Liver resection surgery vs. thermal Ablation
for colorectal liVer metAstases

LAVA Trial Closure Plan

Date of Plan: 25th June 2018

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1.0 LAVA Trial Closure Summary

The LAVA Trial had a pilot study built into the first year of recruitment. One of the objectives of the Pilot study was to assess the feasibility of recruitment and this was measured against a 'go/no go' criteria which meant that the study had to open at least 15 sites to recruitment and achieve a minimum of 45 patients recruited during the first year. If recruitment was below 45 patients, then continuation into the main trial would be reviewed by the DMEC and TSC who would provide recommendations on whether the study should progress to the main trial.

The Pilot study was completed and the progress over the first year reviewed by the oversight committees who recommended that the study should not progress to the main trial due to the poor recruitment and that a main trial is not feasible. After the report was submitted to the HTA Programme Manager, the HTA agreed with the oversight committee's decision not to progress to full trial. Recruitment to the trial ceased on 17th April 2018. After one year of recruitment, 16 sites were opened and 9 participants (of the planned 45) were recruited into the study (3 participants were recruited in the UK and 6 were recruited from The Netherlands). The sites were contacted and asked to stop recruitment.

The Trial Management Group met on 24th May 2018 to discuss the next steps for the participants recruited to the trial and the logistics of trial closure. Out of the 9 participants – 1 has withdrawn, 1 is in the post treatment stage (i.e has not reached the 3 month post randomisation assessment) and 7 have completed the 3 month post randomisation assessment. As both interventions are available as standard care and participant's treatment would not be affected if the trial was stopped, it was agreed that the participants should not be followed up for the 2 years due to the costs and resources required. However, it was agreed that the participants recruited would be followed up until their 3 month post randomisation assessments. Also, CT scans would be collected for a central review to meet the pilot study objective of assessing the outcome of the ablation intervention.

The last participant's 3 month follow up assessment is due in July 2018. It was agreed that the data should be received in house and cleaned by the end of July. This would mean that the trial close down procedures should be completed by the end of August 2018.

No formal analysis will be conducted with the dataset as the numbers are not sufficient to yield any significant interpretation of the trial question (Is ablation of similar efficacy to surgery in patients who are considered high risk for surgical intervention). A summary of the data will be included in any outputs arising from the pilot study.

Although the original research question cannot be addressed the experience of recruiting to this study is recognised as being of great value to the research and trials community. The grant collaborators are keen to publish two papers on the challenges experienced. The protocol for the study has already been published. A paper on the outcomes of the pilot study will include a summary of the barriers and problems that the study team had to overcome whilst trying to deliver the study protocol and the second paper will analyse the qualitative aspect of the pilot study. Following publication of these outputs, these would be uploaded into the HTA Programme's journal library to inform other teams considering conducting this type of study.

Communication with the participants on the trial and access to future publications with regards to the study was discussed. The plan is with the input from the TSC PPI representative, to prepare a statement for the participants explaining why the trial has closed early.

Revised trial timelines (Appendix A)

Follow up (3 months): April – July 2018

The last of the recruited LAVA trial participants will complete treatment of the Index disease during this period. Once completed, the participant will undergo the post treatment assessments including the follow up imaging investigation, tumour markers and the completion of the quality of life questionnaires.

All data received will be verified on receipt and entered onto the trial database. Data cleaning with queries being sent to sites is ongoing to ensure the data is clean and ready for any summaries that are required for publication.

As the screening data provides vital information on the screening population, all data up to the date recruitment was stopped will be continued to be chased during this period.

The site closures will be commenced during this period. The sites that have returned all screening data but did not recruit participants will be prepared for site closure first followed by the remaining sites once all data has been received and cleaned.

The ethics committee have been notified that the trial has stopped recruitment early. However, the End of Trial declaration will not be submitted until the last data item for the last participant is received.

Statistical review (1 month): August 2018

No formal analysis of the data will be conducted as there are insufficient numbers for the data to determine non-inferiority of thermal ablation. However, the data received will be downloaded and summarised in preparation for publication.

It is anticipated that dissemination of the pilot study findings will continue beyond this point. Also, communication will be prepared for the participants to let them know where they can obtain access to the outcome of the pilot study.

Cost Breakdown

The University of Leeds (UoL) are currently reconciling what has been spent to date on the grant (up until the end of April 2018) - this will be available at the beginning of July 2018. In terms of committed and forecast costs for UoL (01/05/2018-31/08/2018), an estimated total of £85,219 will be required.

The University College London (UCL) will also have committed and forecast costs, however, only UoL costs can be provided at this moment. UCL have yet confirm what they have spent to date and how much they need to finish the grant (including site payments to be made etc).

