Melanoma Margins Trial

Melanoma Margins Trial (MelMarT):
A Phase III, multi-centre, multi-national randomised control trial investigating 1cm v 2cm wide excision margins for primary cutaneous melanoma

03.12 MelMarT-I

02.18 MelMarT-II

Version 5.0 dated 12Dec25

The undersigned confirm that the following protocol has been agreed and accepted and that the Study Chair agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct of Research in Humans, the Therapeutic Goods Administration's (TGA) Clinical Trial Handbook, Good Clinical Practice (GCP), the Sponsor's Standard Operating Procedures (SOPs), and other regulatory requirements as amended. • We agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor. • We also confirm that we will make the findings of the study publicly available through publication without unnecessary delay and that an honest accurate and transparent account of the study will be given. Additionally, any discrepancies from the study as planned in this protocol will be explained. This protocol has been designed and is periodically reviewed in consultation with consumer groups, CIs, representatives from MASC Trials Discipline-Specific Advisories (DSAs) and Consumer Advisory Panel (CAP) to inform the focus, design, and secondary objectives of the trial.

Coordinating Principal Investigators:

Australian Principal Investigator: Prof Michael A Henderson
Peter MacCallum Cancer Centre
305 Grattan St
Melbourne VIC 3000
Australia

Signature Date 12Dec25

UK Principal Investigator: Prof Marc D Moncrieff
Norfolk & Norwich University Hospital
Colney Lane
Norwich NR4 7UY
United Kingdom

Signature Date 12Dec25

For information related to the Trial Management Committee membership please refer to the Operations Manual.
This is an independent investigator initiated co-operative group trial.

Trial ID: NCT03860883/ISRCTN99703266

Administration

Sponsor:	Melanoma and Skin Cancer Trials Limited 553 St Kilda Road Melbourne, VIC 3004, Australia Telephone: +61 3 9903 9022 Email: melmart@masc.org.au
Coordinating Group:	Melanoma and Skin Cancer Trials Limited (MASC Trials) 553 St Kilda Road Melbourne, VIC 3004, Australia Telephone: +61 3 9903 9022 Email: melmart@masc.org.au
Collaborative Group:	Peter MacCallum Cancer Center 305 Grattan Street Melbourne, VIC 3004, Australia
Australian Study Chair:	Prof. Michael Henderson Email: Michael.Henderson@petermac.org
Collaborative Group:	Norfolk & Norwich University Hospital University of East Anglia Colney Lane Norwich NR4 7UY United Kingdom Telephone: +44 1603 288127
UK Study Chair:	Prof. Marc Moncrief Email: marc.moncrieff@nnuh.nhs.uk
Collaborative Group:	Canadian Cancer Trials Group (CCTG) Queens University at Kingston 10 Stuart Street Kingston, Ontario, Canada K7L 3N6
Canadian Study Chair:	Dr Frances Wright Email: ME15TrialTeam@ctg.queensu.ca
Swedish Coordinating Centre:	Sahlgrenska University Hospital 413 45 Göteborg, Sweden
Lead Investigator:	Prof Roger Olofsson Bagge Email: roger.olofsson.bagge@gu.se
Collaborative Groups:	SWOG Cancer Research Network 4201 Medical Drive Ste 250 San Antonio TX 78229, United States of America
Lead Investigator:	Dr Joshua Mammen Email: jmammen@unmc.edu
Collaborative Group:	Cancer Trials Ireland CLG Innovation House, Old Finglas Road Glasnevin, Dublin 11, D11 KXN4, Ireland
Lead Investigator:	Dr Shirley Potter Email: shirleypotter@mater.ie
Collaborative Group:	Zuyderland Medical Center Henri Dunantstraat 5, 6419 PC Heerlen The Netherlands
Lead Investigator:	Dr James van Bastelaar Email: j.vanbastelaar@zuyderland.nl

