UK Appendix

Melanoma Margins Trial-II: 1cm v 2cm Wide Surgical Excision Margins for AJCC Stage II Primary Cutaneous Melanoma (MelMarT-II)

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Funder: NIHR HTA Reference Number: NIHR130886

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Prof Marc Moncrieff

None of the applicants have any relevant, non-personal & commercial interest that could be perceived as a conflict of interest.

Confidentiality Statement:

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

UK Appendix:

MelMarT-II is an international collaboration between several countries. Melanoma and Skin Cancer Trials Research Centre in Australia (MASC), as the Lead Group (Sponsor), are providing overall international trial management, randomisation, electronic database management and statistical support.

This trial requires an internationally coordinated effort to recruit but each country is required to apply for their own funding to participate which was obtained for the UK through the National Institute for Health Research (NIHR).

Each country is expected to provide all aspects of trial management at a local level. Within the UK, the trial will be conducted on a daily basis by the Surgical Intervention Trials Unit (SITU) at The University of Oxford, and the UK Sponsor Representative, NNUH.

The UK MelMarT-II trial is a collaboration between the participating NHS Trusts, SITU and the MASC Trials Research Centre.

The UK appendix provides specifics for the UK participating sites and corresponds to (or occasionally supersedes) the Lead Group (MASC) protocol.

Regulatory Considerations:

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, The Human Tissue (Quality and Safety fir Human Application) Regulations 2007,

The UK Data Protection Act 2018 and General Data Protection Regulation (GDPR) 2018, and the UK Policy Framework for Health and Social Care Research, the European Directive 2001/20/EC (where applicable) and other national and local application regulations.

At the end of the trial, MASC will notify sites about archiving procedures. All essential documentation will be archived securely by the trial sites for 15 years from the declaration of the end of trial. Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice and all applicable regulatory requirements.

All archived documents must continue to be available for inspection by appropriate authorities upon request. Any associated trial documents at SITU will be archived according to University of Oxford policies. The trial database and eTMF will be archived in accordance with OCTRU SOP GEN-048. All completed paper worksheets will be kept in the Investigator Site File at each participating site.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs.

All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which requires data to be anonymised as soon as it is practical to do so.

The UK trial data may be used in future studies which will require separate approvals and funding.

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a unique four-digit participant ID on all study documents and electronic databases (REDCap). Consent will be obtained to store participant identifiable data at the central study office in Oxford. This is required to facilitate the follow up regime. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act 2018, which requires data to be anonymised as soon as it is practical to do so.

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1. KEY CONTACTS

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Health Economist	Dr Filipa Landeiro (Senior Health Economist for the UK) Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford
Committees	**Trial Management Committee (TMC)** The responsibility of the TMC is to oversee the conduct of the trial. It is a trial executive that manages the month to month running of MelMarT-II. It is independent of trial sponsorship and is made up of international members. Both the Australian PI, Professor Michael Henderson and the UK PI, Professor Marc Moncrieff are the Committee Chairs. **International Trial Steering Committee (TSC)** The responsibility of the international TSC is to oversee the whole trial. The committee members are still to be confirmed and the Chair will be an independent member who is UK based as stipulated by the NIHR. **Data Safety Monitoring Committee (DSMC)** The international DSMC is responsible for assessing the progress of the trial, the safety data and critical efficacy endpoints at various intervals. The committee will be established by MASC Trials (as the lead collaborative group). **UK Trial Management Group (UK TMG)** A UK TMG will be established, consisting of the CORE Trial Management Group (CORE TMG), UK PIs/Leads and co-applicants. It will report progress to the overall TMC in Australia (organised by the MASC Trials Research Centre) who will collate the reports from the other international groups and produce a report for the overarching international TSC.

	CORE TMG (Trial Management Group) The CORE TMG will be responsible for the day-to-day running of the UK aspects of the trial. This group will comprise the UKPI, MelMarT-II trial manager and SITU Operational Lead.

