THrough knee AMputation's impact on Quality of Life compared to AbovE Knee AmputaTion: The HAMLET Trial

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The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, GCP guidance, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

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Amendment History

Amendment Reference Number	Protocol Version Number	Date Amendment Issued	Details of Changes Made

Contents

Amendment History 4
Contents 5
1.0 Abbreviations 7
2.0 Background and Rationale 9
3.0 Aims and Objectives 11
3.1 Aim 11
3.2 Objectives 11
3.3 Hypothesis 11
4.0 Trial Design 12
4.1 Design 12
4.2 Setting 13
4.3 Outcomes 13
4.3.1 Primary outcome 13
4.3.2 Secondary outcomes 13
4.4 Qualitative/Process Evaluation 18
4.4.1 Intervention, trial acceptability and lived experience 18
4.4.2 Understanding trial conduct and intervention implementation issues 20
4.5 Studies Within a Trial (SWAT) 20
5.0 Study population 23
5.1 Participant inclusion criteria 23
5.2 Participant exclusion criteria 23
6.0 Trial processes 24
6.1 Participant identification 24
6.2 Informed consent 24
6.3 Participant randomisation 25
6.4 Blinding 26
6.5 Participant follow-up 26
6.6 Participant withdrawal 26
7.0 Data Management 27
7.1 Data entry 27
7.2 Data storage 27
7.3 Source data 28
7.4 Source data list 29

8.0 Study treatments 29
8.1 Through Knee Amputation 30
8.2 Above Knee Amputation 30
9.0 Adverse Event Management 30
9.1 Adverse Events 30
9.2 Serious Adverse Events 32
9.3 Reporting procedures for Adverse Events and Serious Adverse Events 32
10.0 Statistical, Health Economics and Qualitative Analyses 34
10.1 Sample size 34
10.2 Internal pilot phase 34
10.3 Statistical analysis 34
10.4 Health economic analysis 35
10.5 Qualitative analysis 36
10.6 SWAT analysis 38
11.0 Ethical arrangements 40
11.1 Risks and benefits 40
11.2 Informing participants of potential risks and benefits 41
11.3 End of trial 41
11.4 Retention of trial documentation 41
12.0 Trial finance and insurance 42
12.1 Trial funding 42
12.2 Trial insurance 42
13.0 Project management 42
13.1 Trial sponsor 42
13.2 Trial management 42
13.3 Trial management group 43
13.4 Trial steering and data monitoring committees 44
13.5 Patient and Public Involvement (PPI) 44
14.0 Dissemination and projected outputs 45
15.0 References 47

1.0 Abbreviations

ABC	Activities-specific Balance Confidence
AE	Adverse Event
AKA	Above knee amputation
AMPnoPRO	Amputee mobility predictor without prosthesis score
ASCOT	Adult Social Care Outcomes Toolkit
BAMS	Basic Amputee Mobility score
BKA	Below knee amputation
CEAC	Cost-effectiveness acceptability curves
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CUA	Cost-utility analysis
DMC	Data Monitoring Committee
EQ5D-5L	EuroQol 5 Dimensions (5L) score
GCP	Good Clinical Practice
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICH	International Council for Harmonisation
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
MLLA	Major lower limb amputation
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
NVR	National Vascular Registry
PI	Principal Investigator
PIS	Patient Information Sheet
PPI	Patient and Public Involvement Group
PSS	Personal Social Services
QALYS	Quality Adjusted Life Years

QoL	Quality of life
REC	Research Ethics Committee
REDCAP	Research Electronic Data Capture
RNLI	The Reintegration to Normal Living Index
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCS	Socket Comfort Score
SIGAM	Special Interest Group in Amputee Medicine Score
SPARG	Scottish Physiotherapy Amputation Research Group
SWAT	Study Within A Trial
TAPES	Trinity Amputation and prosthesis experience score
TMG	Trial Management Group
TMF	Trial Master File
TKA	Through-the-knee amputation
TSC	Trial Steering Committee
VAS	Visual Analogue Scale
WTP	Willingness-to-pay
YTU	York Trials Unit

2.0 Background and Rationale

Approximately 5,000 major lower limb amputations are performed each year in the UK (1), with numbers increasing due to the ageing population and rising prevalence of diabetes (2). Major lower limb amputation (MLLA) includes amputations conducted below the knee (BKA), above the knee (AKA) and through the knee (TKA). Costs to the NHS are approximately £200M/year (3), although this figure does not include the significant costs associated with formal and informal care, homecare visits, residential and nursing home placement. Following MLLA many patients do not return to independent living, with approximately one third of patients being discharged to a care facility (1).

Irrespective of the surgical procedure completed, MLLA has a significant impact on patient quality of life (4). A recent review concluded that the ability to walk successfully with a prosthesis following MLLA had the greatest positive impact on patient quality of life (4). AKA was negatively associated with quality of life due to increased difficulty in walking with a prosthesis (4). In addition to quality of life impacts, MLLA has substantial health implications, including anxiety, depression, altered body image and social discomfort, and the loss of general fitness and independence, which will contribute further to patient burden and healthcare costs (4, 5).

Patients not suitable for a BKA are usually offered an AKA, and less commonly a TKA. There are clear theoretical advantages from a longer residual limb which can be achieved with TKA, with end weight bearing capacity for rehabilitation and biomechanical advantage. However, there is little robust evidence to compare clinical and rehabilitation outcomes and complication rates of TKA and AKA (6). Where evidence is available, this is in the form of observational studies (3, 7) which have included small numbers of participants undergoing TKA compared to AKA and have failed to differentiate between AKA and TKA or between variations of TKA (3, 7). The heterogeneity of the available studies has resulted in variability in rates of uncomplicated healing, reoperation, successful ambulation, and survival but

A recent analysis of UK National Vascular Registry (NVR) and of the Scottish Physiotherapy Amputation Research Group (SPARG) registry data supports the

suggestion of benefits with TKA (1, 8). TKA compared to AKA was found to be associated with fewer medical complications (20% Vs 27% respectively, p=0.005) and quicker discharge from rehabilitation services (99 Vs 133 days respectively, p=0.6) (8, 9), with more patients with TKA than AKA returning to their own home post procedure (51% Vs 43% respectively, p=0.049). No difference was seen between TKA and AKA in rates of wound healing (79% Vs 76% respectively, p=0.23). More people undergoing TKA required reoperation though this was not statistically significant (10% Vs 7%, p=0.06) (9). These results are however based on registry data, and hence important but unmeasured confounders cannot be adjusted for.

Both healthcare professionals and patients have suggested that a sufficiently powered RCT to evaluate TKA and AKA is required. A survey of UK vascular units indicated that TKA was performed in 78% of units but not all surgeons performed this procedure, with the main barrier being lack of evidence of a benefit (3), with separate qualitative data also highlighting the impact of lack of evidence on practice (10). Current guidelines also reflect the lack of evidence and support the need for further research in this area (11) (12). As part of a James Lind Alliance priority setting process for vascular patients with lower limb amputation, patients also highlighted this as a research priority, ranking improvement of clinical outcomes for patients following amputation as the third highest research priority.

There is a need for a high-quality study to determine if there are benefits of performing TKA. Definitive evidence to confirm or refute the potential advantages of TKA compared to AKA would greatly assist amputation multidisciplinary teams working with patients to decide upon the level of amputation that will confer greatest advantage and least risk of complications.