Document Version History

Version	Version date	Main Changes
1.0	18 July 2014	
1.2	20 October 2015	Wide local excision procedure timing changed to allow the excision to take place at the time of biopsy.
Version	**Version date**	**Main Changes**
2.0	16 November 2018	Protocol revised for the second phase of the study, 02.18 MelMarT-II, significant changes include; • **Section 4.4 Stratification** ○ "Risk Group (intermediate; high)" stratification **changed to** stratification by AJCC 8th edition staging ○ Site (institution) stratification **changed to** stratification by Country • **Section 4.5 Endpoints** ○ Co-primary endpoints, Time to local recurrence and Melanoma specific survival **changed to** a single primary endpoint of Disease-Free Survival. ○ Co-Primary endpoints, Time to local recurrence and Melanoma specific survival **changed to** secondary endpoints. • **Section 5 Eligibility Criteria** ○ "primary invasive cutaneous melanoma of Breslow thickness greater than 1 millimetre" **changed to** "Stage II primary invasive cutaneous melanoma with Breslow thickness > 2mm, or 1-2mm with ulceration (pT2b-pT4b, AJCC 8th edition)" ○ "Life expectancy of at least 10 years from the time of diagnosis" **changed to** "Life expectancy of at least 5 years from the time of diagnosis" • **Section 12 Statistical Considerations** ○ The details surrounding statistical analysis, including the sample size (9,864 to 2,998) have been updated to reflect the change in primary endpoint and patient population. • **Study Visit Schedule** ○ Updated, notably Section 8.3, Figure 1 Study Schema and Appendix I • **Transition to electronic Case Report Forms (eCRF)** ○ Relevant changes noted throughout • **General administrative changes** ○ Including but not limited to updated referencing, grammar, formatting and spelling
2.1	01 June 2019	Change in Sponsor and associated administrative updates (e.g., change in contact details etc.)
2.2	25 March 2021	• **Section 4.5 Secondary Endpoints 6** • Surgery related adverse events recorded up to 90 days from the date of surgery (previously 30 days and changed throughout protocol). • **Section 5.1 Study eligibility criteria: Inclusion criterion 1** • Further clarity to remove ambiguity in this inclusion criterion "Breslow thickness >2mm without ulceration, or >1mm with ulceration only" (previously > 2mm, or 1-2mm with ulceration). • **Section 5.1 Study eligibility criteria: Inclusion criterion 4** • **"**Staging sentinel node biopsy must be completed within 3 months (92 days) of the original diagnosis (previously 120 days)." • **Section 5.1 Study eligibility criteria: exclusion criterion 9** • Additional wording to include the exclusion of melanoma located on the genitalia, perineum or anus areas. • **Section 5.1 Study eligibility criteria: exclusion criterion 16**

		• "Oral or parenteral immunosuppressive agents (not topical or inhaled steroids) at enrolment or within 6 months prior to enrolment previously (at any time during study participation or within 6 months prior to enrolment)." • Additional wording to include paragraph around pregnancy. • **Section 6.1 Diagnosis of primary tumours** • Additional wording included to refer to shave biopsies in appendix VI. • **Section 6.3 Sentinel Lymph Node Biopsy** • Additional wording to include "In the rare event that a pregnancy test performed on the day of attendance at the Nuclear Medicine department detects a previously undisclosed or unknown pregnancy, then the patient should be withdrawn from the study and a study withdrawal form completed. From that point on, the patient will be managed according to the treating centre's local policy." • **Section 8.1 Screening assessments** • Additional wording to allow written informed consent to take place in clinic or remotely as per the institutions own policy. • Addition of height (in metres) and weight (in kilograms). • Addition of point 13 **"**Confirmation that no more than 92 days have elapsed since the original diagnosis." • Additional wording around timing of intervention "Once the patient has been randomised, the arm to which the patient has been allocated will be immediately confirmed, and intervention will occur within 28 days." • **Section 8.3 Follow Up Visit Assessments: Maximum of 10 years in Duration** • Wording around telehealth to be permitted during follow up visits and implementation of ePROMs. • Additional wording around the frequency of physical examination and include units (kg). • **Section 8.6 Withdrawal and Lost to Follow up** • Additional paragraph added to clarify patients who are lost to follow up. • **Section 9 Pathology** • Amended to read **"**Wide excision specimens will be examined as per procedures followed by the designated pathologists of each cooperating institution. Please refer to Appendix VI for further information on shave biopsies" (previously "examined according to the instructions described in the operations manual"). • Removal of collection of tumour penetrative depth (Starz thickness) and subsequent section renumbered. • **Section 11 Safety Reporting** • Section 11.1 was reworded and further clarification around reporting AE and pre-existing medical conditions. • Surgery-Related Adverse events reported 90 days after surgery (previously 30 days and changed through protocol). • **Section 12.1 Sample size** • Additional wording for clarity regarding power analysis and sample size **"**The sample size conservatively assumes 690 events will occur and allows for 10 per cent of patients being lost to follow up." • **Section 12.3.1 Statistical Analyses of Primary Endpoint** • Sentence removed and superseded by section 12.3.4 which describes interim monitoring plan and role of DSMB (previously "Interim analyses comparing disease-free survival between trial arms will be carried out as agreed with the DSMB and TSC prior to commencement of the full trial.") • **Section 12.3.2 Statistical Analyses of Secondary Endpoints** • Paragraph added titled "Survival endpoints." • **Section 12.3.4 Interim Analyses** • Addition of an interim analysis plan. • **Section 14 Reporting of Results**

