LESSONS LEARNED REPORT

HTA Reference	14/49/154
Title	The Metoclopramide and selective oral decontamination for Avoiding Pneumonia after Stroke (MAPS-2) Trial: a 2x2 double-blind, randomized controlled trial of metoclopramide and selective oral decontamination for the prevention of pneumonia in patients with dysphagia after an acute stroke.
Brief Title	MAPS-2
Call	Efficient Study Design
Sponsor	University Hospitals of North Midlands NHS Trust
Sponsors reference number	UHNM 1219
Host Organisation	University Hospitals of North Midlands NHS Trust
CTU	Anglia Ruskin
Trial Registration	EudraCT number: 2016-003406-14 ISRCTN: 14124645 IRAS Number: 207212
Chief Investigator	Professor Christine Roffe
Design	2x2 factorial double-blind randomised controlled trial.
Primary Objective	To assess whether metoclopramide and/or selective oral decontamination reduce mortality in patients with dysphagia after stroke.
Study Product, Dose, Route, Regimen	1. Metoclopramide 2. Oral decontaminant paste containing 2% w/w colistin, 2% tobramycin and 2% amphotericin B Metoclopramide solution for injection 10 mg three times a day by slow IV injection or via nasogastric tube. For participants weighing less than 60 kg the dose will be reduced to 5 mg three times a day. Selective oral decontamination paste applied four times a day to the oral mucosa via an applicator.
Duration of administration	21 days or until patient nasogastric tube no longer needed.
Comparator	Placebo metoclopramide and Placebo selective oral decontamination paste
Number of participants	1160
Proposed start date	01.07.2016
Proposed end date	30.06.2019
Study Duration	36 months
HTA Programme Manager	Nick Eaton
Closedown date	03.10.2018

This report was drafted by Prof Tony Fryer (R&D Director, University Hospital of North Midlands) and Prof Christine Roffe (Chief Investigator and Professor of Stroke Medicine, University Hospital of North Midlands/Keele University), with contributions from Dr Keira Watts (Academic Development Lead, University Hospital of North Midlands), Heather Reidy (Senior Research Governance Facilitator, University Hospital of North Midlands), Callam Weldon (Research Monitor & Auditor, University Hospital of North Midlands), Nicky Stringer (Principal Pharmacist, University Hospital of North Midlands), Brin Helliwell Patient and Public Involvement (PPI) , Jill Stacey (Research Nurse Professional Head, University Hospital of North Midlands) and Helen Duffy (Head of NHS Partnerships & Engagement, Keele University).

Executive Summary

The MAPS2 trial was designed to answer the important clinical question: Do early interventions aimed at the prevention of pneumonia reduce mortality and improve recovery after stroke? The 2x2 factorial trial design aimed to establish whether two interventions, prevention of vomiting by the use of an antiemetic (metoclopramide) and selective oral decontamination could prevent pneumonia and reduce mortality after stroke in a definitive trial following evidence from smaller trials.

A multidisciplinary research team lead by clinical academic researchers and patient representatives at University Hospitals of North Midlands NHS Trust with co-applicants from Keele University, Birmingham University, Salford NHS Foundation Trust, Royal Berkshire NHS Foundation Trust, the Anglia Ruskin Clinical Trials Unit (ARCTU) were awarded funding though open national competition by the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) Programme. Contractors to facilitate the Investigational Medicinal Product (IMP) production (Tiofarma), IMP shipping and storage (Mawdsleys) and trial management support (ARCTU) were set up to help in the trial delivery.

We completed the protocol, and obtained approvals from NHS ethics, the HRA, and the MHRA. The trial was registered with ISRCTN and EudraCT. All patient facing documents were developed and database specifications set up. Communication between the parties was strong and was supported by an experienced trial steering committee, the patient representatives and the Clinical Research Networks. However, the complexity of the trial highlighted challenges that had not been anticipated.

The trial was closed on the 3rd October 2018, 27 months after its official start date and without patient recruitment having begun.