3.0 Aims and Objectives

3.1 Aim

To assess the clinical and cost effectiveness of TKA compared to AKA in patients requiring MLLA but who are unsuitable for a BKA.

3.2 Objectives

i) To undertake a parallel group randomised controlled trial to compare the effects of TKA and AKA on quality of life and surgical and rehabilitation outcomes.

ii) To include a 12-month internal pilot phase to obtain robust estimates of recruitment rates, site set up and outcome data collection, and to evaluate intervention and trial process acceptability.

iii) To undertake an integrated qualitative study to assess patient's lived experiences and acceptability of TKA and AKA and the trial.

iv) To conduct a detailed economic evaluation to compare the cost-effectiveness of TKA and AKA to determine the most efficient provision for future care and resources.

v) To explore how TKA may be implemented into clinical practice (if effective).

3.3 Hypothesis

Quality of life following TKA is superior to quality of life following AKA for patients requiring MMLA but who are unsuitable for BKA.

4.0 Trial Design

4.1 Design

The trial objectives will be addressed using a multicentre, two-arm, non-blinded, pragmatic, parallel group randomised controlled superiority trial.

The study will consist of a three-year recruitment phase, including the 12-month internal pilot phase, followed by the main recruitment period. Following collection of baseline measures, randomisation and treatment, all participants will be followed up for 24 months. Follow-up data will be collected from participants via a remote questionnaire every four months, at 4, 8, 12, 16, 20 and 24-months post randomisation.

The 12-month internal pilot will assess recruitment and retention and patient acceptability of both the intervention and trial processes. The pilot study will be set up in sites with existing surgical, rehabilitation and prosthetic experience of TKA, allowing additional time for other sites to receive training and support to implement or expand TKA services if required.

Semi-structured interviews will be conducted to include study participants, those who withdraw from the study and patients who decline to participate. The findings of these interviews will be used to inform aspects of trial design and delivery during this phase. These interviews will take place 8-10 weeks post-treatment.

To understand the longer-term impact of TKA and AKA on patient's lives and recovery, as part of the qualitative study, we will follow up a subgroup of 20-24 patients for up to 3 years, with interviews at 12, 24 and 36 months post-operatively.

A report will be provided to the funder at the end of the pilot phase and subject to their approval (assuming feasibility has been established) will proceed to the main trial.

4.2 Setting

Patients will be recruited from NHS hospitals within the UK that both provide MLLA care and have the facilities to support research activity. All participating hospitals will have the necessary resource and capability to perform both AKA and TKA surgery. A list of all study sites will be maintained by the trial management team and held in the trial master file.

4.3 Outcomes

4.3.1 Primary outcome

The primary outcome will be the quality of life (QoL) collected using the EuroQol 5 Dimensions (5L) score (EQ5D-5L) via remote questionnaire (telephone, electronic or postal) at 24 months post randomisation (Table 1 and 2). The EQ-5D-5L measures health-related quality of life in terms of 5 dimensions: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, anxiety and depression across 5 levels. The EQ-5D-5L will be scored according to the user guide (13).

4.3.2 Secondary outcomes

Secondary outcomes will be collected at baseline, within the hospital 5 days post procedure, during early assessment at a prosthetic centre (if applicable) and at 4 monthly intervals post-randomisation (4, 8, 12-, 16-, 20- and 24-months post-randomisation). These will include quality of life, surgical and rehabilitation outcomes, as well as longer term social and functional outcomes. Where possible, data collection will rely on routinely collected information in clinical notes to minimise the requirement for active input from participants (Table 2). To ensure timely collection of data a visit window of +/- 21 days will apply to each visit timepoint.

Quality of life

- EQ-5D-5L data collected at baseline and 4, 8-, 12-, 16- and 20-months post randomisation as recorded by the participant via remote questionnaire.

Surgical outcomes

- Perioperative blood loss – estimated using the pre and post operative Haemoglobin (14) (15), alongside details of any blood products used in the perioperative period, as documented in the patient medical record.
- Planned or unplanned high observation or intensive care admission, collected from the patient medical record.
- Procedural pain using a Visual Analog Scale (VAS).The VAS consists of a 100-milimeter line representing a continuous scale. The line is anchored at both ends with the verbal descriptors ‘No pain’ (=0) and ‘Worst imaginable pain’ (=100). The outcome will be recorded by the participant at daily intervals over the first 5 days post procedure and will require the research team to visit them daily to collect this.
- Within hospital complications. Specifically referring to major adverse cardiovascular events, renal impairment and delirium. This information will be collected from the patient medical record.
- Impaired wound healing (including wound infection), as recorded in the patient medical record and via patient reported data.
- Return to theatre for revision surgery at either the same or a higher level of amputation, as documented in the patient medical record.
- 30-day mortality, as documented in the patient medical record.
- Total post operative length of stay, (from day of surgery to the day of discharge from treating hub) as documented in the patient medical record.
- The number of days alive and out of hospital, measured at 90 days through review of the patient medical record.
- The participant’s destination on discharge from primary surgical bed. This will be derived from the patient medical record and recorded as own home/rehab facility/respite facility/residential care/nursing care.
- Contralateral limb outcomes including both minor and major amputation. This will be collected either via self-report at telephone follow up or collected from the patient medical record.

Rehabilitation outcomes

- Basic Amputee Mobility Score (BAMS): A score which can be used for daily assessment of the basic mobility of patients with leg amputation. This score will be used to assess the participants early mobility and will be measured by review of the participant's medical records at 5 days post procedure. Scores will be derived in alignment with the BAMS manual (16).
- Prosthesis assessment measured using the Special Interest Group in Amputee Medicine Score (SIGAM) (17): a single-item scale comprising six clinical grades (A-F) of amputee mobility. This score will be assessed from the review of the patient medical record at both the point of discharge from hospital and discharge from rehabilitation.
- Participant referral for prosthetic assessment, as recorded in the patient medical record it will be documented whether the participant has been referred or not.

If a participant is referred for prosthetic assessment:

- Amputee mobility predictor without prosthesis score (AMPnoPRO): an assessment tool designed to measure the functional status of lower-limb amputees without the use of a prosthesis (18). This will be recorded during the assessment of the initial visit at a prosthetic centre.
- The achieved expected level of rehabilitation. This will be the difference in score between the patients initial AMPnoPRO and final AMPnoPRO (non-prosthesis users) and AMPPro (prosthesis users) scores.

For participants issued with a prosthetic limb (to each be collected from participants remotely at 8-month intervals post randomisation):

- Trinity Amputation and prosthesis experience score (TAPES): consisting of 9 subscales which address psychosocial factors, activity restriction and satisfaction with the prosthesis (19). This score will be used to assess the participants experience of the prosthesis.
- Socket comfort score (SCS): an 11-point scale from 0-10, where 0 represents the most uncomfortable and 10, the most comfortable socket imaginable (20).
- Self-reported prosthetic wear time and usage.

