LAVA End of Pilot Phase Report – March 2018

Progress Summary – Please provide a summary of progress since your last report (7500)

This report summarises the measure of progress and success against the 'go/no go' criteria set out in the original grant application.

Achieve a minimum of 15 (target of 20) sites open to recruit by the end of the 12 month pilot.

The LAVA trial encountered numerous challenges and obstacles which delayed site set up. These delays were experienced at centres in both the UK and the Netherlands.

Interest in taking part in the trial was high as 12 centres registered an interest with a further 7 expressions of interest received. However, the number of centres to set up in the UK was capped at 15 sites due to funding. The sites were selected and set up commenced. The trial document packages were circulated to the sites at the beginning of August 2016. In line with the new HRA approval process sites have a target of recruiting their first patients within 70 days of receiving the trial document pack. However we found that this target was exceeded at the majority of sites. With our extensive experience and knowledge of clinical trials processes and management in trial set up these set up delays were kept to a minimum and the first UK site opening to recruitment on 30th November 2016 (Kings College London).

The first delay to site set up and recruitment was whilst approval was sought from the REC and HRA for additional exposure to ionising radiation due to extra scans being used at some sites during the ablation intervention and the addition of CT scans not conducted as part of routine imaging in a few centres. Following approval of the amendment on 22nd March 2017, the first UK site re-opened on 28th March 2017 (The Royal Free Hopsital, London) followed closely by another 4 sites (Cambridge, Oxford, King's College (London) and Newcastle)

The general lack of research infrastructure (seen across numerous surgical trials) to support the trial and links with the radiology departments, which play a key role in approving the study at site set up, have also caused significant delays. Two sites (Bristol and the Royal London) were keen to take part but were delayed due to research nurses leaving resulting in capacity issues. Contact was maintained with these sites to facilitate set up once the local network provided additional support.

Another contributing factor was the radiology approvals. Although the study has received National radiology approval, each department internally conducted a radiology review. This led to further delays in receiving confirmation of capability and capacity from the R&D and finance departments. In particular, at Cardiff the radiology department took five months to approve the study due to their backlog of studies awaiting radiology review.

At three sites (Liverpool, Bournemouth and Cardiff) where the intervention is delivered across two centres (i.e. surgery at one centre and ablation in the other) caused initial delays whilst the complexities of the process and accrual allocation werediscussed. Two of the sites

(Liverpool and Cardiff) were put in contact with one another to help expedite the set up process.

Set up at the Netherlands also took longer than anticipated. Each site had to submit the study and contract template for review to their local board to obtain approval before they could open to recruit. This caused major delays due to contract negotiations and the need to meet Dutch Law requirements for participant insurance cover.

Obtaining participant insurance cover presented a major obstacle as to who should provide this. The Dutch REC stated that UCL liability insurance was not sufficient for the Dutch Participants and that there needed to be an indemnity insurance for participants according to European Law. Originally it was suggested that the Sponsor obtain the insurance from an Insurance broker. However, as this was not accepted by the Dutch Ethics Committee, it was later agreed that the lead Dutch site - Maastricht would obtain the policy to cover all Dutch participants.

Whilst the UK use the model non-commercial agreement for research sites in which the main body of the agreement is used without modification or negotiation, this was not the case for the International sites. All changes had to undergo review and negotiation between the Sponsor and site lawyers which took several months as the contract went back and forth between both parties.

The Maastricht site obtained their local approval on 13th April 2017, received their initiation teleconference on 7th June 2017 and was opened to recruitment on Friday 16th June 2017. Despite the above problems, site openings progressed well with at least one site opening per month. As of 16th March 2018, we have a total of 17 sites open to recruitment (13 UK sites and 4 Dutch sites).

Achieve a minimum of 45 (target of 60) participants by the end of the 12 month pilot phase

To date recruitment for the trial is currently at 7 patients randomised (2 in UK and 5 in The Netherlands). Due to the delays in site openings not all sites have been open for the duration of the pilot study. Only 8 of the sites have been opened for more than 6 months. However, the Leeds site opened on 13th October 2017 and recruited the first two UK participants on 28th December 2017 and 22 January 2018.

We have remained in close contact with all of our sites throughout set up and recruitment. We have used our knowledge to implemented recruitment strategies which included maintaining weekly contact with sites, communicating updates via newsletters and providing additional resources to help with identifying patients.