2. SYNOPSIS

Study Title	Melanoma Margins Trial-II: 1cm v 2cm Wide Surgical Excision Margins for AJCC Stage II Primary Cutaneous Melanoma (MelMarT-II)
Study Design	The trial will have two stages: 1. An internal pilot study with stop/go criteria at month 18 (after 12 months of recruitment) to ensure a minimum of 110 patients have been randomised and 13 centres open to recruitment 2. A multicentre phase III full RCT.
Study Participants	750 (The UK arm of the study is 25% of the total study sample size).
Planned Study Period	96 months (starting 1st July 2021)
Planned Recruitment period	48 months
Follow-up	All participants will be followed up for a minimum of 3 years
Analysis and Reporting	6 months to complete data analysis, close-down sites and final reporting of results. *N.B. If the internal pilot target is met, the trial will continue to recruit for a further 36 months. Data from the patients in the internal pilot phase will be included in the final analysis.*

3. ABBREVIATIONS

AJCC	American Joint Committee on Cancer (8th Edition, unless otherwise stated)
ARSAC	Administration of Radioactive Substances Advisory Committee
BAD	British Association of Dermatologists
BAPRAS	The British Association of Plastic, Reconstructive and Aesthetic Surgeons
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
DSMC	Data Safety Monitoring Committee
GCP	Good Clinical Practice

GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
HREC	Human Research Ethics Committee
HRQoL	Health Related Quality of Life
ICER	Incremental Cost-effectiveness Ratio
ICF	Informed Consent Form
MASC	Melanoma and Skin Cancer Trials Research Centre in Australia
NMB	Net Monetary Benefit
NHS	National Health Service
NICE	National Institute for Clinical Effectiveness
NIHR	National Institute for Health Research
NHMRC	National Health and Medical Research Council (this is an Australian research entity)
NNUH	Norfolk & Norwich University Hospitals NHS Foundation Trust
OCTRU	Oxford Clinical Trials Research Unit
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PPI	Patient and Public Involvement
QALY	Quality Adjusted Life Year
R&D	NHS Trust R&D Department
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SITU	Surgical Intervention Trials Unit
SMC	Scottish Medical Council
SOP	Standard Operating Procedure
SUSAR	Suspected and Unexpected Serious Adverse Reaction
TMC	Trial Management Committee
TSC	Trial Steering Committee
UKPI	United Kingdom Principle Investigator
UKTMG	United Kingdom Trial Management Group

4. BACKGROUND AND RATIONALE

Melanoma skin cancer is the 5th most common cancer in the UK, accounting for 4% of all new cancer cases. Since the early 1990s, incidence rates have more than doubled (increase of 134%) and are projected to continue to rise beyond 2034. In contrast to most cancer types, melanoma occurs relatively frequently at younger ages. Melanoma has a preponderance for extensive local recurrence (LR) and this event is often a very challenging problem to treat. The current standard treatment to prevent this is a wider excision of a prophylactic safety margin of normal skin and soft tissue (a wide local excision "WLE") around the previous melanoma biopsy site. However, despite being offered as a treatment to every patient diagnosed with melanoma, the effective margins have yet to be standardised. In particular, for patients with high-risk melanomas (stage II) the optimal WLE margin is controversial. The current NICE Melanoma Guidelines (2015) recommend a 2cm or 3cm margin for patients with stage II melanoma, although other international guidelines recommend between 1-3cm margins, reflecting the paucity of the existing evidence.

5. AIMS/OBJECTIVES

The primary aim of the trial is to assess whether there is no difference in disease free survival for patients treated with a 1cm excision margin when compared to a 2cm margin for stage II primary melanomas. The secondary aims are to assess whether health related quality of life (HRQoL) and surgical complication rates are improved for patients receiving the narrower excision and whether there is a benefit on resource use within the UK.

6. METHODS

This is a prospective, phase III, multinational, non-inferiority randomised controlled trial (RCT); a multinational effort between Australia, the UK, Canada, Sweden and the US. Overall, the aim is to recruit a total of 2998 adults with histologically confirmed, primary invasive cutaneous melanoma; it is expected that the UK will contribute 750 of this total (25%) from at least 20 NHS sites. Patients will be randomised 1:1 to receive a WLE with 1cm radial margin versus a WLE with 2cm radial margin. The primary outcome is time to disease free survival; secondary outcomes will assess local recurrence, distant recurrence, disease-specific and all-cause mortality, HRQoL and adverse events. A standalone health economic analysis will be performed for the UK cohort of patients to determine cost-effectiveness and inform NICE guidelines.