2.0 Trial closure activities

2.1 Notification of End of Recruitment

Activity	Who	Progress update
Notification to sites to stop recruiting	SR/EB	Completed 17/04/2018.
Notification to REC- End of recruitment	SR	26/04/2018 Spoke with REC regarding early closure of trial. Advised to call back once the TMG have met and a decision on whether the participants recruited will be followed up.
Notification to DMEC trial stopping	SR	Completed 11/05/2018.
Notification to TSC trial stopping	SR	Completed 25/04/2018.
Notification to TMG trial stopping	SR	Completed 24/04/2018
Notification to Sponsor	SR	27/04/2018 Sponsor contacted for confirmation of payments to be made as per site agreement. 01/05/18 Chased for an update. 11/05/18 Chased again.
Prepare draft Trial Closedown Plan (TCP)	SR	Draft prepared.
Arrange TMG meeting to discuss future of study and input into TCP.	EB	Completed 24/05/2018.

2.2 Trial Closure – Trial Level

Activity	Who	Progress update
Circulate draft TCP for review.	SR	Completed 07/06/2018
Obtain approvals for TCP from DMEC & TSC	SR	Requested 07/06/2018
Prepare financial reconciliation	JC	
Submit Trial Closedown Plan to NIHR HTA via MIS	SR	
Chase screening logs up to April 2018	PM	Chase screening logs up to April 2018
Confirm all data expected received in house.	PM	
Clean data received in house.	PM	
Confirm site ready for closure.	PM	
Review data received in house to check if any analysis is possible	AP	

Submit End of Trial Declaration to REC	BD/SR	24/05/2018 Await receipt of last data item from last participant before submitting.
Review TMF	SR	
Send EOT declaration to Sponsor	SR	
Send EOT declaration to CTRU QA	SR	
Close randomisation system to new recruits.	PM	Completed 17/04/2018.

2.3 Trial Closure – Site Level

Activity	Who	Progress update
Request return of recorders used for recruitment encounters.	EB	12 out of 13 recorders returned.
Request invoices from sites for per patient payments	EB	Awaiting confirmation of UCL's processes. Preparing to send requests w/c Mon 11/06/2018.
Confirmation invoices paid.	UCL	
Inform sites and PIs future plans ie EOT letter, archiving arrangements.	EB/SR	07/06/2018 Sites updated with plans for trial closure.
Prepare ISF Checklist	EB/SR	
Collect final essential docs from site e.g. APL, subject enrolment log.	EB	
Send ISF checklist to sites & confirm ISF ready for archiving.	EB	

3.0 Study Dissemination

Activity	Who	Progress update
Prepare End of Trial Report/Pilot Study findings/publications	TMG	
Submit End of Trial Report/Pilot Study findings/publications	TMG	
Check approvals required for End of Study information for participants	SR	26/04/18: REC confirmed no approvals required.
Prepare draft End of Study information for participants	SR/BD	TSC PPI to review.
Update trial websites with trial closure dates e.g. CRUK, ISRCTN	SR	

4.0 Archiving

Activity	Who	Progress update
CTRU to confirm location of TMF and study related material for archiving which will be retained for at least 5 years from the date of termination of the trial.	SR	

Abbreviations used

ACRONYM	DEFINITION
APL	Authorised personnel log
CI	Chief Investigator
CLM	Colorectal liver metastases
CRF	Case Report Form
CTRU	Clinical Trials Research Unit
DMEC	Data monitoring & ethics committee
EOR	End of Recruitment
EOT	End of Trial
HRA	Health Research Authority
HTA	Health Technology Assessment
ISF	Investigator site file
LIHS	Leeds Institute of Health Sciences
MIS	Management Information System
NIHR	National Institute for Health Research
PDG	Project Delivery Group – CTRU internal team
PI	Principal Investigator
PPI	Patient & Public Involvement
QA	Quality Assurance
REC	Research ethics committee
RGF	Research governance framework
TCP	Trial Closedown Plan
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial steering committee
UCL	University College London
UoL	University of Leeds