Important lessons learnt from MAPS2 are as follows:

- It became apparent during the set-up of MAPS2 that the Sponsor Quality Management System (QMS) would not be robust enough to ensure regulatory compliance for a multicentre CTIMP. This study has highlighted the need for a robust Sponsor infrastructure to support such a complex multicentre Type B CTIMP. The amalgamation of R&D functions from NHS Trusts and Higher Education Institutions (HEIs) is a model that is increasingly being adopted and we have been engaging with other similar organisations to learn from their experiences and have begun to explore models of sponsorship with our local HEI.
- A review of existing procedures for grant approval and issues that arose throughout the development process for MAPS2 has highlighted that (i) sponsorship in principle procedures were not robust; (ii) the complexity of this type of large multi-centre CTiMP trial meant that the costings developed were not sufficient. We have responded to this by developing a more robust process for grant development and sponsorship in principle approval, and are working to ensure that all appropriate stakeholders are engaged at the earliest possible stage of development and that all applications are accurately costed. This this has led to new sponsor oversight structure being implemented at UHNM to oversee the portfolio of

sponsored trials and closer links being explored with Keele University systems for grant development and research oversight.

- It is essential that interventional trials of this scale and complexity (particularly involving CTIMPS) are delivered through an accredited Clinical Trials Unit (CTU). This is likely to lead to increased costs but enables the Sponsor to delegate responsibilities to experienced trials staff and ensures processes are streamlined and have appropriate oversight. Within the Sponsor Pharmacy Clinical Trials Team there was limited experience managing Sponsored CTIMP trials to the scale and complexity of MAPS2. This highlighted the need for expertise in procuring, manufacturing and importing of IMPs from an EEA member state. A research Pharmacist from an external CTU was contracted in to support the Pharmacy Clinical Trials Team to ensure sufficient pharmacy oversight during 2017/18.
- MAPS2 highlighted that (i) all arrangements related to sponsor delegation must be in place prior to commencement; (ii) closer links to the procurement team in the Sponsor organisation are necessary to ensure robust contracting and vendor assessment; (iii) there must be approved pathways in place to agree and sign off contracts with industry, NHS and academic partners.
- During the lifetime of the project there were changes in the clinical pathway which resulted in stroke patients being repatriated from the acute hospital setting to repatriation sites. This necessitated a three-fold increase in the number of sites participating required in the study. As such, there were additional logistical issues around moving IMP with the patients and the capacity and resources required to coordinate the additional sites.

Overall sponsor infrastructure was the main area of difficulty for MAPS-2. It highlighted the need for a robust Sponsor infrastructure to support such a complex multicentre Type B CTIMP. The amalgamation of R&D functions from NHS Trusts and HEIs is a model that is increasingly being adopted, and we have been linking with other organisations to learn their lessons as we develop our future models for Sponsorship.

Background

Stroke is the second most common cause of death worldwide. With approximately 110,000 strokes per annum in England, it accounts for 11% of deaths. Half of all stroke survivors are left dependent on others for everyday activities, making stroke the largest cause of complex disability.

Pneumonia is a common complication of stroke and associated with a 2-6 fold increase in mortality in individual studies, longer length of stay, and an increase in long-term disability. In the UK the incidence of stroke-associated pneumonia was 8.3% in the first week after stroke in the Stroke National Sentinel Audit Programme, which included 18,839 patients from 160 hospitals. After a stroke more patients die from pneumonia than from neurological damage. Pneumonia weakens patients, and affects their ability to engage with therapy. A stroke survivor in our Patient and Public Involvement (PPI) group described vividly how pneumonia delayed his ability to participate in physiotherapy and affected his recovery. Prevention of pneumonia as the most common severe complication of stroke has the potential to make a large impact on stroke mortality and functional outcome.

Stroke-associated pneumonia is most likely to occur in patients who have problems swallowing. A meta-analysis of 24 studies has shown an overall prevalence of dysphagia after stroke of 50-55% by clinical testing and 64-78% by instrumental assessment. Dysphagia and stroke severity are the most important predictors of pneumonia. Mild dysphagia can be managed by modification of diet and fluids, whereas severe dysphagia requires cessation of oral intake and nutrition via the enteral route using feeding tubes. However, patients fed exclusively via the enteral rather than oral route still develop pneumonia. Indeed, stroke patients who require nasogastric feeding are at very high risk of pneumonia (39-68%). Additional measures are therefore needed to prevent pneumonia in this patient group.