7. ANTICPATED IMPACT AND DISSEMINATION

This trial will provide important evidence to safely reduce the standard surgical procedure with the potential to benefit 1 in 4 of all patients with melanoma who are at highest risk of recurrence. It is anticipated that the narrower excision will maintain equivalent oncological outcomes compared to the wider excision whilst also improving HRQoL, reducing surgical complications and resulting in substantial cost savings for the NHS. If this trial shows that the narrower excision is beneficial to patients then it is anticipated that it will become standard of care and result in a change to current NICE Melanoma Guidelines.

All participating patients and their families/carers will be asked at the time of recruitment if they would like to receive a copy of the trial results. This will be written collaboratively with clinicians and PPI representatives and distributed accordingly. Engagement will be maintained with Melanoma Focus. The wider public will be alerted via links with relevant organisations/charities, and the Research Media Offices. Engagement with the

NIHR Dissemination Centre will be sought, to ensure global awareness of study findings; as well as utilising the communication departments at Norfolk & Norwich University Hospitals NHS Foundation Trust and Oxford University. It is anticipated that together these individuals, and NIHR equivalents, will agree on effective communication strategies including co-ordinated press releases, interviews etc.

Given the potential involvement of up to 20 NHS Trusts in the UK, and the positions held by co-applicants and collaborators within the national and international plastic & reconstructive surgery community, the results will rapidly reach the melanoma cancer Multi-Disciplinary Teams, ensuring the trial findings improve practice and service delivery for melanoma patients within the NHS.

The MelMarT-II trial manager, based at SITU, will develop a study website and social media strategy; actively promoting the trial and maintaining engagement.

SITU also maintains a list of ongoing and completed trials, with all current and archived publications on its website (https://www.situ.ox.ac.uk).

7.1. Presentations and Publications

Findings from this project will be presented at national (Melanoma Focus UK & British Association of Plastic and Reconstructive Surgeons) and international (Society of Surgical Oncology & American Society of Clinical Oncology and The International Health Economics Association) conferences. The professional development of individuals working on the trial will also be supported, with poster and/or oral presentation submissions regarding specific aspects of the trial at meetings regularly attended by the different specialities (e.g. the UK Trial Managers Network Annual Meeting, the biannual International Clinical Trials Methodology Conference). The work will be submitted for publication to appropriate peer-reviewed, open access journals and the NIHR Journals Library. This will permit dissemination of the work beyond cutaneous surgical oncology. It is planned to publish at least 4 papers from this trial: 1. Protocol paper 2. Primary results paper 3. UK health economic evaluation paper 4. HTA journal monograph.

8. PROTOCOL PROCEDURES

8.1. Recruitment: UK Setting

All recruiting institutions will be required to demonstrate an adequate annual caseload of primary melanoma and will need to be performing a minimum of 30 sentinel lymph node biopsies (SNLB) per annum in the AJCC II category. This is verified through ARSAC licence certification for performing SLNB for melanoma held at participating UK sites and a copy is to be forwarded to SITU for their records. Patients eligible for the trial should be assessed by the specialist multidisciplinary teams including pathology slide review to confirm the diagnosis of primary melanoma.

Blood or tissue samples may be taken for research. With participant consent, de-identified samples will be stored, in a biorepository, for use in future ethically approved research studies.

8.2. Clinician Engagement

The British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS: www.bapras.org.uk) and the British Association of Dermatologists (BAD: www.bad.org.uk) have officially endorsed this clinical trial. Accordingly, it is anticipated that those involved in multidisciplinary melanoma treatment decisions such as the UK plastic surgery community with a specialist interest in skin cancer, alongside the respectively diagnosing and referring dermatologists, will remain fully engaged and actively recruit patients for the trial. Plastic surgeons are senior clinicians and core members in the majority of skin cancer specialist MDTs, based at regional cancer centres throughout the UK, and will be able to identify potential recruits through routine referral patterns. To facilitate continued engagement in MelMarT-II, the biannual BAPRAS, BAD and Melanoma Focus conferences will be used as platforms to promote the trial and update the PIs. Furthermore, for any trial meetings held, CPD will be applied, to encourage attendance from across the community.

8.3. Recruitment Strategy

We anticipate that at least 20 NHS centres will recruit participants into the MelMaRT-II study and that each site will treat a minimum of 40 eligible patients per year. Assuming approximately 40-50% of eligible patients consent to involvement in the study we expect each site to recruit approximately 10-25 patients (28.1% of eligible patients) per year.