		• Clarification around contributing authors and addition of minor wording to include reference to ICMJE recommendations.
		• **Appendix I:**
		  • Table of Assessments and Follow up Visits: minor correction to timing of Pre-operative mapping lymphoscintigraphy to be performed prior to the study intervention (previously to be performed prior to randomisation).
		  • "Surgical Intervention" entry modified to: Patients will be randomised to undergo wide local excision with either a 1cm or 2cm margin + sentinel lymph node biopsy at the baseline visit. The surgery must be performed within 120 days following original diagnosis and within 28 days of randomisation.
		  • Further clarification around reporting of AE and SAE's.
		  • Sr AEs reported 90 days after WLE amended in table and footnote updated (previously 30 days).
		• **Addition of Appendix VI**
		  • Managing Patients with Shave Biopsies.
		• **Administrative updates**
		  • Change in trial inbox address, update of contact details, addition of collaborating groups/lead investigators, additional references and minor formatting.

2.3	1 Sept 2021	• ISRCTN number added to title page
		• Ireland & Netherlands collaborative groups' contact details added to Administration page
		• DSMC changed to DSMB throughout protocol
		• Added statement about use of a patient-facing advertisement
		• **Figure 1 – Trial Schema**
		  • Replaced "surgery" with "intervention" in endpoints section
		  • Replaced statement "confirmation of diagnosis no more than 120 days prior to WLE surgery" with "Day 0 up to 28 days" in "screening" section
		  • Replaced "Day 0 +<28 days" with "Confirmation of diagnosis no more than 120 days prior to WLE surgery" in "intervention" section
		• **Section 5.1 Study Eligibility Criteria: inclusion criterion 4**
		  • Clarified timing of study intervention surgery which is to be completed within 120 days of original diagnosis, and surgery refers to both the staging sentinel node biopsy and the wide local excision because these are both to be done on the same day.
		• **Section 5.1 Study Eligibility Criteria: exclusion criterion 4**
		  • Additional detail added Previous stated "Desmoplastic or neurotropic melanoma". Details now state "With any patient where pathology determines melanoma as PURE desmoplastic (as per WHO definition of >90% desmoplasia), they are not eligible for this study. However other desmoplasia or mixed subtypes are eligible unless there is neurotropism present (perineural invasion). Perineural invasion does not include entrapment of nerves within the main primary tumour mass".
		• **Section 6.2 Wide Local Excision Procedure**
		  • Removed hyphen from the word "pre-determined"
		  • Corrected grammar from "surgeons" to "surgeon's"
		• **Section 8.1 Screening Assessments**
		  • Corrected timing of screening in relation to date of diagnosis to clarify that no more than 120 days should have elapsed since diagnosis.
		  • Clarified timing of randomisation and study intervention
		• **Section 8.3 Follow Up Visit Assessments: Maximum of 10 years in Duration**
		  • Added detail regarding physical assessments. "Physical assessment is to be done at each follow up visit; however, if the treating doctor's next physical assessment follow-up is scheduled later than the trial follow up