The main cause of post stroke pneumonia is aspiration of vomited and regurgitated stomach contents or material lodged in the oral cavity. Members of our team conducted two pilot studies to address these problems. The first focussed on aspiration of infectious material from the oral cavity. A programme of selective oral decontamination (SOD) using antibiotic paste (2% w/w colistin, 2% w/w tobramycin, and 2% w/w amphotericin B) applied to the oral mucosa was compared with standard care and resulted in a significant reduction in the incidence of pneumonia in a randomized controlled trial (RCT) including 203 patients (1). While promising, this has been not translated into routine practice, as the trial was small, and the antibiotic paste has to be made up by pharmacy, as it is not routinely available in the NHS. The second study used an antiemetic to prevent vomiting and regurgitation of gastric contents. This RCT showed a significant reduction of pneumonia and a trend towards lower mortality (2). This is promising, but needs to be confirmed in a larger trial.

The aim of the MAPS-2 study was to establish whether either of both of these two interventions, prevention of vomiting by the use of an antiemetic (metoclopramide) and selective oral decontamination could prevent pneumonia and reduce mortality after stroke.

Methods & Protocol

The hypothesis that post-stroke pneumonia can be prevented by the prophylactic use of an antiemetic (metoclopramide) and/or by selective oral decontamination was to be tested in a factorial 2x2 multicentre RCT. Patients with a severe stroke and dysphagia were to be recruited as soon as possible after the stroke (within 9 hours of onset) and randomized to one of 4 treatment options:

1. Metoclopramide and oral decontamination paste
2. Metoclopramide and placebo paste
3. Metoclopramide placebo and oral decontamination paste
4. Metoclopramide placebo and placebo paste

Treatment would be started within 2 hours of enrolment and continued for 21 days or until nasogastric feeding was no longer required (whichever came earlier). Follow up was to be daily for 14 days, then at 30 days, 90 days and at the end of the trial (mortality only). Details of trial procedures and timings are shown in figure 1. As patients are commonly transferred within a few days of the stroke to a rehabilitation ward in another hospital the long treatment course meant, that the trial treatments had to be transferred with the patient, and assessments had to be made in several hospital sites, and in the community after discharge.

The primary objective was to determine whether metoclopramide and/or selective oral decontamination could reduce mortality after stroke. We also intended to assess the following: pneumonia incidence, neurological recovery at 30 days, dependency at 90 days, safety, and costs.

We intended to recruit 1160 patients from 50 hospitals admitting stroke patients acutely, and to involve another 50-80 centres in continuation of the treatment. Assuming 1:1 allocation, a 5% two-tailed significance level, and a maximum of 10% loss of follow-up, this would give us 90% power to detect a hazard ratio ≤ 0.78 for death at the end of the trial.

