hours of key clinic visits was mandated initially.

Data review was expedited, with data entry within 24 hours of receipt of paper CRFs and all data entry validation and querying within 48 hours. Drug dosing and safety data were actioned immediately if required. Data monitoring focused on early treatment cycles to monitor closely events that may meet DLT criteria or could

possibly become a DLT. Regular communication with sites regarding these events was essential in delivering safe, robust and timely trials. Safety and endpoint data were monitored stringently in an ongoing basis, via both automated data validation and manual review. Data queries were sent to sites with a tight turnaround time to allow data cleaning; this was especially pertinent for data required for dose escalation decision meetings. Sites were chased for outstanding data on a weekly basis and were requested to return CRFs within 24 hours of completion. Priority queries were raised immediately and requested to be returned within 48 hours.

These strict turnaround times led inevitably to frequent intensive data chases. Many sites were unable to achieve this strict turnaround requirement and, although the importance of returning data within these timelines was re-iterated, the original timelines set were not viable. The timelines were reviewed to ensure essential data were appropriately returned within 24 hours, and other data within 48 hours to 1 week, CRF dependent. However, data compliance and quality issues still continue due to high staff turnover at sites; an issue beyond the control of a trials unit. In an attempt to improve data return there is now a move to use EDC specifically within the early phase division at CTRU. This is currently being implemented for the next Myeloma UK trial.

Source data verification was conducted on a more frequent basis than in our phase III trials. A risk assessment was undertaken during trial set-up to determine key areas of risk within the trial and an appropriate monitoring plan created. For phase I trials this typically involved a monitoring visit within 2 weeks of each patient being

enrolled and a further visit at the end of the first treatment cycle to ensure 100% of data relating to patient safety and dose escalation review was verified. At phase II a typical monitoring plan involved a minimum of 3 visits per site, the first visit taking place within 6–8 weeks of first patient enrolled, with 100% of their data monitored at this time point. Second and third visits would be scheduled in line with key risk points such as second randomisations or transition to maintenance treatment for patients already enrolled in the study, and typically 100% of data relating to the primary endpoint would be monitored for a random sample of approximately 2-3 further patients at each site, to highlight any issues with data recording.

The intensive monitoring required for early phase drug trials inevitably impacts on resource and cost, with more staff required to ensure monitoring is completed fully in the timeframes required.

*Independent oversight committees*

Within phase I trials the requirement for more frequent, detailed independent review of safety data is a key process that differs to phase III. Reflecting on the experiences of other units it was agreed that a Dose Escalation Review Group including independent clinical members, physicians recruiting to the trial, the Chief Investigator and key CTRU staff (statistician and trial manager), would be convened to meet regularly throughout the trial to assess safety data and determine dosing decisions (escalation, de-escalation, or remaining at the same dose level). The choice of Dose Escalation Review Group members was made to ensure expertise with the specific treatment under evaluation, and to ensure input from recruiting clinicians to enable detailed discussion about individual patients. Independent members with expertise

both in phase I and the disease and/or treatment under evaluation ensured an unbiased opinion in decision-making. All members were made aware of the need to contribute and be available for these discussions.

A report comprising individual patient safety and treatment data for patients treated at each dose level was generated via a database report and presented to the Dose Escalation Review Group. Specific emphasis was placed on DLTs, Serious Adverse Events, Suspected Unexpected Serious Adverse Reactions, all adverse events and any dose modifications made. It was important that the decision to dose escalate or not was made in a quick and timely manner to allow the trial to continue to recruit without significant delays whilst maintaining rigor. Meetings were planned as soon as the last patient was recruited to each dose level, or with pre-emptive monthly meetings in the diary to be cancelled should the meeting not be needed at that time. Perhaps inevitably, the latter approach has proved more successful since scheduling ad hoc meetings with only few weeks' notice and a number of attendees was problematic.

For phase II trials, more traditional oversight committees were established (Data Monitoring and Ethics Committee (DMEC) and Trial Steering Committee (TSC)). For the Myeloma UK trials, umbrella committees were established to review all phase II trials within the Network, facilitating knowledge retention and consistency. To further facilitate this, standard DMEC and TSC template reports were developed, incorporating detailed safety reporting. Choice of DMEC and TSC members was

driven by expertise in the disease area, and early phase clinical and statistical expertise.