We estimate that we will open at least one site per month starting in month 4 (with recruitment to start in month 6) and that all sites will be open to recruitment by month 27. Therefore, assuming staggered opening of sites, we will need to recruit approximately 1-2 patients per month/per site, which we consider feasible.

8.4. Internal Pilot Phase

Built into the UK recruitment is an internal pilot of recruitment to the RCT. There will be a formal stop/go review at month 18 (after 12 months of recruitment) to review the number of randomisations over the pilot period. If a target of at least 110 patients have been randomised (assuming all centres recruit at least 1 patient per month) and at least 13 centres have been opened, the trial will continue to recruit in the UK for a further 24 months. Data from the internal pilot phase will be included in the final analysis. The following stop-go criteria are proposed for the international Trial Steering Committee (submitted via MASC) after 12 months of recruitment:

Target	**Actual recruitment in 12 months**		
110	> 110 participants	90-110 participants	<90 participants
'Stop-Go' criteria	• Recruitment feasible • Proceed with study	• Review recruitment strategies • Report to TSC (via MASC) • Continue but modify and monitor closely	• Recruitment not feasible • Decision not to proceed

8.5. Adjuvant Therapy & Concurrent Trials

MelMarT-II has a permissive, pragmatic trial design. Thus, adjuvant systemic therapy to reduce the risk of melanoma recurrence is permitted during the study, either as a standard of care or as part of a separate clinical trial, at the discretion of the clinical team at each participating centre. Adjuvant therapies, including participation in other trials will be recorded in the case report forms (CRFs). In the UK, adjuvant systemic therapy is not indicated for patients with AJCC stage II disease, though clinical trials have commenced. It is likely that disease-free survival data will only be available or published during the latter stages of the recruitment phase of this trial. It is uncertain whether NICE will approve the use of adjuvant systemic therapy for the sentinel node negative cohort during the recruitment phase in the UK.

8.6. Pregnancy

Nuclear medicine departments routinely check pregnancy status for women of childbearing age, according to local protocols/as per departmental policy, before an administration of radioactive materials is given.

Please also refer to section 5.1 of the Lead Group Protocol 02.18 MelMarT-II version 2.2 dated 25 Mar 2021

8.7. COVID – 19 Impact

The COVID-19 pandemic may result in a delay in the study being opened and a delay in patient recruitment internationally. There is evidence for this in Australia where the trial has opened. The situation is evolving and it is difficult to quantify exactly the extent of the delay that may be required at this stage. In the current climate, participant recruitment will be guided by the policies of individual hospitals and their availability of resources including research staff, space and equipment. Clinically, however, cancer patients remain a priority in the UK, and several surgeons have confirmed to the lead applicant that they are able to treat melanoma patients currently. In Australia at the international trial co-ordinating centre negotiations are currently underway with the NHMRC for funding to extend the recruitment period for both the entire trial and for Australia specifically, since recruitment has been effectively frozen during the pandemic. Given that the intended commencement date in the UK is 2021, we are confident that melanoma services in the UK will have effectively returned to normal and UK recruitment should therefore not be affected for MelMarT-II.

9. SAFETY REPORTING

For SAE reporting please complete the paper form and email a pdf copy to both MASC Trials and SITU within 24 hours of awareness of the event.

For further details please refer to the Lead Group Protocol 02.18 MelMarT-II version 2.2 dated 25 Mar 2021, section 11 and section 11 of the Study Operations Manual Version 3.4 dated 29 Jan 2019 for further details.

Reports of ‘related’ and ‘unexpected’ SAEs (SUSAR – Suspected and Unexpected Serious Adverse Reaction – a serious adverse reaction, the nature and severity of which is not consistent with the information documented about the procedure or treatment in question) will be submitted within 15 working days of the UKPI/Lead becoming aware of the event; using the HRA form found at

https://www.hra.nhs.uk/documents/1087/safety-report-form-non-ctimp.docx.

N.B. MASC do not record SUSAR's for non-CTIMP trials so for their safety reporting documentation this would be classed as an SAE. However, SITU will forward all copies of SUSAR correspondence to MASC for their records.

10. STATISTICS AND ANALYSIS

10.1. Sample Size

The UK recruitment target is 750 patients. Additionally, based on previous UK data 19, a sample size of 750 UK patients will provide 80.5% power to detect a utility cost difference of £150 and a 96.4% power to detect a difference of £200, at a two-sided significance level of 0.05.