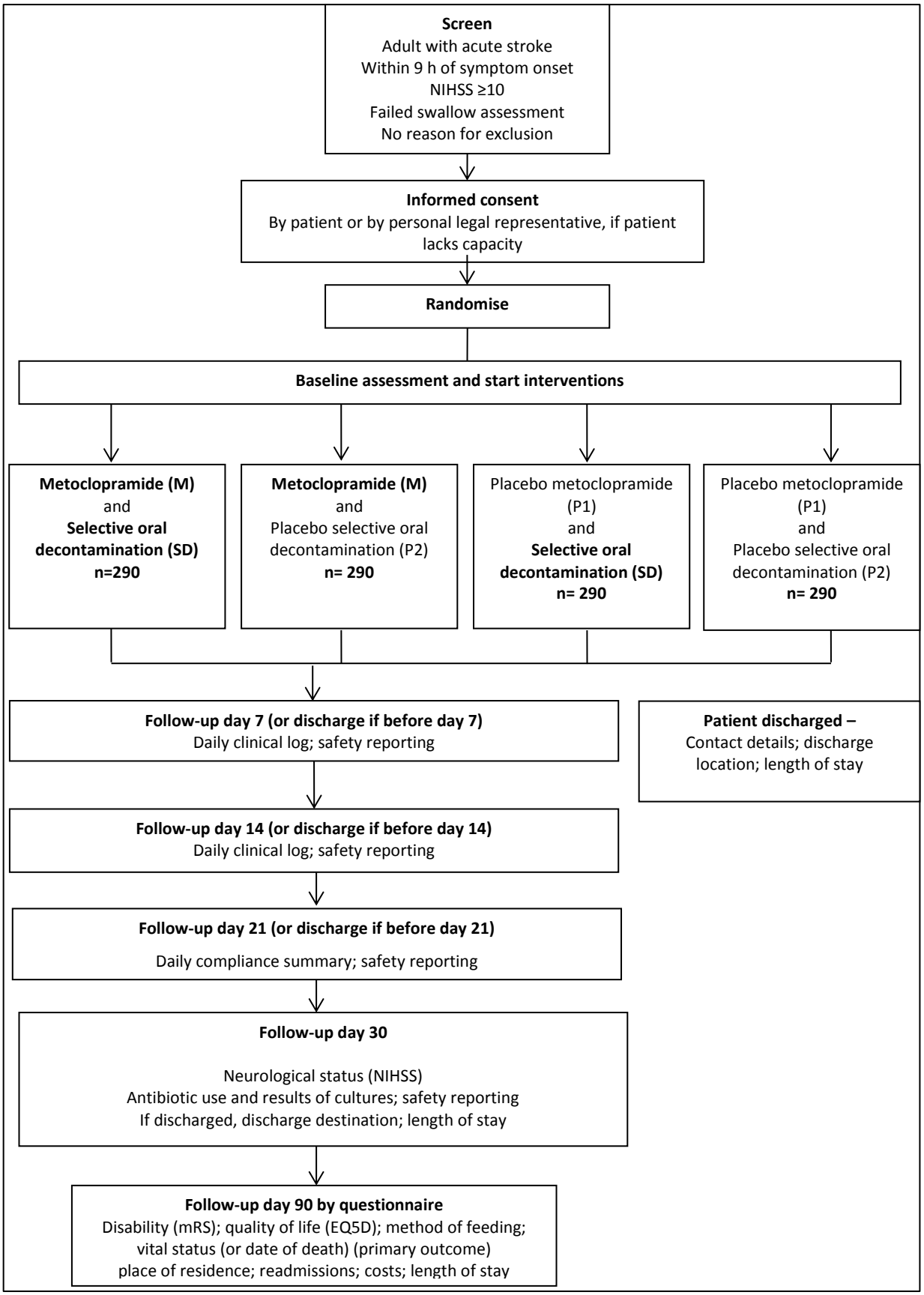

Figure 1 Trial Flow Chart

Progress

We completed the protocol, and obtained approvals by NHS ethics, the HRA, and the MHRA. The trial was registered with ISRCTN and EudraCT. Tiofarma, based in the Netherlands, was selected by the Sponsor CI to produce the SOD paste and placebo. Stability testing was completed, including on-going extended testing to allow for a potential longer shelf life. Blinding and labelling of all the trial packs was carried out by Tiofarma. Import, storage, and distribution of the trial medication was agreed with Mawdsleys, and awaiting activation. We liaised with Clinical Research Networks and individual hospitals to identify sites, and preliminary visits to teams to discuss the study were completed. We presented the study on a stand at the UK Stroke Forum on 2 successive years.