MDT site visits were conducted by the Chief Investigator, Prof Davidson, Mr Gurusamy, a Reader in Surgery and the Senior Trial Coordinator at sites that had been open for at least 3 months from October 2017 up to February 2018 to help facilitate identification of potentially eligible patients. The Birmingham, Oxford, Cambridge, Royal London, Southampton and King's College London sites all received a visit to their site specialist multidisciplinary meeting (sMDT). The LAVA Trial was presented at the start of the meeting, then the meeting was

observed and a discussion around the potentially eligible patients highlighted. Following these visits, the sites began to highlight more eligible patients. The Leeds site was visited at the beginning of February and feedback received from the Investigator was that they are confident that the patient population exists and could potentially recruit up to 12 patients per year. All sites visited to date were confident that they could recruit the number of patients required.

However, despite our efforts recruitment still remains low. A few sites suggested there were insufficient participancts who were suitable for the trial. Other sites identified and approached participants who then identified a strong treatment preference. Another possible reason for lack of trial recruitment is the way in which the trial is introduced to potentially eligible patient. In large centres, the patients are allocated to clinics run by clinicians who may not be directly involved in the trial and may not feel confident in describing the trial without introducing bias. Also, some surgeons may not feel comfortable with presenting themselves as not knowing which is best treatment for an individual patient. This was reflected in a very low up take of recorded consultations between the surgeons and patients used for qualitative assessment.

Since the eligibility criteria was amended, the screening data has shown an increase in eligible patients from 6 to 29. However, the main reasons for non-randomisation were due to the patient having a treatment preference. Patients who had a preference for surgery had often received information from relatives or other sources to indicate that this was the best option for them. The patients who opted for ablation had usually done so following a bad experience with prior bowel surgery.

Explore the patient & clinician acceptability of the trial- Qualitative study update

The Qualitative Substudy Team interviewed 13 members of staff (6 clinicians including Interventional Radiology) and six other recruiting staff. Despite reminders, recruitment encounters have been submitted by only 2 sites; others have declined /ignored requests. Despite reminding teams about the qualitative study, only two patients were interviewed (both decliners).

All clinical interviewees are adamant this is an important question that needs answering.

Acceptability varies across sites with some having most of the surgical team signed up, and others facing a lack of buy-in from colleagues. Even when clinicians are engaged, equipoise is still an issue.

There is very little data available to assess patient acceptability of the trial. Two patients were interviewed. Both felt the trial had been presented in a balanced way, but both had a treatment preference so declined to be recruited and randomised.

Clinicians are split on whether they believe that there is a sufficient pool of eligible high risk patients. Most believe there are eligible patients who are not put forward for consideration in the trial and numbers could be increased (see equipoise). A few believe there insufficient eligible UK patients.

Basic training on equipoise was given at the site initiation meeting, a manual provided and the CI visited sites. Despite this, most clinicians (5/7) acknowledged that the sMDT regularly argue that eligible patients are not suitable for the LAVA trial. Eligibility criteria involve clinical opinion and surgeons largely see patients as operable, or not, leaving few middle ground patients. Recruitment encounter recordings (2 clinicians) provided no evidence of systematic bias in describing the trial to patients, but little data was available. Some non-surgical interviewees said the trial being presented by surgeon alone introduced bias as "a patient seeing a surgeon expects surgery", and "surgeons want to operate". Few surgeons felt comfortable challenging patient preferences, providing treatment options had been discussed. Finally, although a trial of ablation, there was no interventional radiologist (IR) input at the recruitment interview, and IR did not appear well engaged at most sites.

The main barriers to recruitment are an unwillingness by MDT members to engage fully with the eligibility criteria and accepting that a patient who is operable, could be eligible. It should be recognised that a main aspect of the trial suitability is co-morbidity and that this information is often absent or lacking at the time of sMDT discussion. Lack of equipoise could potentially be addressed with more training.

Quality Control assessment of Interventions

There is currently little data available to assess the quality of the ablations and liver resection surgery due to the low number of patients recruited. Should the trial progress past the pilot stage this could be conducted once at least 45 patients are recruited.

Central review of the CT Scan findings

There are insufficient patients recruited to conduct a central review of the CT Scans. Should the trial progress past the pilot stage this could be conducted once at least 45 patients are recruited.

Milestone update – With reference to the milestones you outlined in your latest approved full proposal or protocol, please list the milestones that have been completed (3000)

The following milestones have been reached since the last update:

- First MDT Training visit conducted (Birmingham): 26th October 2017
- 3 Dutch sites opened to recruit: 30 November 2017
- Protocol version 4.0 dated 3rd November 2017 received HRA Approval: 13th December 2017
- First patient recruited UK (at Leeds): 28th December 2017
- Protocol published in Trials: 13th February 2018

Ongoing Problems – Please outline any ongoing problems (7500)

The Investigators were asked if they believed that there was a sufficient pool of eligible high risk patients, for their thoughts on equipoise and main barriers to recruitment.