*Table 2 Recommendations for establishing standard practice*

- Awareness of time commitment and statistical input required in designing and setting up phase I and II trials is essential, for the trials unit, funders and Networks.
- Decision-making criteria for dose escalation in phase I and for interim and final analysis in phase II must be fully specified in the protocol and statistical analysis plan, prior to opening to recruitment.
- Include only 3-4 centres in recruitment during dose escalation in a phase I trial, to enable close monitoring of patients
- Implement regular communication with sites to ensure they meet their set-up timeframes required by National Institute for Health Research, to ensure tracking of patients recruited to phase I trials, and to ensure timely data return.
- Ensure sites are fully trained and aware of timeframes for data capture and return
- Select oversight committee members on the basis of their experience in the disease area of interest, as well as specific phase I and/or phase II clinical or statistical expertise. Should a clinician have only disease-specific expertise, additional clinical members should be sought to ensure phase I and/or phase II expertise is incorporated within the committee.
- While phase II trial oversight committees do not differ from those of larger

phase III drug trials, the key differences are within the phase I setting where a dose escalation review group who meet regularly and incorporate independent clinicians is essential to the expedited review of safety and dose escalation decision making.

- Ensure the Chief Investigator and independent reviewer are fully aware of timeframes required for reviewing pharmacovigilance reports.
- Ensure regular dose escalation review group meetings are pre-arranged and regular safety reports provided to the DMEC.

**Establishing a training plan**

Key recommendations for establishing a training plan are summarised in Table 3. Training a dedicated team of early phase specialists was intensive, requiring them to fully understand the processes being implemented and the urgency of the information dealt with on a daily basis. An in-house training plan was developed covering each of the processes associated with early phase trials including extended pharmacovigilance to ensure correct reporting of dose limiting toxicities and an in depth understanding of intensive data review. External training was sought where required (e.g. disease- and treatment-specific and statistical methodology training including courses at Lancaster University, Society for Clinical Trials conference [18], and the first Early Phase Dose Finding Symposium). Regular staff development and re-training was implemented to ensure continuing professional development and a high level of attention to detail. In particular, training was developed to provide staff with a thorough understanding of the different roles of Dose Escalation Review

Group, DMEC and TSC groups, highlighting where these differ to the phase III drug setting and the importance of timely review by each of these. Although early phase specialists can move from trial to trial with more ease than those with experience of late phase moving to early phase, a detailed in-house training plan was still required to ensure staff were familiar with a new trial's design and requirements. The benefits of having a highly trained team ensured trials ran efficiently and without serious error, and enabled staff to develop a specific area of expertise.

As previously discussed, we developed statistical expertise in the design of phase I and II trials. Methodological training courses external to CTRU were identified to support this, as well as providing dedicated time to develop an understanding of the methodology and to implement this in practice.

*Table 3 Recommendations for establishing a training plan*

- An in-house training plan should be developed to provide staff with a thorough understanding of early phase trials and the specific elements that differ to undertaking late phase drug trials.
- Key training includes pharmacovigilance reporting, independent review committees for phase I, and statistical methodology.
- Regular review of training plans and re-training is required.

**Discussion**

Within the first six years of establishing the Myeloma UK Clinical Trials Network and Coordinating Office, a total of 13 trials have been developed,[6-8] two of which did not open due to safety concerns during development and withdrawal of industry support. During this time we have learnt that, due to the early phase nature of these studies and working closely with industry, there is a significant time investment in developing a study whilst negotiations are ongoing. This inevitably leads to amendments to study design and logistics, requiring a degree of flexibility in study development.

A dedicated team of CTRU staff has proven essential in maintaining high standards of trial, data and statistical management required for these trials and ensuring knowledge retention. While some of the processes may be similar to those for phase III drug trials, having a dedicated team for the duration of a trial allows an expertise to be built in early phase processes. Learning from day-to-day contact with sites and repetition of trial-specific queries has allowed relationships to be built with sites, facilitating promotion of trials and resolution of issues. This has also proven effective when setting up new trials. Staff retention has been aided by the training and development programme which encourages staff to progress and develop their skills and expertise within early phase drug trials. Most recently this has enabled implementation of novel statistical methodology for new trials in development,[13, 14, 19] supported by focused training, increased engagement with the clinical team, and dedicated time to learn, understand and implement new methods.

The high throughput of trials within the early phase portfolio has led to continued review of processes and review of areas where efficiencies may be made. For

example, publication policies used for late phase trials were implemented for early phase restricting publication to the end of the trial when the primary end point would have been available and preventing the publication of pertinent data such as laboratory data or dose escalation data not linked to the primary efficacy end point. This has been problematic for some of our early phase trials where presentation of early data on safety, activity and translational research has been important to communicate to the wider clinical community. An early phase publication policy is currently being drafted to allow flexibility to report findings in a timely manner. We would recommend all early phase trials have an associated publication plan which is reviewed and agreed with the trial oversight committees, to ensure transparency in reporting of data throughout the trial and at final analysis.

In many areas it has been possible to standardise processes and documents. This has been particularly apparent within the MUK Network due to similarities between trials with regard to disease background, trial endpoints and reporting processes. Standardising documents has helped reduce the need for multiple document reviews and enabled familiarity with processes and paperwork both at CTRU and at recruiting sites, which are often the same for many trials. Standardisation of processes and documentation specific to Myeloma UK trials includes patient registration, protocol writing, patient information sheets and informed consent, case report forms & database specifications, data reports (e.g. DMEC and TSC reports) and contracts. Many of these processes have been developed to be more widely applicable to all phase I and II trials within CTRU, with key components relating to phase I compared to phase II acknowledged.