Trial start-up was delayed by the realisation of the Sponsor that running such a large study of a moderate risk Clinical Trial of an Investigational Medicinal Product (CTIMP) required an overhaul of the existing Quality Management System (QMS). An external review was completed in December 2017 to provide a gap analysis of the QMS and from that a number of working groups were created by the Sponsor to address the gaps identified. A no-cost pause of 6 months was agreed in January 2018 to allow time to address those gaps. We had strong support from Keele University in assessing our QMS capability and in developing our structures, systems and procedures for sponsorship; as well as supporting staff to deliver the trial itself. During the pause, liaison with sites continued. We had excellent support from the West Midlands Clinical Research Network (CRN) in setting up the study and providing expertise. There was great interest in the study. We had selected the initial sites for start-up in Manchester and the West Midlands and liaised with other teams and pharmacies to prepare for site visits. Site packs, including Site Pharmacy Manual and associated documents, had been sent to critical friends for comment and we updated these in response to feed-back. The first site initiation visit was planned for October 2018.

Trial committees were set up and provided important support and advice during study preparation, and when it became clear that there were delays. Input and advice of the trial steering committee (TSC) chair, Professor Martin Dennis, was frequent, even between meetings, and invaluable. The patient representatives set up PPI meetings, attended Trial Management and Trial Steering Committee meetings, and reassured us that they continued to consider the trial important.

However, due to continued staffing problems in the Sponsor Research and Development (R&D) office and associated delay on progress of the QMS, the Sponsor was unable to give permission to open the study. Through ongoing discussions with the HTA a decision was made by the HTA to stop funding the trial in October 2018. This information was shared with potential sites, and oversight committee. Both The TSC and Data Management Committee (DMC) stressed that they still consider this a very important trial and agreed to resume their roles if this study were to be opened in future.

Positive Contributions and Outputs

- The aim of the MAPS2 trial to determine whether early interventions aimed at the prevention of pneumonia reduce mortality and improve recovery after stroke remains a clinically important question and the importance of the trial has never been questioned.
- The failure to open and deliver on the MAPS-2 project was a major disappointment to all those involved in it, particularly the PPI co-applicants, who played such an active role in a

project that they were strongly in favour of, and the research team members who had worked enthusiastically on the trial.

- Despite its failure, MAPS-2 did highlight some processes that worked well, produced some tangible outputs that will benefit future research design (particularly around the challenges around repatriation of patients and CTIMPs to other centres), as well as being a catalyst for closer working with our HEI partner to create a more robust infrastructure for Sponsored studies.
- Both UHNM's Sponsor and Keele University Clinical Trials Unit structures and processes were already evolving when MAPS-2 was funded, however the complexity of this multi-centre CTiMP provided the Sponsor with concrete examples of gaps in systems and processes for Pharmacovigilance (PV) for CTIMPs, for sponsor oversight structures, key skills and knowledge that required strengthening, and where the roles and responsibilities of members of the research team needed clarification.
- We had strong support from Keele University in assessing our QMS capability, and in developing our structures, systems and procedures for sponsorship; as well as supporting staff to deliver the trial itself.
- PPI throughout was strong and remains supportive of the study concept and future desire to deliver the study.
- Given the internal challenges, it was a positive move to outsource data management to ARCTU. A clear data management plan was put together by the Trial Data Manager and a strategy put in place of how the data would be controlled and managed.
- The changes to the patient pathways during study set-up presented a major challenge, increasing the number of sites by around three-fold (from ~50 to ~150, including repatriation sites). However, the research team were incredibly responsive to the additional design and operational needs that this presented and we therefore learned a huge amount about future trial design both for repatriation studies, and in internal agility.
- The Trial files and pharmacy files were developed including patient pathways and risks around repatriation of patients along with control of IMPs including temperature control.
- Lots of training material was developed for the sites including a pharmacy manual.
- The pharmacy team reviewed and updated the suite of Standard Operating Procedures to support the sponsorship of CTIMP trials and gained valuable experience in the management of IMP from product development, manufacturing, through importing, storage and delivery to site.
- The multidisciplinary team worked together to develop the necessary linkages to the new patient pathway, anticipate any issues around the IMP management and how these could be overcome as the two IMPs had different temperature storage requirements.
- There was strong collaboration from CRN managers, especially in the West Midlands and North West (Manchester). This allowed us to develop a strategy for rapid set up of recruiting and repatriation sites.
- After consultation with CRN research staff at sites, we came up with a 'Trial Transfer Bag' which included the treatments CRF and trial manual to ensure that all processes were adhered to on transfer to patients to other hospitals and prevent loss of trial medication.
- Despite the challenges identified within the Trust's R&D systems, the team has received strong endorsement from the Trust executive team that research remains a key priority for

the Trust, and recognition that the infrastructure required to develop robust sponsor infrastructure, clinical academic and CI capacity is a challenge that will be supported at an executive level.