		window, it is advised that participants should complete questionnaires via post to ensure quality of life data is captured in a timely way."
		• **Section 11.1 Adverse Events**
		  • Surgery-related adverse events: replaced the word 'surgery' with 'intervention' and clarified that AEs will be recorded up to 90 days following intervention and clarified use of Clavien-Dindo system.
		• **Section 11.2 Serious Adverse Events**
		  • Removed the word "toxicity" as this is not a drug trial, therefore not applicable.
		• **Section 12.3.4 Interim Analysis**
		  • Removed the word "toxicity" as this is not a drug trial, therefore not applicable.
		• **Appendix I: Table of Assessments and Follow Up Visits**
		  • Replaced the word "surgery" with "intervention" to clarify that AEs related to the intervention are to be recorded up to 90 days post-surgery.

3.0	30 Oct 2023	• **Section 4.4 Stratification and Randomisation**
		  • Additional information to provide clarification "The wide local excision (WLE) and staging SLNB procedures are referred to as the surgical intervention throughout the protocol."
		• **Section 5.1 Study Eligibility Criteria: inclusion criterion 1**
		  • Updated to provide clarification "Patients must have a Stage II primary invasive cutaneous melanoma with Breslow thickness >2mm (with or without ulceration), or 1-2mm (with ulceration) (pT2b-pT4b, AJCC 8th edition) as determined by diagnostic biopsy (narrow excision, incision or punch biopsy) and subsequent histopathological analysis."
		• **Section 5.1 Study Eligibility Criteria: exclusion criterion 4**
		  • Additional information to provide clarification "Desmoplastic or neurotropic melanoma: with any patient where pathology determines melanoma as PURE desmoplastic (as per WHO definition of >90% desmoplasia), they are not eligible for this study. However other melanomas with less than 90% desmoplasia or mixed subtypes are eligible unless there is neurotropism present (perineural invasion). Neurotropism in any type of melanoma is an exclusion. Perineural invasion does not include entrapment of nerves within the main primary tumour mass."
		• **Section 5.1 Study Eligibility Criteria: exclusion criterion 4**
		  • Updated to ensure the following exclusion criterion is a stand-alone exclusion criterion "5. Microsatellitosis as per AJCC 8th edition definition" Therefore updating the preceding exclusion criteria numbering.
		• **Section 6.2 Wide Local Excision Procedure**
		• **Section 6.2.1 Calculating WLE**
		  • Addition of WLE calculation flowchart-Figure2
		• **Section 6.2.1.1 Wide Local Excision Procedure**
		  • Additional wording included "If the peripheral margin has been completely excised according to the primary biopsy report, proceed to section 6.2a, even if the deep margin has not been completely excised. If the peripheral margin has NOT been completely excised according to the primary biopsy report, then proceed to section 6.2b, even if the deep margin has been completely excised."
		• **Section 6.2.1.2 a iii. Wide Local Excision Procedure**
		  • Additional wording included "If the primary excision biopsy was left to heal by secondary intention, or a complete shave excision has been performed, then the radial excision margin is measured from the edge of the wound"
		• **Section 6.2.1.2 b. Wide Local Excision Procedure**
		  • Additional wording included "Where the primary has not been completely excised at the peripheral margin, at diagnostic excision biopsy and or