The UK Investigators report that the high risk patients may exist however may not be fit enough for liver resection and therefore, end up not being randomised. The general feeling is that there is little equipoise amongst the patients rather than the clinicians. These issues have been the main barriers to the sites recruiting.

Staff changes – Please list any changes to project staff since your last report (2500)

Paul McGarry has taken over from Ester Katona as the Data Manager for the trial.

Additional comments – Please note any additional comments relating to this report (7500)

If the trial were to progress past the pilot study stage, the following changes would be made:

- Provide more training on equipoise to the local research teams.
- Conduct more MDT visits to help the sites identify eligible patients.
- Increase the visibility of LAVA to patients through cancer research websites.
- Increase the patient support group communication regarding the trial.
- With sites struggling to identify suitable patients increase MDT support and consider changing site PI.
- Amend the exclusion of concurrent malignant disease - to clarify patients with non-life threatening cancers could be included (eg skin cancer, local prostate cancer).
- Learn for the Dutch sites about their approach to trial presentation and recruitment.
- Explore opening more Dutch sites as recruitment at these sites is progressing well.
- Hold an Interventional Radiologist forum to get more engagement from the local IRs and discuss issues raised.
- Invite and fund the UK HPB site Clinical Nurse Specialists to a LAVA forum.
- Contuinue to use UK surgical meetings as a forum for discussion re LAVA
- Produce a video for patients suitable for the LAVA trial regarding a recruitment encounter which also highlights the background information on the trial.

Network support – Please identify any clinical research networks your project is associated with and provide a brief summary of their support (2500)

We have been working closely with the North Thames CRN to help supporting site set up locally. In particular, the network has provided staff support to facilitate set up of LAVA at the Royal Free Hospital. Furthermore, the network are helping the Royal London site to find support to set up the study and once opened to recruitment will help to deliver the study.

Due to delays experienced in site set up and the subsequent effect on recruitment, we invited two additional UK sites to take part in the trial in Bournemouth and Guildford. The Research Delivery Manager (RDM) at the local networks were contacted to ensure that resources were in place for the sites to deliver the study.

The study was discussed with the local networks and as a result of feedback, help to identify eligible patients was incorporated into our recruitment strategy.

Project oversight update – List oversight group recommended actions and response

The TSC and DMEC of the LAVA trial had a teleconference with the trial management group on March 9th 2018. This included a private TSC and DMEC discussion.

The LAVA trial has been open for over 12 months and it is at the end of the internal pilot phase.

The group considered the trial progress and conduct and reviewed the pre-agreed progression criteria.

Clinical question

There was universal agreement of the on-going importance of the question that LAVA is aiming to address

Progress

Screening and recruitment

16 centres are open (13 UK, 3 The Netherlands)

7 patients have been recruited (2 from the UK and 5 from the Netherlands). All have received their allocated treatment and no withdrawals have occurred.

8 (of 13) UK centres have returned screening log data on 166 patients with colorectal liver metastases. Of these 29 (17%) were considered eligible (21 UK, 8 The Netherlands), 22 approached and 7 randomised, 2 UK (9.5%) and 5The Netherlands) (62.5%).

The nested qualitative study has interviewed 13 staff members and two patients. Audio recordings of consultations have not been undertaken despite requesting these.

Two visits with the CI and trial team has been made (Birmingham and Leeds) and the CI has visited four other centres by himself.

The target sample size for the main trial is 330 patients

Quality control of interventions

Insufficient data available to assess

Central review of CT scans

Insufficient data available to assess

Recommendation

The TSC and DMEC recognised how hard the trial team has worked and congratulated them on opening a good number of centres. Based on these results the TSC and DMEC, however, recommend that the study is closed because on the basis of screening and recruitment data a main trial is not feasible.

Changes to project

None.

Please outline any key changes to your project management plan (5000)

There have been no key changes to our project management plan.

Please outline any key changes to project staff (5000)

There have been no further changes to project staff since the last report.

IP update

There has been no change to the IP nor any new IP identified now the project is underway.

PPI update

A PPI representative sat on the TMG and attended the various meetings. The PPI rep was involved in the development of participant information resources e.g. Patient Information Sheet/Informed Consent Sheet.

There were plans for the PPI representative to input into the Qualitative Research. However, he had to resign due to poor health and therefore, was unable to provide feedback. A replacement PPI representative will be approached if the trial progresses beyond the pilot stage.

Dissemination plan – Please provide an update on progress with dissemination with reference to your dissemination plan. Please also outline any key changes to your dissemination plan

There have been no changes to our dissemination plan.