10.2. Health Economics Analysis

We will conduct a within trial cost-utility analysis to assess the cost-effectiveness of implementing 1cm compared to 2cm wide local excision margin for AJCC stage II primary invasive cutaneous melanomas using the UK patient cohort. Before the trial data are made available to the researchers we will prepare a health economics analysis plan. We will use an NHS and Personal Social Services perspective for the base-case analysis and adopt a societal perspective as sensitivity analysis. We will compare the two trial arms in terms of incremental costs and QALYs and estimate the incremental cost-effectiveness ratio (ICER). We will follow the good practice guidelines for economic analysis alongside clinical trials.22,23

A health economics questionnaire will be used to collect healthcare resource use (primary care appointments, prescribed and over the counter medications, hospital admissions, contact with other healthcare professionals) and non-healthcare resource use (time off work, formal and informal care received) of all patients enrolled in the trial. The questionnaire will be administered at baseline (covering the 3-month prior to enrolment in the trial), 3, 6, 12, 24 and 36-months. Resource utilisation items will be valued using the most up-to-date issue of the Department of Health English National Schedule of Reference Costs and Prescription Cost Analysis.

The EQ-5D-5L instrument will be used to measure HRQoL at baseline, 3, 6, 12, 24 and 36-months. The EQ-5D-5L instrument will be valued using the UK value set, if available at the time of analysis, or converted into the EQ-5D-3L using a cross-mapping algorithm and valued using the UK set. QALYs will be calculated using the area under the curve approach, which involves estimating the average EQ-5D utility between each follow-up time, and weighting it by survival time.

We will test for differences in resource use patterns and HR-QoL between the two arms of the trial and adjust the incremental QALYs for these differences, if required.

Missing data concerning resource use and EQ-5D-5L will be imputed following best practice methods in cost-effectiveness studies.26 All costs and QALYs will be discounted at 3.5% following NICE guidelines.

Incremental costs and QALYs will be reported as means with 95% confidence intervals. We will test for baseline difference in utilities between the trial arms and if required adjust the incremental QALYs

estimation for these differences. The ICER will be estimated by dividing the difference in costs by the difference in QALYs between the two treatments under analysis and will be depicted on the cost-effectiveness plane. The ICER will be compared against the threshold used to establish value for money in the NHS (currently in the region of £20,000 to £30,000 per QALY).

We will estimate the joint uncertainty around incremental costs and QALYs in cost-effectiveness using a bootstrapping approach. From these bootstrapped results, we will calculate the probability that the 1cm excision margin is more cost-effective than the 2cm for different threshold values per QALY gained. These will be calculated by estimating the proportion of bootstrap replicates with a net monetary benefit (NMB) above 0 for each threshold value, where the NMB is given by the product of the mean difference in QALYs and the threshold value minus the mean difference in costs.

10.3. UK Administration of QoL & Tools:

In order to analyse specific UK Health Economic data for the UK cohort, both the Baseline Employment Questionnaire and the Follow up Cost Questionnaire have been amended.

SITU may need to contact participants directly to send reminders for questionnaire completion; further details will be provided at the UK site initiation visits.

For details regarding completion of the QoL and Tools please refer to section 9 of the Study Operations Manual Version 3.4 dated 29 Jan 2019.

11. TRIAL MANAGEMENT

All UK related aspects of the trial will be managed by an established team at SITU, the University of Oxford. A dedicated Trial Manager within SITU will oversee all aspects of the day-to-day UK trial management, with oversight from senior members. All aspects of UK trial set-up (including obtaining ethics, regulatory and R&D approvals), UK trial recruitment and follow-up, and HTA progress report writing will be managed by the trial manager within SITU. All data queries and preparation for the TMC and DSMC meetings will be managed by MASC and site initiation will be managed by both MASC and SITU. Full details of these processes will be provided at the UK site initiation visits. There is no provision for support for UK based recruitment and trial management from the NHMRC awarded grant already obtained for this study. Funding to run MelMart-II in the UK was obtained through a grant from the NIHR HTA programme (NIHR130886)