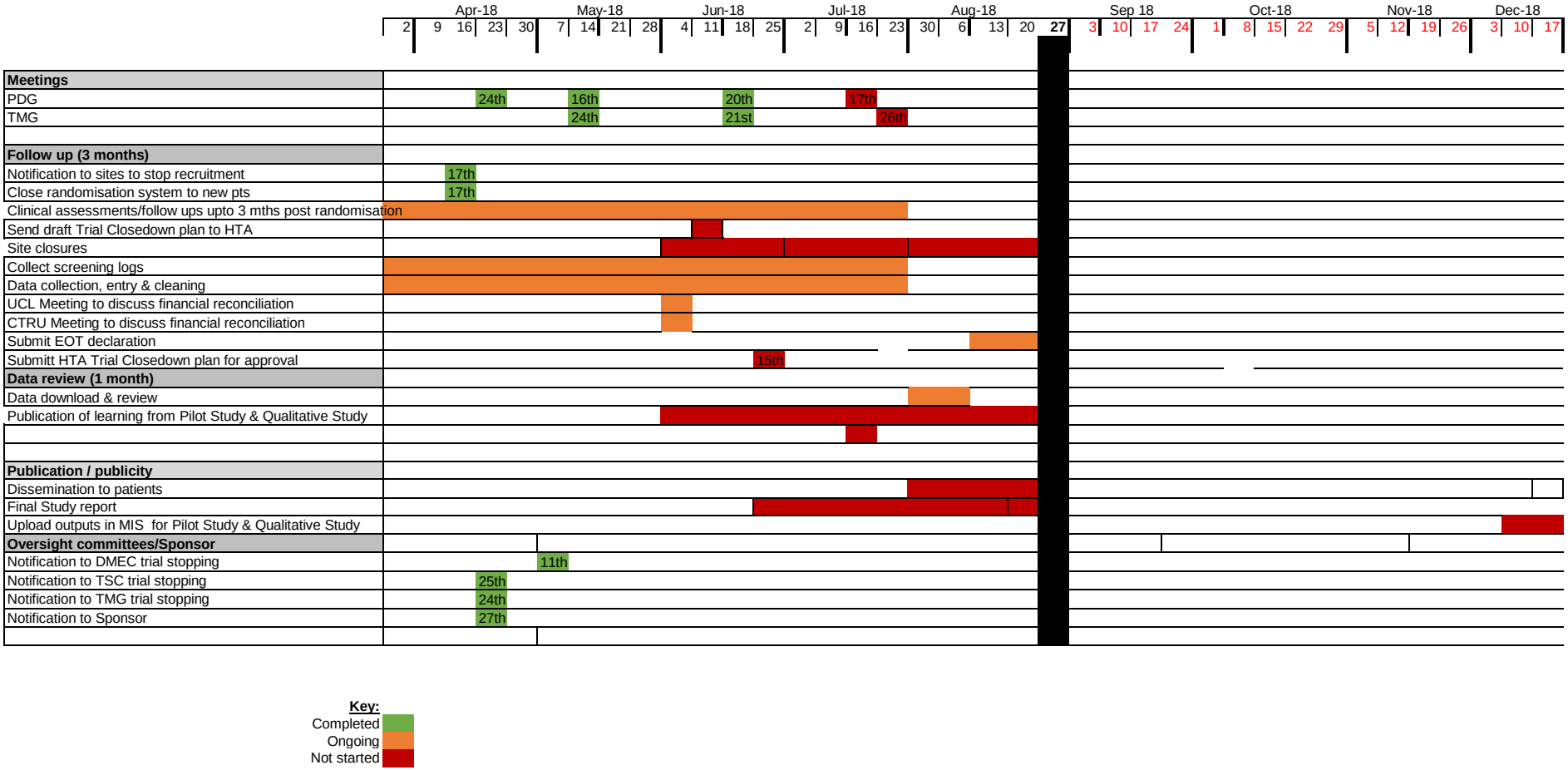
Appendices

Appendix A - Gantt Chart

Appendix B – Financial reconciliation - to follow

Appendix C - Letters from TSC, DMEC & Sponsor

LAVA Closure Timeline



Key:

Completed
Ongoing
Not started

Appendix C – Letters from TSC, DMEC & Sponsor (to follow)

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13 June 2018

Dear Ms Gregory,

Re: HTA Project 13/153/04 LAVA Trial – Trial Closure Plan

Further to your notification of the Outcome of the pilot phase, the Trial Management Team have circulated the Trial Closure Plan to the Trial Steering Committee.

This letter is to confirm that the Trial Steering Committee have reviewed and endorse the Trial Closure Plan for the LAVA trial.

The Data Monitoring Ethics Committee letter will be sent separately.

Yours sincerely,

Professor Jane M Blazeby
Chair of TSC
Director Bristol Surgical Trials Centre
Director of ConDuCT-II Hub
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14 June 2018

To whom it may concern

Re: LAVA Liver resection surgery versus thermal ablation for colorectal liver metastases trial.

This letter is to confirm that the Data Monitoring and Ethics Committee have reviewed and endorse the trial closure plan for this trial. You will already be aware of the recommendation from the Trials Steering Committee (Professor Blazeby and the DMEC (myself) to close the trial after the pilot phase due to inadequate patient recruitment.

Yours sincerely

Stephen J Wigmore

Chair of the DMEC

Professor of Transplantation Surgery
Honorary Consultant Surgeon