We are under no illusions that MAPS-2 would have been a challenging trial to deliver, especially following the change in the clinical pathway, associated with the introduction of new patient repatriation processes, after the grant was awarded. Along the way, we identified that our initial costings were insufficient, particularly following the additional strain of changes to clinical pathways. We used a model of CTU support that heavily relied on local MAPS-2 research staff with advisory input from ARCTU staff. Data management and storage was intended to be handled by the Sponsor and the MAPS-2 trial staff with supervision and statistical and programming input from ARCTU. When it became clear that regulatory requirements would prevent the Sponsor from holding and storing research data, this aspect was taken over by ARCTU, who were flexible and very helpful in implementing the change. While this worked very well and provided us with a randomization and data management system fit for purpose, it led to a reduction of trial coordination input from ARCTU to mitigate the additional costs. However, the trial ultimately foundered on shortfalls in the Sponsor systems & processes, oversight structures and staff capability & capacity in some key areas. The following section provides some additional detail on those lessons learned.

LESSONS LEARNED AND FUTURE AREAS FOR DEVELOPMENT

1. Grant Development

- A review of existing procedures for grant approval and issues that arose throughout the development of MAPS2 has highlighted that i) sponsorship in principle procedures were not robust; ii) the complexity of this type of large multi-centre CTiMP trial meant that the costings developed were not sufficient. The lesson learnt is that UHNM has developed a more robust process for grant development, sponsorship in principle approval and is working to ensure to ensure that all appropriate stakeholders are engaged at the earliest possible stage of development and the applications are accurately costed. This has led to new sponsor oversight structure being implemented at UHNM to oversee the portfolio of sponsored trials and closer links with the Keele University systems for grant development and research oversight.

Lessons Learnt

A new framework for grant development and approval (sponsorship in principle) has been established. This framework ensures engagement of academic development and sponsor expertise enabling methodological support to be offered (including involvement of the RDS and an accredited CTU, where appropriate) and that full costings can be provided and reviewed by the Sponsor Finance Department. For example, any trial involving CTIMPs should follow the new processes and include senior pharmacy oversight from the initial protocol creation and grant development stage. This would then be subject to the scrutiny of the newly formed Clinical Oversight Group (for 'sponsorship-in-principle' decision) and the R&D Directorate Board (for final approval).

2. Sponsorship Decision

The MAPS-2 study posed significant challenges to the Sponsor as it was a large multi-centre CTIMP of a nature that had not currently been sponsored before by UHNM. A more in depth review of the study should have taken place to enable a more informed decision around sponsorship of this trial to be made at a very early stage in the trial's development. The sponsorship decision was made by a single individual (R&D Manager) without a full risk assessment.

Lessons Learnt

A new process for gaining sponsorship has been implemented to ensure sponsorship 'in principle' decision is made following a full risk assessment of the study and review by the new Clinical Oversight Group. Final sponsorship review and decision is made at the Trust's R&D Directorate Board meeting. This ensures sponsorship decisions are not reliant on a single individual's view and that a full assessment on the capability and capacity of the Directorate to run such studies is considered.

3. Staffing challenges

There were a number of staffing issues that contributed to the challenges of this trial, including staff changes during the life time of the study. In order to support the study our HEI partner (Keele University) employed trial management staff to underpin the UHNM delivery of MAPS2. A number of problems arose including problems in obtaining NHS contracts for the trial management staff and ultimately Keele supported us by advising that as a result of these contractual difficulties, the trial management team had a lack of oversight both by the Sponsor and their employer, thus raising concerns about the capability of our QMS to support this study. Furthermore, the Trust R&D Manager left in August 2017 and has not yet been replaced, despite repeated attempts to do so. This created a gap in roles and responsibilities that are key to the effective management of Trust sponsored trials.