Social care and long-term outcomes

The following measures will be collected from participants remotely at 8-month intervals post randomisation)

- Participant requirement for both paid/formal care and unpaid friends and family care.
- The Adult Social Care Outcomes Toolkit (ASCOT) SCT4 questionnaire: a multi-attribute utility index designed for the evaluation of long-term social care services, comprised of eight attributes that capture aspects of social care-related quality of life (21).
- The number of participant self-reported falls (defined as the participant falling, tripping, stumbling or making contact with the ground) and associated complications. Participants will be asked to recall this information for the previous 4 weeks.
- Activities-specific Balance Confidence (ABC) scale: a questionnaire developed to assess the balance confidence of individuals when performing daily activities, on a wide continuum of less and more challenging activities (22).
- The Reintegration to Normal Living Index (RNLI): a measure to assess the reintegration into normal social activities for those with chronic illness. The 11 items within the index are each accompanied by a VAS anchored by phrases reflecting whether the statement describes the situation of the patient (23).
- Pain and phantom pain assessment assessed using a VAS (as previously described for the procedural pain outcome).

Health economics outcomes

- Resource use: a tailored questionnaire will collect data on healthcare resource use, prosthetics, private health services, and productivity loss.

Table 1: Timeline of all outcomes to be collected

Outcomes	Timepoint					
	Baseline		**Pre/Peri/Post Procedure**	**Discharge**	**Between randomisation and FU**	**Follow-up**
Quality of Life (EQ5D)	x					x
Falls	x					x
Frailty assessment	x					
Pain	x		x	x		x
Perioperative blood loss			x			
High observation/intensive care admission				x		
Within hospital complications			x	x		
Wound healing			x	x		x
Further amputation surgery			x	x		x
30-day mortality						x
Total post-operative length of stay						x
Number of days alive and out of hospital (at 90 days)						x
Discharge destination				x		
Contralateral limb outcomes	x					x
BAMS					x	
SIGAM					x	
Prosthesis referral				x		x
AMPnoPRO					x	
Achieved expected level of rehabilitation					x	
Prosthetic wear time and usage					x	
Use of formal and informal care						x
Resource use						x
TAPES					x	
SCS					x	
ASCOT						x
Balance (ABC)						x
RNLI						x

RANDOMISATION

Table 2: The follow-up timeline for all outcomes which require active participant input.

Timepoint*	Questionnaires				
Month 4	Quality of Life (EQ5D)	Pain	ASCOT	Balance (ABC)	Wound Healing
Month 8	Quality of Life (EQ5D)	Pain	Falls	RNLI	TAPES+
Month 12	Quality of Life (EQ5D)	Pain	ASCOT	Balance (ABC)	Wound Healing
Month 16	Quality of Life (EQ5D)	Pain	Falls	RNLI	TAPES+
Month 20	Quality of Life (EQ5D)	Pain	ASCOT	Balance (ABC)	Wound Healing
Month 24	Quality of Life (EQ5D)	Pain	Falls	RNLI	TAPES+

**Visit window for data collection of +/- 21 days +Prosthesis users only*

4.4 Qualitative/Process Evaluation

Qualitative research will be conducted within the pilot phase of the study to understand the acceptability of the intervention and trial processes and inform the main study. Interviews will continue into the main study to understand patient recovery.

Objectives of the qualitative work are to understand:

1) The acceptability of the interventions and trial processes from the perspective of patients (cross-sectional study).

2) Patient's lived experience and acceptability of AKA and TKA surgery and the impact on quality of life and recovery (longitudinal study).

3) The implementation of TKA into clinical practice.

4.4.1 Intervention, trial acceptability and lived experience

All individuals who have consented to participate in the trial will be invited to participate to capture their experiences of the trial, acceptability of the trial processes, and views of TKA and AKA. Those who decline participation will also be invited to participate in relation to intervention acceptability and trial processes only.

A purposive sample of maximum 48 patients to include both sexes, a range of ages, clinical presentation, socio-economic status (based on postcode converted to Index of multiple deprivation score), geography (region/site) (24), ethnicities and patients living with multi-morbidity. Guided by information power (22), with a narrow study aim and exploratory analysis, this sample size should provide sufficient data to address the associated research questions. Recruitment will end when the trial closes to recruitment, or when the final sample size is reached.

Patients will be approached to take part in an interview by the local research team. This will be following the participant's surgery and once clinically appropriate. For those who agree to receive further information, a 'consent to contact' form will be completed. The HAMLET qualitative researcher will then contact the patient by phone, email or post to discuss further.

Any patient who verbally gives consent to contact and subsequently agrees to take part in an interview, will be asked to provide written consent. If it is not possible for the patient to sign the consent form prior to the date of the interview, verbal consent will be taken at the start of the interview, and the associated audio recording saved. If a signed consent form is subsequently received the audio recording will be deleted. Patients may consent immediately, decline immediately, or defer their consent. Patients will have the option to have their partner or informal carer join them for the interviews, but this will not be a requirement of participation.

Initial interviews will take place eight to ten weeks post-operatively. Those who drop out of the study post randomisation may be interviewed at the point they drop out of the trial. Participants will also be invited to participate in a longitudinal interview study to gain insight into the impact on QoL and longer-term recovery (at 6, 12, 24 and where possible 36 months post amputation).

Interviews will take place face-to-face, telephone or video, depending on patient preference. The interview will be informed by a topic guide developed for the study with PPI input.

All interviews will be audio recorded using an encrypted dictaphone or directly onto a university laptop/PC (online interviews). Interviews will be transcribed, and

pseudoanonymised for analysis. Field notes will be taken after each interview and used in analysis.

Though the interview will focus on sensitive information and participants may describe distressful times and feelings, the interview itself should not cause distress. If any participants do become distressed or fatigued the interview will be paused or stopped. If appropriate, the patient's clinician will be contacted (e.g. GP).

4.4.2 Understanding trial conduct and intervention implementation issues

Regular meetings will be held with sites to explore how sites envisage implementing the study results into clinical practice. These meetings will enable identification and understanding of logistical barriers, set up delays and any difficulties with data collection or loss to follow-up, and to identify facilitators to optimise delivery of the trial protocol locally (25).

4.5 Studies Within a Trial (SWAT)

The HAMLET study will act as a host trial for two individual Studies Within a Trial (SWAT), designed to evaluate the effectiveness of either a participant recruitment or retention strategy. The protocols for each are available on the MRC SWAT repository (recruitment: SWAT 15 (26), retention: SWAT 180 (27)). As is usual with embedded trials, the sample size will be informed by the number of participants approached to participate in the main study (for the recruitment SWAT) or those participating in the study (for the retention SWAT).

4.5.1 Recruitment SWAT: The effectiveness of a study explanatory animation

We will evaluate the effects of mode of presentation of the study design to participants on recruitment rate. Participants will be randomised (on a site basis) to receive an animated explanatory video (explaining the study) plus the standard patient information sheet (PIS) or just the PIS.

Successful clinical trial recruitment is an ongoing challenge, with a recent review estimating that 37% of trials fail to meet their recruitment targets (28). The PRioRiTy study of recruitment research prioritised "what are the best approaches

for designing and delivering information?" to potential participants as the fourth most important unanswered issue (29).

A review of recruitment strategies identified 35 studies focusing on information delivery, but almost all were low or very low methodological quality (30). Only three studies evaluated use of video information provision, with very low-GRADE certainty evidence. At the time of the review, no studies evaluated animations as a method of providing study information. The popularity of animations is however increasing and hence evaluation is required.

As is usual with embedded trials, the sample size is constrained by the number of patients approached about the study hence a formal power calculation to determine sample size has not been conducted.