The experiences described focus on academic early phase oncology trials, which can be considered somewhat different to early phase trials in other disease areas. The nature of trial design, in particular phase I, outside of cancer will also differ according to the specific indication, and patient populations may be less restrictive, with initial dose finding studies being conducted in healthy volunteers rather than patients. Standardisation of processes and documentation across disease areas will differ according to different requirements of other disease areas. However many of the concepts described are transferable. In depth knowledge of disease area, trial protocol and individual patients in the study is essential for any early phase trial, as is a tailored training program for staff. The recommendations provided may be seen as an initial starting point for those undertaking academic early phase trial design and management in other disease areas.

Learning from experiences of each trial and reflecting on elements that work well and areas that are more challenging ensures continued improvement with each new trial. Initial scoping of early phase trial management and conduct was an essential process in establishing the CTRU's early phase portfolio, however much more has been learned from setting up and conducting each of the trials and learning from our experiences. For academic trials units embarking on early phase clinical trials it would be strongly recommend to build on the experiences described to assist in portfolio set-up.

**Declaration of Conflicting Interests**

The Authors declare that there is no conflict of interest.

**Funding**

This work was supported by Myeloma UK (grant CD10/01) and Yorkshire Cancer Research (grant L375PA)

## References


1. Cooksey D. A review of UK health research funding. 2006.

2. Williams RJ, Walker I and Takle AK. Collaborative approaches to anticancer drug discovery and development: a Cancer Research UK perspective. *Drug Discovery Today*. 2012; 17: 185-7.

3. McFadden E, Bashir S, Canham S, et al. The impact of registration of clinical trials units: The UK experience. *Clinical Trials*. 2015; 12: 166-73.

4. http://www.ukcrc.org/. UK Clinical Research Collaboration. Last accessed 20/03/2017.

5. Kuchinke W, Ohmann C, Yang Q, et al. Heterogeneity prevails: the state of clinical trial data management in Europe - results of a survey of ECRIN centres. *Trials*. 2010; 11: 79.

6. Schey S, Brown SR, Tillotson AL, et al. Bendamustine, thalidomide and dexamethasone combination therapy for relapsed/refractory myeloma patients: results of the MUKone randomized dose selection trial. *British journal of haematology*. 2015; 170: 336-48.

7. Brown S, Hinsley S, Ballesteros M, et al. The MUK five protocol: a phase II randomised, controlled, parallel group, multi-centre trial of carfilzomib, cyclophosphamide and dexamethasone (CCD) vs. cyclophosphamide, bortezomib (Velcade) and dexamethasone (CVD) for first relapse and primary refractory multiple myeloma. *BMC hematology*. 2016; 16: 14.

8. Popat R, Brown S, Flanagan L, et al. Bortezomib, Thalidomide, Dexamethasone plus Panobinostat (VTD-P) for patients with Relapsed Multiple Myeloma: results of the MUK six phase I/II Clinical Trial. *Lancet Haematology*. 2016; 3 e572-80.

9. EMEA. EMA Guideline on the evaluation of anticancer medicinal products in man. 2013.

10. Expert Scientific Group on Phase One Clinical T. Expert Scientific Group on Phase One Clinical Trials: Final Report. Great Britain.: TSO, 2006.

11. O'Quigley J, Pepe M and Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics*. 1990; 46: 33-48.

12. Thall PF and Cook JD. Dose-finding based on efficacy-toxicity trade-offs. *Biometrics*. 2004; 60: 684-93.

13. Ji Y, Liu P, Li Y and Bekele BN. A modified toxicity probability interval method for dose-finding trials. *Clinical trials (London, England)*. 2010; 7: 653-63.

14. Thall PF and Sung HG. Some extensions and applications of a Bayesian strategy for monitoring multiple outcomes in clinical trials. *Statistics in medicine*. 1998; 17: 1563-80.

15. Jaki T, Clive S and Weir CJ. Principles of dose finding studies in cancer: a comparison of trial designs. *Cancer chemotherapy and pharmacology*. 2013; 71: 1107-14.

16. Le Tourneau C, Lee JJ and Siu LL. Dose Escalation Methods in Phase I Cancer Clinical Trials. *JNCI Journal of the National Cancer Institute*. 2009; 101: 708-20.

17. http://www.ecmcnetwork.org.uk/. Experimental Cancer Medicine Centres Network. Last accessed 20/3/2017.

18. http://www.sctweb.org/public/home.cfm. Society for Clinical Trials. Last accessed 20/03/2017.

19. Cheung YK and Chappell R. Sequential designs for phase I clinical trials with late-onset toxicities. *Biometrics*. 2000; 56: 1177-82.