Lessons Learnt

The most efficient way for this type of multi-centre trial to be delivered is through an accredited CTU. If a CTU had been involved to deliver the trial in its entirety, the trial staff would not need separate contracts of employment with the Sponsor, but would be part of the Delegation of Responsibilities process from the Sponsor to deliver the study. This is our preferred model for the future. Regarding the R&D Manager, this function is being addressed as part of the current Sponsor review of capacity & capability.

4. CTU issues

The model of Sponsor interaction with CTUs changed during the development and set up of the trial. While running a study by a dedicated internal trial team with oversight from a CTU was standard practice when this trial was planned, and indeed successfully delivered the HTA funded Stroke Oxygen Study (Type A CTIMP with 8003 patients across 136 sites), a grant of this size is now more commonly run in its entirety through a CTU. This trial was initially discussed with Keele CTU, but at the time of the application the Keele CTU did not have the capacity to take on this study. Since then Keele CTU infrastructure has been enhanced and closer links have been forged with UHNM.

As a result, a CTU was chosen that was inexperienced in supporting CTIMP studies of this nature. The CTU had sub-contracted out the data management system to a European based company Tenalea and this further complicated contracting arrangements particularly in relation to new General Data Protection Regulations (GDPR).

Lessons Learnt

As part of our review of Sponsor processes, it has now been agreed that, for all large multicentre CTIMP trials, an accredited CTU will be contracted to conduct the full trial management and delivery. Through this study we have developed closer processes of working with Keele and established reliable academic partnerships. For future projects, we would wish to work more closely with the Keele CTU to develop their capacity to deliver studies of this type; where they are unable to do so we will use the UK CRC accredited CTU network to seek the expertise required..

5. IMP Management

UHNM as Sponsor of the study did not have prior experience of the process of procuring a manufacturer of CTIMPs.

The decision to award the manufacturing of the IMP to a specific supplier was agreed outside due procurement process at the Trust. This was due to a lack of detail within the QMS setting out the Trust procurement processes, and the lack of an adequate vendor selection process at the Trust. The IMP formulation was developed by Tiofarma, and in routine clinical use in the Netherlands. UHNM pharmacy input highlighted problems with the short shelf-life and led to extended stability studies, which helped with the planned future management of the IMP.

The production runs for the IMP were approved too far in advance of the study opening. This was due to the delay in study start.

The manufacturer had to deal with multiple staff from the Sponsor team to address issues around production and supply.

For the UHNM Pharmacy Clinical Trials team, there was limited experience managing sponsored clinical trials and there was no experience around procuring the manufacturing and importing of IMPs from an EEA member state. This lack of experience was identified and a specialist pharmacist was contracted in to support the team to ensure appropriate pharmacy oversight.

Lessons learnt

Moving forward, UHNM as Sponsor will consider all aspects of IMP management prior to agreeing to sponsor any study. Hence, there is pharmacy membership on the two key committees determining the decision to sponsor studies (Clinical Oversight Group, R&D Directorate Board).

There should be an open and transparent method for vendor selection for manufacturers and distributors for CTIMPs. Once a manufacturer and distributor have been approved, there will be a single point of contact between them and the Sponsor which could be either the trial manager or pharmacy lead and will be explicit in the delegation of responsibilities.

UHNM as Sponsor will contract an experienced CTU to undertake the IMP management for studies such as MAPS-2, given its size and complexity.

Financial risk will be incorporated into the planning of a study of this size with respect to production runs of IMP and stability studies.

A good working relationship with the Manufacturer and Distributor is essential for the Sponsor of a CTIMP with regular correspondence. This was achieved with the companies selected for the MAPS 2 Trial and much appreciated by the trial management team.