This will be a cluster trial; randomisation will be carried out at the site level to reduce cross contamination. The allocation ratio will be 1 to 1. Generation of the allocation sequence will be undertaken independently by a researcher not involved with the recruitment of participants.

The primary outcome of this embedded trial will be the recruitment rate, i.e. the proportion of participants in each group who are randomised into the host trial. Secondary outcomes will include the proportion of patients in each group who are screened but do not go on to be randomised, and the cost effectiveness of the intervention.

4.5.2 Retention SWAT: A cash vs voucher monetary incentive

Poor participant retention rates can have adverse consequences on the validity of randomised trials. There is a lack of evidence on efficient ways to retain participants in trials.

Monetary incentives consisting of either shopping/gift vouchers or cash are a common strategy used by trial teams to encourage participants to complete follow-up

questionnaires, attend follow-up assessment appointments or both. A previous review of strategies to improve retention in trials found monetary incentives may improve retention rates compared with no incentive; but the certainty of the evidence was low [1]. As a result, evaluation of monetary incentives as a retention method requires further evaluation.

We will evaluate the effect of an unconditional £25 shopping voucher incentive compared with an unconditional £25 cash incentive, provided before the 12 and 24 month follow up questionnaire. Participants will be asked to confirm their voucher preference at Baseline so that this can be provided should the participant be randomised to receive the voucher intervention.

As is usual with embedded trials, the sample size is constrained by the number of patients approached about the study hence a formal power calculation to determine sample size has not been conducted.

All participants recruited into the HAMLET trial, who remain as fully participating (i.e. have not fully withdrawn, withdrawn from postal follow up or have died) and who have yet to reach the 12-month time point will be eligible for the SWAT. There are no additional inclusion or exclusion criteria.

Generation of the allocation sequence will be undertaken independently by a researcher not involved with the follow up of participants. Participants will be allocated 1:1 using block randomisation, stratified by the host trial's treatment arm, using randomly varying block sizes to avoid imbalance between the SWAT intervention arms.

The primary outcome of this embedded trial will be retention rate, i.e. the proportion of participants who return their questionnaire in each group.
Secondary outcomes will be:
1) Cost-effectiveness (cost per participant retained)
3) Number of contact attempts with participants before completion of follow-up

assessment
4) Questionnaire completeness (e.g., primary outcome measure obtained)

The effects of the strategies in different patient populations will be explored, including sex, age and ethnic subgroups.

The acceptability of vouchers vs cash as an incentive will be explored with consenting participants as part of the embedded HAMLET Process Evaluation. Data will be shared with the IMPLEMENT SWATs team at the University of York for inclusion in a wider process evaluation of this intervention.

5.0 Study population

The target population for the HAMLET study will be patients who require a MLLA and are suitable for TKA and AKA but are unsuitable for BKA. To ensure the study results are representative of all those requiring a MLLA, all adult patients requiring a MLLA for any reason will be eligible.

5.1 Participant inclusion criteria

- Aged 18 years or older.
- Requiring unilateral MLLA, including patients with a pre-existing BKA who require revision to a TKA or AKA
- Able to provide consent and willing to adhere to the follow-up protocol.

5.2 Participant exclusion criteria

- Suitable for a BKA – as determined by the local surgical team.
- Contraindication to either AKA or TKA – as determined by the local surgical team.
- Limited life expectancy (of ≤6 months)
- Patients who require concurrent bilateral MLLA
- Evidence that the patient would be unable to adhere to trial procedures or complete questionnaires.
- Previously recruited to the HAMLET Trial

6.0 Trial processes

6.1 Participant identification

The study management team at York Trials Unit (YTU) will work closely with surgeons, clinicians and research teams at each study site to optimise the screening and recruitment process for local circumstances. Participating sites will retain screening logs to capture the number of ineligible and non-consenting patients, which will be transferred to YTU on a regular basis. For all patients who require a MLLA and are not suitable for a BKA, we will record whether the patient has been approached and/or consented to take part in the trial. If the patient has not been recruited into the trial, the reason for this will be recorded (e.g. ineligible, not approached, not consented). The trial team will use this information, alongside the qualitative investigations during the pilot phase, to identify potential areas where recruitment processes require improvement.

The screening process will be consistent for all patients undergoing a MLLA and will be performed by the treating clinician or research team in the ward or clinic when the decision to proceed to MLLA is made. Once a patient has been screened against the study eligibility criteria and deemed suitable for inclusion, they will be approached for study participation.

6.2 Informed consent

Patients will be provided with a detailed participant information sheet (PIS), which outlines the study and clearly explains the risks and benefits of trial participation. The PIS will be developed in collaboration with members of the study patient and public involvement (PPI) group.

Potential participants will receive a contact phone number so that they can ask questions of the surgeon and local research team and will be given time before deciding to participate. The patient may be asked at the time of approach whether they have had sufficient time to consider study participation, and if required to

discuss the study with friends and family. They will be given further time to reach a decision if necessary.

For those who it is applicable, as part of the recruitment SWAT (refer to section 4.6.1), a recruitment video animation will also be provided.

Where participants agree to participate in the study, written consent for the study will be obtained. Specific consent will be sought to enable the sharing of identifiable data with the coordinating centre (YTU) as part of the study to facilitate the collection of outcome data. Permission will also be sought to inform the patient's GP of their study participation. All members of staff involved in eligibility sign-off and informed consent process will be required to have Good Clinical Practice (GCP) training. Depending on local circumstances, consent will be obtained in advance of, or on the day of admission for the procedure.

The responsibility for recording written informed consent will be with the site Principal Investigator (PI), or persons designated by the PI, who conducted the informed consent discussion. Designated responsibility should be recorded on the site delegation log. All consent forms will be stored in accordance with local requirements. A copy of the consent form will be given to the participant, a further copy filed in the patient medical records and the original signed copy kept in the Investigator Site File (ISF). A copy will be sent through an agreed secure method to YTU or uploaded onto the data collection database (REDCap) for central monitoring purposes.

6.3 Participant randomisation

When patients have provided written informed consent and all baseline data has been collected, an authorised and delegated member of the clinical or research team will access the randomisation area of the REDCap system managed by YTU. Randomisation will take place in the seven days prior to the date of surgery. This will ensure that the participant's treatment allocation is known to both the operating surgeon and participant beforehand. The randomisation instruments within REDCap will require the recording of information and a check of patient eligibility to avoid inappropriate entry of patients into the study. The REDCap system will then perform

independent and concealed random allocation. Patients will be randomised in a 1:1 ratio, minimised by amputation aetiology (trauma vs non trauma), frailty (3 levels as per Rockwood Frailty Scale: no frailty (Score 1 to 4), mild to moderate frailty (Score 5 to 6), severe to very severe frailty (Score 7 to 8),sex, and presence or absence of pre-existing contralateral major lower limb amputation, to receive either TKA or AKA.

6.4 Blinding

The operating surgeon will be informed of the allocation and will not be blind to the intervention. Due to the nature of the intervention, blinding of participants and assessors is not possible. Data on patient preferences will be collected at baseline.