All countries recruiting to MelMarT-II are expected to obtain their own individual funding for management at a local level, and trial management responsibilities are akin to as if this were a standalone UK trial. We will utilise the database infrastructure developed by the MASC Trials Research Centre and all data will be held centrally on this database. A UK Trial Management Group (UK TMG) will be established, consisting of the CORE Trial Management Group (CORE TMG), UKPI/Lead UK PIs/Leads and co-applicants. The CORE TMG will be responsible for the day-to-day running of UK aspects of the trial and will meet monthly to provide progress reports and ensure milestones are met. These include completion of regulatory requirements (i.e. ethical approval), site set-up, preparation of study materials, and recruitment monitoring for the main trial to ensure the strict recruitment targets are met. They will report to the UK TMG at monthly

meetings. The UK TMG will report progress to the overall international Trial Management Committee established and organised by the MASC Trials Research Centre. The trial will be run in accordance with MASC Trials Research Centre SOPs. The trial has been prospectively registered on the International Standard Randomised Controlled Trial Number register (ISRCTN:) and ClinicalTrials.gov (Identifier: NCT03860883). The trial protocol will be available via the NIHR HTA website and published in an open access peer reviewed journal in accordance with the SPIRIT Statement (www.spiritstatement.org/).

11.1 UK Site Activation

SITU will be responsible for preparing the necessary approvals, documentation and running the UK site visits for the UK site set up. They will liaise with the MASC team in preparing the necessary documentation and activating the UK sites for recruitment.

12. QUALITY ASSURANCE PROCEDURES

12.1. Study Monitoring

Regular monitoring will be performed according to the study specific Monitoring Plan. Study monitoring visits will be conducted by SITU in consultation with MASC Trials and the participating UK sites. Monitoring will be limited to central monitoring activities – there will be no site monitoring, missing data will be queried with sites where mandatory. Monitoring of the data will occur as the data is being entered onto the database.

Please refer to the Lead Group Protocol 02.18 MelMarT-II Version 2.2 dated 25 Mar 2021, section 15 and section 14 of the Study Operations Manual Version 3.4 dated 29 Jan 2019 for further details.

13. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

MASC Trials, SITU and the UKPI/Lead should be notified immediately if a Protocol Waiver is requested or a Protocol Deviation has occurred.

A Protocol Deviation form should be completed and emailed to both MASC and SITU. MASC will ask the Study Chair to review and sign. The deviation also needs to be reported to the ethics committee for approval for the participant to continue.

For further details please refer to section 7.3 of the 'Research Electronic Data Capture (REDCap) Manual + Electronic Case Report Form (eCRF) Completion Guideline for Site Staff', Version 1.1, dated 24 July 2020

14. SERIOUS BREACHES

A 'serious breach' is a breach of the protocol, or of the conditions or principles of GCP, which is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the trial subjects; or
(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the UKPI/Lead, MASC and SITU, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Reporting

The UKPI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required), and the international trial coordinating centre (MASC Trials). In addition, an End of Study notification and final report will be submitted to the same parties. MASC will be consulted when preparing these documents.

15.2. Expenses and Benefits

There is no budget to pay for any expenses incurred as a result of the study. However, study visits at the hospital have been scheduled to coincide with routine clinical appointments.

16. FINANCE AND INSURANCE

16.1. Funding

The UK recruitment for MelMarT-II is supported by the National Institute for Health Research Health Technology Assessment programme under the reference NIHR130886. The views expressed in this document are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

16.2. NHS Indemnity

The NHS indemnity scheme will apply to the potential liability of the sponsor for harm to participants arising from the management and conduct of the research. **MASC** holds insurance to cover harm to participants arising from the design of the study.

16.3. Contractual Arrangements

Appropriate contractual arrangements will be put in place between all third parties. Participating UK sites will not be activated until contractual agreements are fully signed.

17. PUBLIC AND PATIENT INVOLVEMENT

Gillian Nuttall, founder and CEO of Melanoma UK has agreed to act as PPI representative for the duration of the study. Ms Nuttall brings significant expertise through previous collaboration with the Christie and Royal Marsden Hospitals and already has connections with the lead Australian team.

Melanoma UK (www.melanomauk.org.uk) has been participating in NICE and Scottish Medical Council (SMC) appraisal for almost ten years. In addition to clinical trials, Melanoma UK designed the "My Melanoma" app which allows patients, amongst many other things, to submit quality of life data to researchers via their own smartphones/tablets. The Australian and international TMC endorsed Gillian Nuttall for the role of PPI for MelMarT-II based on her previous collaborations and through her work with melanoma patient conventions and the International Patient Alliance for Melanoma (https://www.melanomauk.org.uk/Pages/Events/Category/past-events).