5. Clinical Pathway changes

During the lifetime of the project there were changes in the clinical pathway which resulted in stroke patients being repatriated from the acute hospital setting to repatriation sites. This necessitated a considerable increase in the number of sites participating required in the study. As such, there were additional logistical issues around moving IMP with the patients and the capacity and resources required to coordinate the additional sites.

Lessons Learnt

Although the changes to the clinical pathway with early transfer of patients from acute receiving hospitals to repatriation sites were outside the control of the Sponsor, it is important to be responsive to change and work with the collaborators and funders to identify possible solutions. The clinical change in this case required rewriting the protocol and changing the financial plans to include additional sites, which had a significant impact on the study delivery. IMP management across sites is complex and requires careful planning especially where temperature control of medications is a factor. After consultation with CRN research staff at sites, we came up with a 'Trial Transfer Bag' which contained the relevant materials required during transfer between recruiting site and repatriation sites (e.g. treatments, CRF and trial manual) to ensure that all processes were adhered to and to prevent loss of trial medication. We believe that this innovative approach could be utilised in other trials where repatriation is a feature.

6. Contracting and vendor assessment

At the time of the development of this study there was no robust vendor selection process in place. The contracts were not reviewed by the Procurement Department at the Sponsor organisation.

Lessons Learnt

As part of the review of the QMS, we have now developed a robust vendor selection process. Closer links have been established with the Sponsor Procurement Department to facilitate the vendor selection and contracting process. The Procurement Department have been involved in the contract termination of vendors during the study close out.

7. Sponsor oversight

It became apparent during the set-up of this study that the Sponsor Quality Management System (QMS) would not be robust enough to ensure regulatory compliance for this multicentre CTIMP. There were gaps in the QMS, identified as part of an external review of the Sponsor QMS in December 2017, that needed addressing before a trial of this nature could be opened and there were significant funding and resource issues that made it challenging to address these. Some of the processes that needed to be implemented include:

- Pharmacovigilance/safety reporting
- Emergency Unblinding
- IMP recall

As a new QMS was developed, it became clear that the current capacity and competencies of staff within the Sponsor R&D office was insufficient to be able to implement the new QMS.

It also became apparent that the Sponsor reporting structures needed to be updated to facilitate effective sponsor oversight of sponsored studies.

Lessons Learnt

Using a CTU to deliver the whole study would have enabled many of these processes to be delegated to the CTU with Sponsor oversight, however for MAPS2 the Sponsor oversight function was not sufficiently developed. As such, the Sponsor implemented a comprehensive action plan following the external review of its GCP compliance. This action plan included development and implementation of new reporting structures to ensure robust Sponsor oversight (including integration with the wider Trust Quality and Safety infrastructure), overhaul of the Sponsor R&D QMS and a review of the roles and responsibilities of Sponsor R&D staff. We also conducted a review of all other sponsored studies, with help from the CRN and Keele University, to provide independence. This identified key themes that were included in the action plan. The action plan has now been completed and is now being developed into an improvement plan.

New Sponsor reporting structures (including a Quality Assurance Steering Group and Clinical Oversight Group) have been implemented to allow for robust Sponsor oversight of sponsored trials.
In terms of staffing, the Sponsor has embarked on a Directorate-wide staffing restructure. Phase 1, which encompasses the Research Delivery Team, has been completed and will include an infrastructure to support regulatory compliance support with revised job descriptions. Phase 2, which involves the key support staff who will be critical to provide governance and quality assurance oversight as well as grant development is being developed in consultation with Keele University. Keele has an accredited CTU and is GCP compliant following MHRA inspection. There is an active, ongoing project to enhance joint working between the two institutions, supported by the Head of NHS Partnerships at Keele University. The work involved in setting up this study and the QMS supporting, together with addressing the lessons learnt it has strengthened and accelerated these developments.

Overall sponsor infrastructure was the main area of difficulty for MAPS-2. It highlighted the need for a robust Sponsor infrastructure to support such a complex multicentre Type B CTIMP. The amalgamation of R&D functions from NHS Trusts and HEIs is a model that is increasingly being adopted, and we have been linking with other organisations to learn their lessons as we develop our future models for Sponsorship.

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