6.5 Participant follow-up

As detailed in section 4.3 participants will be followed-up within the hospital 5 days post procedure, during early assessment at a prosthetic centre (if applicable) and at 4 monthly intervals post-randomisation (4, 8, 12-, 16-, 20- and 24-months post-randomisation). The data collected both within the hospital and prosthetic centre will be done so in person by study research staff. As informed by our PPI members, remote data will be collected by study research staff via phone call with the participant. If preferred by participants, they will also have the option to provide data via digital media or postal questionnaire. Participant phone-calls will be conducted in line with the appropriate YTU Standard Operating Procedures.

Study participants should also attend any routine clinical appointments that may be scheduled outside of the study, in line with routine care pathway at the participating site.

6.6 Participant withdrawal

Participants will have the right to withdraw from the study at any time and the reason for which will be recorded in the case report form (CRF). Any participant wishing to withdraw from the study will be requested to state what personal details already collected they wish to allow the study team to retain following withdrawal. The study staff member documenting the withdrawal will request participant consent to

continue to access clinical records to facilitate some level of outcome assessment in the absence of ongoing active participation in the study. If this consent is not provided, no further participant data of any kind will be collected from then onwards.

7.0 Data Management

7.1 Data entry

The data collected by sites will be entered onto REDCap, a secure online interface, specifically developed for this study. For data that are collected via participant report, only the study data in REDCap will be the source data. Data not captured on REDCap, will be stored and transferred following YTU standard operating procedures and/or University of York policies. The staff involved in the trial (both at the sites and YTU) will receive training on data protection. The staff will be monitored to ensure compliance with privacy standards.

Computerised data cleaning and validation checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Data will be checked according to procedures detailed in the trial specific Data Management Plan or REDCap specification document. An electronic audit trail system will be maintained within the data collection system to track all data changes in the database once the data has been saved initially into the system or electronically loaded.

7.2 Data storage

Data will be collated in REDCap with participants identified by a unique identification number (i.e. the participant identification number) only. A Trial Enrolment Log at the sites will list the participant identification numbers. YTU will maintain a list of participant identification numbers for all trial participants at each site. At the University of York, data will be held securely on the cloud-hosted REDCap server. Access to the study interface will be restricted to named authorised individuals granted user rights by a REDCap administrator at YTU. Data not within REDCap will be hosted on University of York servers. All YTU data recorded electronically will be

held in a secure environment at the University of York, with permissions for access as detailed in the delegation log. Backups are taken daily and stored in a separate location. Snapshots are also taken at regular intervals throughout the day. The University's backup policy can be found here: https://www.york.ac.uk/it-services/services/backups/#tab-4

All study files will be stored in accordance with GCP guidelines. Study documents (paper and electronic) held at the YTU will be retained in a secure (kept locked when not in use) location for the duration of the trial. All essential documents, including source documents, will be retained for a minimum period of five years after study completion. The separate archival of electronic data will be performed at the end of the trial, to safeguard the data for the period(s) established by relevant regulatory requirements. All work will be conducted following the University of York's data protection policy which is publicly available (https://www.york.ac.uk/records-management/dp/).

7.3 Source data

The Investigator(s)/institution(s) will permit authorised representatives of the Sponsor and applicable regulatory agencies direct access to source data/documents to conduct trial-related monitoring, audits and regulatory inspection. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

Essential trial documentation (i.e. the documents which individually and collectively permit evaluation of the conduct of a clinical trial and the quality of the data produced) will be kept with the Trial Master File (TMF) and Investigator Site Files (ISF). The Sponsor will ensure that this documentation will be retained for a minimum of five years after the conclusion of the trial to comply with standards of Good Clinical Practice.

At YTU, the CRF data will be stored for a minimum of five years after the conclusion of the trial as paper records and in electronic format in accordance with guidelines on Good Research Practice. All paper records will be stored in a secure storage facility or off-site by York Trials Unit. All electronic records will be stored on a password protected server. The PI at any participating site will archive the trial essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site agreement or Organisational Information Document.

Once reporting and analysis are completed and published in all intended scientific journals, the anonymised data will be made available for other researchers if requested. In principle, anonymised data will be made available for meta-analysis and, where requested by other authorised researchers and journals, for publication purposes. Requests for access to data will be reviewed by the co-Chief Investigators, study Sponsor and trial team.

7.4 Source data list

Source documents are original documents, data, and records from which participants' CRF data are obtained. CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). In this study source data will be captured by site staff within CRFs and also by participants during follow-up data collection.

8.0 Study treatments

All recruiting centres will have surgeons who are qualified and able to perform the treatments for both study arms. To maintain consistency within the interventions, direct clinical training in TKA techniques will be offered to centres joining the main phase of the trial if required.

8.1 Through Knee Amputation

TKA will be adopted as the study intervention. TKA will be defined as any technique of amputation within the vicinity of the knee joint that removes the leg below the knee joint but preserves and reattaches the patella tendon. As a pragmatic study, and in the absence of evidence to support any one technique of TKA above another, all patella tendon preserving TKA variants will be included as the perceived benefits of a longer lever and majority intact muscle insertions will be preserved. A 4-component classification system as previously described for TKA operative techniques use on the femur, patella, muscular flaps and skin incision will be used to capture the exact type of TKA performed for each participant(31).

During the recruitment period of the HAMLET study the number of TKA procedures received by patients would be expected to increase. Other aspects of the patient's care in the perioperative period will be according to local standards and as per current pathways. There are no expected excess treatment costs for the intervention arm over the control arm.

8.2 Above Knee Amputation

For the HAMLET study an AKA will be the study comparator treatment and defined as femoral division at 10-15cm above the superior margin of the patella with a standard anterior and posterior fish-mouth flap incision. As current care pathways for patients requiring MLLA often lead to patients receiving AKA, participants allocated to the comparator arm of the study will most likely receive no change in care due to study participation.

9.0 Adverse Event Management

9.1 Adverse Events

For the purposes of the HAMLET Trial, adverse events (AE) are defined as any untoward medical occurrence (i.e. any unfavourable and unintended sign, symptom or disease), experienced by a clinical trial participant and which is temporally associated with study treatment (interventions or control) and is concerned with the amputation stump, the original (index) surgery, or any event requiring medical or surgical intervention to the residual limb.

Adverse events, which might be expected with this intervention are listed in Table 3.

Table 3: Expected Adverse events in relation to the HAMLET study

Blood and lymphatic system disorders	**Renal and urinary disorders**	**Nervous system disorders**
Anaemia Postoperative hemorrhage Hematoma	Acute kidney injury Hematuria Urinary retention	Dizziness Dysarthria Headache Paraestheis Presyncope Seizure/convulsions Spasticity Stroke Transient ischemic attacks (TIAs) Tremor Phantom pain
Ear and labyrinth disorders	**Immune system disorders**	**Psychiatric disorders**
Tinnitus	Allergic reaction	Agitation Anxiety Confusion Delirium Delusions Hallucinations Psychosis
Cardiac disorders	**Infections and infestations**	**Respiratory, thoracic and mediastinal disorders**
Chest pain – cardiac (includes angina) Sinus bradycardia Sinus tachycardia Heart failure Myocardial infarction	Phlebitis infective urinary tract infection (UTI) Wound infection	Atelectasis Dysponea Pleural effusion Lung infection (including pneumonia)

	Enterocolitis infectious (includes clostridium dificile)	

9.2 Serious Adverse Events

A serious adverse event (SAE) will be defined as any untoward occurrence which is concerned with the amputation stump, the original (index) surgery, or any event requiring medical or surgical intervention to the residual limb and that:

- Results in death.
- Is a life-threatening event (that is it places the participant, in the view of the Investigator, at immediate risk of death).
- Requires unplanned hospitalisation or prolongation of existing hospitalisation (unplanned refers to emergency hospitalisations resulting in an inpatient stay; prolonged hospitalisation is deemed to be where a participant's stay is longer than expected).
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions).
- Is another important medical condition.