Representatives from Melanoma Focus, the largest dedicated melanoma charity in the UK were part of the trial design committee and were pivotal in informing the committee regarding the primary endpoints that would be important for consumers.

We will aim to provide updates for the UK public through Melanoma UK and Melanoma Focus. MelMarT-II represents an excellent opportunity for the formation of an international network of patient advocacy groups for melanoma.

With our patient co-applicant, PPI groups, Melanoma UK and Melanoma Focus, communication for patients/carers and the public will be developed. Newsletters, Facebook, Twitter etc. will be used to ensure the results of MelMarT-II are communicated to the wider community.

Patients and the public will continue to be actively involved throughout the trial and costed according to INVOLVE guidelines.

18. REFERENCES

22. National Institute for Health and Clinical Excellence *Guide to the methods of technology appraisal 2013*.

23. Glick, H.A., et al., *Economic Evaluation in Clinical Trials*, ed. V. Handbooks in Health Economics. Vol. Volume 2. 2015, Oxford: Oxford University Press.

26. Faria, R., et al., *A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials.* Pharmacoeconomics, 2014. **32**(12): p. 1157-70.

19. APPENDIX A: STUDY FLOW CHART

<table>
<tr><th colspan="2">MELMART-II TRIAL SCHEMA</th><th>TRIAL PHASE</th><th>TIME</th></tr>
<tr><td colspan="2">Diagnosis of Primary Cutaneous Melanoma pT2b-pT4b (N0M0)

AJCC Stage IIA-IIC</td><td rowspan="2">Screening</td><td rowspan="2">Confirmation of diagnosis no more than 120 days prior to WLE surgery</td></tr>
<tr><td colspan="2">Confirmation of Diagnosis – Pathology review at Specialist MDT (Trial Centre)

Informed Consent</td></tr>
<tr><td colspan="2">RANDOMISATION

(Stratification Factors: AJCC Stage (IIA, IIB, IIC); Age, Sex; Country)</td><td colspan="2">Total patients = 2,998</td></tr>
<tr><td colspan="2">AJCC IIA-IIC (pT2b, pT3a, pT3b, pT4a, pT4b)

N=2,998</td><td>Stratification

& Randomisation</td><td>Day 0</td></tr>
<tr><td colspan="2">At participating sites:

QOL component (FACT-M, EQ-5D-5L and Neuropathic Pain (PainDetect)) & Health economic component (Form BE)</td><td rowspan="3">Intervention</td><td>Day 0</td></tr>
<tr><td>ARM A: Experimental Arm

Wide Local Excision = 1cm Margin

+ Sentinel Lymph Node Biopsy
+/- Reconstruction

N=1,499</td><td>ARM B: Control Arm

Wide Local Excision = 2cm Margin

+ Sentinel Lymph Node Biopsy
+/- Reconstruction

N=1,499</td><td>Day 0 + <28 days</td></tr>
<tr><td colspan="2"></td><td></td></tr>
<tr><td colspan="4">FOLLOW UP</td></tr>
<tr><td>Clinical Information & Health Status</td><td>Years 1-2: Baseline, 3, 6, 12, 18 and 24 months

Years 3-5: Annually</td><td>Follow Up</td><td>Day 0 - Trial Completion (max. 120 months)</td></tr>
</table>

	Years 6-10: Annually (optional based on local standard of care or clinicians discretion)		
At participating sites: FACT-M, EQ-5D-5L, PainDetect (Neuropathic pain), Follow Up Employment* and Cost Questionnaire completion	At 3,6,12 and 24 months, and at melanoma recurrence ***Follow Up Employment Questionnaire** only at 3 and 6 months, and at melanoma recurrence		Day 0 – Month 24 (Year 2)
Melanoma Recurrence(s)		At the time of Recurrence	
Death		At the time of Death	
ENDPOINTS			
Disease Free Survival		Primary Endpoint	Day 0 – Month 60 (Year 5)
Distant Disease Free Survival Overall Survival Local Recurrence Melanoma Specific Survival		Secondary Endpoints	Day 0 – Trial Completion (max. 120 months)
Surgery Related Adverse Events			Day 0 – 90 Days
Adverse Events			Day 0 – 12 Months
Quality of Life Health Economics			Day 0, Month 3,6,12 and 24

20. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made