Important medical events that may not be immediately life-threatening, result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the outcomes listed in the definition of an SAE will also be considered serious.

9.3 Reporting procedures for Adverse Events and Serious Adverse Events

An appropriate member of the research team will record all directly observed AEs and all AEs reported by the trial participant following their trial treatment. In addition, sites should follow their own local procedures for the reporting of any adverse events linked to clinical care. All AEs requiring reporting will be recorded on an (S)AE form or REDCap data collection tool and will be reported to YTU within 24 hours (SAE) or 5 days (AE) of the research staff or clinical team becoming aware of the event.

The severity and likely relationship to study treatments of any adverse events will be documented by the designated site clinician. An event is defined as ‘related’ if the event was due to the administration of any research procedure. Whereas an ‘unexpected event’ is defined as a type of event not listed in the protocol as an expected occurrence. All non-serious AEs, whether expected or not, should be recorded in the participant’s medical notes.

At the time of reporting, the PI or delegated clinician will be asked to record an assessment of causality (to trial treatment) selecting an option from the list below:

- Definitely related- there is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- Probably related- there is evidence to suggest a causal relationship, and the influence of other factors is unlikely
- Possibly related- there is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial procedures). However, the influence of other factors may have contributed to the event (i.e. the participant’s clinical condition, other concomitant events).
- Unlikely to be related- there is little evidence to suggest there is a casual relationship (e.g. the event did not occur within a reasonable time after administration of the trial procedures). There is another reasonable explanation for the event (e.g. the participant’s clinical condition, or other concomitant treatments).
- Unrelated- there is no evidence of any causal relationship.

Once received, causality and expectedness will be confirmed by the CI. SAEs that are deemed to be unexpected and related to the trial will be notified to the REC and Sponsor within 15 days.

All such events will be reported to the Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) at their next meetings. All participants experiencing SAEs will be followed up as per protocol until the end of the trial.

10.0 Statistical, Health Economics and Qualitative Analyses

10.1 Sample size

For the HAMLET study, a total target sample size of 386 participants, to be recruited over a period of 36 months, will be required to achieve 90% statistical power. This target was derived from a minimum clinically important difference of the EQ-5D-5L among a variety of patients with multiple co-morbidities and of similar demographics to the amputation population of 0.074 (mean) or 0.081 (median) (32). Estimating a loss to follow up rate of 20% and assuming an EQ-5D-5L difference of 0.074 with an estimated standard deviation of 0.2 (33), we would need to randomise 183 participants to each arm of the study to have 90% power (2p = 0.05); therefore, requiring a total of 386 participants.

10.2 Internal pilot phase

During the 12-month internal pilot phase, we plan to open sites at a rate of 1-2 sites per month and recruit at least one participant for every two months that a site is open, equating to a total of at least 77 participants from 12 sites within the allocated 12 months. The progression criteria from the internal pilot phase to the main study are highlighted in Table 4 below.

Table 4: Progression criteria from the internal pilot phase to the main study.

Progression criteria	Red	Amber	Green
Recruitment rate (per site/per month)	<0.3	≥0.3 but ≤0.5	≥0.5
Number of centres opened	<9	9-11	12
The % return of EQ-5D-5L data at 4-months	<75%	75 – 79%	≥80%
Total number of participants recruited	<50	50-77	>77

10.3 Statistical analysis

All analyses will be described in detail in a statistical analysis plan (SAP) which will be finalised prior to the end of data collection and will be reviewed and approved by

the TSC and DMC. The SAP will be made publicly available via the ISRCTN registry. Analyses will be carried out on a locked dataset and performed using two-sided statistical tests at 5% significance under the principles of intention-to-treat. All analyses will be conducted taking into consideration the reporting requirements of the Consolidated Standards of Reporting Trials (CONSORT).

The primary analysis will compare the EQ-5D-5L scores between groups using a covariance pattern mixed-effect linear regression model, incorporating all post randomisation time points.
Treatment group, time, treatment-by-time interaction, stratification factors and baseline covariates will be included as fixed effects. Participants will be included as a random effect accounting for repeated observations per patient. Estimates of the difference in EQ-5D-5L scores will be extracted for each time point (primary outcome at 24 months) and overall, with two sided 95% CIs. Three planned subgroup analyses will be performed by including the additional baseline variable, two- and three-way interactions between the subgroup, allocation and time point in the primary analysis: frailty; amputation aetiology and sex.

10.4 Health economic analysis

A within-trial cost-utility analysis (CUA) will be undertaken from an NHS and personal social services (PSS) perspective to assess the cost effectiveness of TKA compared to AKA in adult patients requiring MMLA but who are unsuitable for a BKA

Costs considered in this economic analysis will include intervention costs within hospitals and costs of post-surgery healthcare service use. Intervention costs will be calculated by quantifying hospital record data extracted after discharge and applying national average costs (34). Post-surgery service use costs will be calculated by collecting data using a bespoke patient self-report resource utilisation questionnaire and multiplying by unit costs obtained from national databases, such as the UK national database of National Cost Collection (34) and the Unit Costs of Health and Social Care report produced by the Personal Social Services Research Unit (35). The post-surgery service use will include residential care, primary care, hospital care, social services and wider societal costs, such as productivity and patient costs.

Effectiveness for the health economic analysis will be measured using EQ-5D-5L (13) administered at each follow up. The EQ-5D-5L results will be valued and mapped to 3L values using the approach recommended by NICE (36) to provide utility scores at multiple follow-up time points, while Quality Adjusted Life Years (QALYs) will be calculated using the area under the curve (AUC) method over the study period (37).

The primary outcome of the cost-utility analysis will be the incremental cost-effectiveness ratio (ICER) to combine the estimated costs and QALYs. Rubin's multiple imputation method will be used to impute missing data (38); while regression methods will be used to control for differences in baseline utility (39) and other prognostic variables, following the approach recommended by Glick and colleagues (40). The regression coefficient on treatment will then represent the mean difference in cost and QALYs between TKA and AKA. To assess the uncertainty, a, a non-parametric bootstrap method with 5000 iterations will be used to produce confidence intervals around the cost and QALY differences. Results will be presented in the conventional form of cost-effectiveness acceptability curves (CEAC) (41) to show the probability of the intervention being cost-effective over a range of willingness-to-pay (WTP) thresholds.

A range of pre-specified sensitivity analyses will be conducted to test the robustness of the primary outcomes under different scenarios. This includes a cost-utility analysis using complete cases, defined as patients who had both complete cost and EQ-5D-5L data at all follow-up time points, to access the impact of missingness and a cost-utility analysis from a societal perspective to explore the impact of wider costs, such as private expenses and productivity costs.

A detailed *a priori* health economics analysis plan will be developed to maintain the integrity and neutrality of the heath economic evaluation.

10.5 Qualitative analysis

Analysis of the interviews conducted during the pilot study will focus on exploring patient views of the trial and how the interventions were described, to inform

changes to recruitment materials; this will be fed back to recruiting staff. Semi-structured longitudinal interviews with trial participants will capture longer-term recovery and will focus on understanding the trade-offs made to allow trial participants to adapt to their new circumstances, the impact of multi-morbidity, and perceived functionality of their amputation level. Towards the end of the recruitment period, semi-structured interviews with ~20 clinicians from across sites will explore implementation issues. Data from trial participant interviews / site staff interviews will provide insight into the perceived factors influencing intervention adoption at sites. Data analysis will be undertaken in parallel with data collection so analysis of early interviews can inform later sampling decisions and interview questions.

Transcription of all interview data will be undertaken by a company contracted to the University of Hull under an existing confidentiality agreement. All data will be sent to the transcription company via secure upload links. Transcripts will be anonymised at point of transcription, and checked manually when received by the research team before analysis begins. NVivo qualitative data analysis software will be used to store and manage the transcripts during analysis. Field notes taken after each interview will be used to support the analysis.

For patient interviews, inductive thematic data analysis will be undertaken with transcripts coded by ascribing words and phrases to capture the meaning in the text to identify common emerging ideas. Staff interviews will be coded using a deductive and inductive approach with Normalisation Process theory used to guide the analysis (42).

To ensure reliability in the coding a subset of transcripts will be dual coded by two experienced qualitative researchers and any discrepancies discussed with the core research team until consensus reached. A coding index will be developed using the first five transcripts and applied to the remaining transcripts by one researcher. Regular qualitative team meetings (qualitative lead, PPI, and Chief investigator) will be used to discuss the possible themes identified in the data, and to ensure the analysis remains grounded in the data. PPI input will inform the interpretation of the

key findings. The Pillar integration process (43) will be used as a framework to integrate the quantitative trial data and qualitative findings.

10.6 SWAT analysis

The protocols for each are available on the MRC SWAT repository (recruitment: SWAT 15 (26), retention: SWAT 180 (27).

10.6.1 Recruitment SWAT

An ‘intention-to-treat’ analysis will be performed including all randomised sites analysed in the SWAT group to which they were allocated.

Both demographic characteristics, including age, sex, and ethnic group of randomised participants and site characteristics, including geographical location and catchment size, will be presented descriptively as mean (standard deviation) or number (%), as appropriate.

The primary analysis will compare the difference in recruitment rates between those receiving the animation in addition to the PIL and those not receiving the animation. This outcome will be analysed using mixed effect logistic regression with a fixed effect for SWAT allocation and a random intercept for site.

Secondary analysis: The difference in the proportion of those responding to a recruitment invitation who received the animation in addition to the PIL but who do not go on to be randomised, and those not receiving the animation but who do not go on to be randomised will also be analysed using a similar model to the primary outcome.

The difference in cost per recruited participant between those offered the animation and those not offered the animation will be calculated. In addition to the direct costs of the animation, it may also be necessary to include the cost of staff time spent administering the recruitment packs.

The following sensitivity analyses will be performed for the primary analysis:

● Excluding participants who did/could not receive allocation as randomised.

Subgroup analysis may also be performed for key demographic subgroups (e.g. age, gender, ethnicity) by adding interaction terms to the logistic regression or Cox regression model, where the sample size is deemed sufficiently large.

Where available, a meta-analysis, including data from existing SWATs will be undertaken to incorporate the results from this SWAT.

10.6.2 Retention SWAT

An ‘intention-to-treat’ analysis will be performed including all randomised participants analysed in the SWAT group to which they were allocated.

Demographic characteristics, including age, sex, and ethnic group, will be presented descriptively as mean (standard deviation) or number (%), as appropriate.

Primary analysis: Comparison of the questionnaire response rate between the SWAT groups will use logistic regression. The regression model will include the randomised group factor and the SWAT stratification factor (i.e., host trial intervention arms). The between-groups difference will be presented as number (%) and as both adjusted absolute (i.e., risk difference) and relative (i.e., odds ratio or relative risk) effect estimates, with 95% confidence intervals from the logistic regression model.

Any randomised participant who does not provide outcome data for any reason (including participants who were deceased or withdrawn from the host trial) will be categorised as ‘No’ for the primary outcome.

Secondary analysis: The between-groups difference in time taken to collection of outcome data will be analysed using techniques suitable for time to response (event) data such as Kaplan-Meier curves, log-rank test or Cox regression (adjusted for SWAT stratification/minimisation factors). Time zero will be set as ‘day before expected completion date’ (equivalent to adding 1 to the time variable to avoid exclusion from the analysis set). The analysis of questionnaire

completeness will be as for the primary outcome. The incremental cost per participant retained will be calculated for the comparisons under evaluation as the difference in costs between the SWAT groups, divided by the difference between groups in completion rates. Direct costs of the retention strategies, and indirect costs associated with administering the strategies and the comparators will be included.

The following sensitivity analyses will be performed for the primary analysis:

● Excluding participants who did/could not receive allocation as randomised.

● Excluding participants who were retrospectively found to have died or withdrawn from the host trial before the expected completion date.

Subgroup analysis may also be performed for key demographic subgroups (e.g. age, gender, ethnicity) by adding interaction terms to the logistic regression or Cox regression model, where the sample size is deemed sufficiently large.

Meta-analyses will include data from existing SWATs and will estimate differences in retention rates between the intervention and comparator groups. Within the meta-analysis, remote self-completion of questionnaires by trial participants and face-to-face data collection should be evaluated in subgroups and a combined treatment effect should be presented only if it is deemed that the effects are homogeneous between subgroups.

11.0 Ethical arrangements

11.1 Risks and benefits

Both procedures will have the general surgical risks of wound infection, haematoma, bleeding, wound healing problems, seroma, heart attack, stroke, venous thromboembolism and death. Risks to participants from the intervention or control treatments are not increased through trial participation. Measures, such as emphasis on good practice and standardised protocols/care pathways throughout, are likely to reduce risk and could bring additional benefits. In the unlikely event that new

information arises during the trial that may affect participants' willingness to take part, the TSC will review this information to determine whether changes are required to the patient information leaflet. A revised consent form will also be produced if necessary.

Within the trial, participants allocated to receive a through knee amputation may experience a functional benefit to the longer residual limb and both an improved rehabilitation and resultant quality of life because of this procedure. As the purpose of the study is to provide evidence regarding this, this cannot however be guaranteed.

11.2 Informing participants of potential risks and benefits

Patients will be provided with a detailed participant information sheet, outlining and clearly explaining the risks and benefits of trial participation. They will also be provided with the opportunity to discuss the potential risks and benefits with a clinical member of research staff.

11.3 End of trial

The end of trial will be defined as the last participant contact, which will occur at approximately 24 months after the end of the recruitment period (end of follow-up for the last participant) and after all the data are entered and queries resolved.

An end of study declaration form will be submitted to the Research Ethics Committee (REC) and sponsor within 90 days of trial completion and within 15 days if the trial is discontinued prematurely. A summary of the trial report and/or publication will be submitted to the REC Sponsor and Funders within one year of the end of the trial.

11.4 Retention of trial documentation

In compliance with the ICH/GCP guidelines and regulations, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for 5 years, and we will follow the archiving procedures described in YTU standard operating procedure YT03 Storage and Archiving. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

12.0 Trial finance and insurance

12.1 Trial funding

This research is funded by the NIHR HTA (National Institute of Health Research Health Technology Assessment) programme (Ref:157343). The financial arrangements for the study will be as contractually agreed between the funder (HTA), and the sponsor (Hull University Teaching Hospitals Trust). Separate collaboration agreements will be put in place between the sponsor and each of the collaborating organisations.

12.2 Trial insurance

The Clinical Negligence Scheme for Trusts can provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. Clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

13.0 Project management

13.1 Trial sponsor

The study sponsor will be the Hull University Teaching Hospitals NHS Trust.

13.2 Trial management

YTU will manage the study as formally delegated by the trial sponsor. The Trial Manager at YTU will be responsible for all aspects of trial management. They will be supported by a Trial Co-ordinator(s) and/or Trial Support Officer(s), who will be responsible for the day-to-day support of trial sites, coordinate recruitment, data handling and the management of the administrative trial team. The team at YTU will meet on a regular basis during the study and will work closely with the Chief Investigator, particularly at the start of the project and during the internal pilot of the study, including regular teleconferences to ensure that all aspects of preparation of

study material, study site set up and the start of recruitment progress smoothly. We will keep in close contact via email and telephone throughout.

The Trial manager, on behalf of the Chief Investigator, will submit and, where necessary, obtain approval from all relevant parties for all substantial amendments to approved documents. Regular progress reports will be submitted as requested to the funding body, the Research Ethics Committee and the sponsor. The Chief Investigator has overall responsibility for the study and shall oversee all study management. The data custodian will be the Director, York Trials Unit. Each site will have a site Principal Investigator (PI), who will be either the CI or one of the co-applicants. The PI will be responsible for managing the research team at their site.

The primary responsibility for monitoring the safety of participants in clinical trials lies with the trial sponsor. Data monitoring will be undertaken by the Trial Management Group (TMG), TSC and DMC, on behalf of the Sponsor and Funder. The project will be monitored by the Sponsor for whom a representative will be invited to attend the TMG meetings. The minutes/records of these meetings will be stored at YTU and will be shared with the sponsor on a routine basis.

13.3 Trial management group

A TMG has been established to monitor the day-to-day management (e.g. protocol and ethics approvals, set-up, recruitment, data collection, data management) of the study. Members will include the chief investigator, co-applicants including PPI representatives, collaborators, trial manager and the lead statistician. This group will have oversight of the whole trial and be responsible for trial delivery. This group will meet monthly throughout the set-up and the pilot study, subsequent meetings will be at least every two months during the recruitment phase.

13.4 Trial steering and data monitoring committees

Independent oversight of the study will be conducted by the TSC which will provide overall supervision for HAMLET on behalf of the Sponsor and Funder to ensure that the project is conducted to the rigorous standard set out in the UK policy Framework for Health and Social Care Research and the GCP. The TSC will monitor the progress of the trial and provide independent advice. Other study collaborators may also attend the meeting with the agreement of the Chair. The TSC will meet at least annually and will work to a Charter which has been agreed.

The study will also be regularly reviewed by the independent DMC. Attendance at DMC by non-members will be at the discretion of the Chair. The role of the committee will be to review accumulating trial data and advise the sponsor (directly or indirectly) on the future management of the trial. The DMC will meet throughout, including following completion of the pilot study and then prior to each subsequent meeting of the TSC. The DMC will review safety and efficacy data as well as quality and compliance data. The DMC will review all serious adverse events which are thought to be treatment related and unexpected.

The DMC will adopt a DAMOCLES charter (44) which will define its terms of reference and responsibilities in relation to oversight of the trial.

13.5 Patient and Public Involvement (PPI)

Patient co-applicant(s) and a PPI group with lived experience will contribute to ensure the trial reflects the priorities and needs of the amputee population. The aim is to secure patient and public input to the study recruitment, retention, interpretation of results and its dissemination.

The HAMLET PPI group will advise the study team throughout the study. PPI members for the study have been involved since the first PPI focus group to inform the funding application and their valuable input has been costed into all aspects of the ongoing trial setup, delivery and reporting. Our experienced PPI lead will facilitate their involvement and assist in training and support.

Patient representatives will sit on the independent steering committee and trial management group. The PPI group will co-develop all patient-facing trial documentation; input into design of qualitative interview guides, training/information videos, equipoise statement and recruitment strategy. Additional PPI meetings will be held throughout the trial to discuss matters that arise at each stage.

At the close out and write up phase, PPI input will be obtained to aid with interpretation of the key findings. A series of plain language outputs will also be developed with the PPI group for dissemination targeted at a wide audience through online and social media channels.

14.0 Dissemination and projected outputs

The HAMLET study will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) registry. The protocol will be published on the NIHR HTA website and in an open access journal.

On completion of the study, publication of the main study paper will be undertaken in a high impact, peer-reviewed journal. The NIHR threaded publication model will be followed with a synopsis submitted for publication in the NIHR HTA Journal.

A dissemination and publication policy will be developed with an agreement between partners including ownership and exploitation of intellectual property, and publication rights. The publication policy and the agreement will ensure that any intellectual property generated during the project is protected and that the publication process is organised in a fair, balanced, and transparent manner. The TMG will be responsible for overseeing these arrangements. The creation and signature of the agreements (if required) will be the responsibility of the coordinating centre (University of York). It will be ensured that all partners have input into the document.

We have identified three key target audiences for dissemination:

Patients. An accessible plain language summary of the study results will be developed in collaboration with our PPI group. Participants will be directly contacted by email or post, as per their preferences, to receive this summary.

In addition to the summary, a series of plain language outputs will be developed with our PPI group for dissemination targeted at a wide audience through online and social media channels. Throughout the duration of the study, we will maintain a website to offer up to date information on trial progress. Once completed the results for the trial will be available via this site in plain language and professional summary form. Results will also be disseminated via social media pages of supporting organisations. Press releases to both the local and national media will be prepared and distributed in plain language forms.

Policy makers. The results of the HAMLET study are anticipated to provide the first evidence to support decision making in level selection for MLLA when a BKA is not possible and should allow improved outcomes for this patient group in the future. The study results will inform national and international guidelines in MLLA and will be specifically distributed to writing committees. Publications will be targeted to inform commissioning decisions, and we will work with both NICE and healthcare commissioners to inform national guidelines. Implementation of the intervention (if proven effective) to the wider NHS will be guided by the qualitative work and the model of training and service development conceived for opening new TKA sites included in the trial.

The study protocols and associated results will be published in high impact open-access journals.

Healthcare workers. The inclusion of sites that are not currently providing TKA surgery, alongside our qualitative work, will assist in the development of an implementation model for developing the use of TKA routinely in other non-trial centers if the trial suggests benefit from TKA. Our study group contains members who are well-placed to disseminate findings and implement change through The Limbless Association, The Vascular Charity, Vascular Society of Great Britain & Ireland, British Association of Chartered Physiotherapists in Limb Absence Rehabilitation and the Royal college of surgeons of England. Slide decks of results will be made available to all principal investigators to enable local and regional presentation of results at each participating site.

Trial outcomes targeted at healthcare professionals will be disseminated via multiple formats including publication of online videos in an established study YouTube channel, international presentation and by social media release via institutional, charity and research team member's personal accounts.

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