		there is residual pigmentation clinically consistent with residual melanoma (see appendix IVb):"
		• **Section 6.2.1.2 b i. Wide Local Excision Procedure**
		  • Additional wording included "Where the primary has not been completely excised at the peripheral margin, at diagnostic excision biopsy and or there is residual pigmentation clinically consistent with residual melanoma (see appendix IVb)."
		• **Section 6.2.1.2 b ii. Wide Local Excision Procedure**
		  • Additional wording included "intra-operatively the marked 2 mm margin is scored with a scalpel as a reference for the reporting histopathologist. The lesion is then removed using the marked randomised margin."
		• **Section 6.2.2.4. Wide Local Excision Procedure**
		  • Deleted "Where the primary has been incompletely excised at the original diagnostic biopsy then the excision biopsy will be completed by excising the specimen according to the marking
		  as in 2b(i) above, with a cuff of subcutaneous fat. This specimen will be orientated with a marking suture and sent for histological analysis separately" Therefore updating the preceding numbering in Section 6.2.
		• **Section 6.2.2.9. Wide Local Excision Procedure**
		  • Section added "If the final pathology, after the wide excision has been performed, demonstrates clinically unacceptable margins the treating clinician may take a further margin as deemed clinically appropriate."
		• **Section 6.3 Sentinel Lymph Node Biopsy**
		  • Additional sentence "Injection of nuclear contrast material and intra-operative SLN localisation without a pre-operative mapping lymphoscintogram is not acceptable."
		• **Section 11.1 Adverse Events**
		  • Modified wording "Pre-existing medical conditions will be recorded at the Bas Assessment. All AEs related to the surgical intervention will be recorded randomisation until 12 months post the surgical intervention or the patient witho or dies. The site Principal Investigator or their delegate is responsible fo assessment of causality of AEs. AEs will be classified for type and se according to the CTCAE criteria, v 5.0 (appendix III)."
		• **Section 11.1 Surgery-Related Adverse Events SrAEs (Surgical complications)**
		  • Modified wording "The following AEs will be considered related to the intervention and recorded from the time of trial treatment up to 12 months following the study intervention (inclusive):
		  • wound separation
		  • seroma/haematoma
		  • haemorrhage
		  • infection
		  • skin graft failure
		  • necrosis of flap used for reconstruction
		  • deep venous thrombosis
		  • urinary tract infection
		  • pneumonia
		  • cardiac complications"
		  • Deleted "Intervention-related AEs within the first 30 days post-surgery also requires grading in severity according to the Clavien-Dindo system[19] (See appendix V)."
		• **Section 11.2 Serious Adverse Events**
		  • Additional wording "All SAEs, regardless of relationship to surgical intervention, will be recorded from randomisation until 12 months post the surgical intervention or the patient withdraws or dies. The site Principal Investigator or their delegate is responsible for the assessment of causality of SAEs."

		• Deleted "and could be related to the wide local excision surgery, including sentinel lymph node biopsy procedure."
		
		• **Section 12.1 Sample Size**
		  • Additional wording included "A non-inferiority logrank test with an overall sample size of 2,998 patients (1,499 in each arm) will achieve 90% power at a 1-sided 0.05 significance level to detect a non-inferiority HR of 1.25"
		  • Additional sentence included "The above sample size calculation was performed using the gsDesign (3) package in R, and results were confirmed using simulation with 10,000 iterations using the npsurvSS package (4)."
		  • Additional sentence included "The analysis set for the primary endpoint will consist of exactly 5 years of patient follow up time."
		  • Additional sentence included "A statistical analysis plan describing the data synthesis, analysis principles and statistical procedures for the final analysis of the trial data is developed along with the protocol."
		• **Section 12.3.2 Statistical Analyses of Secondary Endpoints**
		  • Additional wording included "Cox Proportional Hazards models will be used for all secondary time to event endpoints with results presented as HRs with 95% CIs."
		  • Additional sentence included "The stratification and additional pre-specified prognostic factors will be controlled for in multivariable models to give adjusted HRs."
		  • Additional sentence included "All secondary time to event outcomes will be described using the Kaplan-Meier method stratified by treatment arm."
		• **Appendix I: Table of Assessments and Follow Up Visits**
		  • Updated to indicate that "Pre-Randomisation" assessment does not require "QoL questionnaires" and "Health system resource use questionnaires" to be completed.
		• **Appendix IV Procedure for incompletely excised peripheral margin after shave biopsy**
		  • Appendix IV has been updated to IVa with the addition of Appendix IVb
		• **Appendix V: The Clavien-Dindo Scale For Surgical Complications**
		  • Appendix V deleted.

4.0	08Nov24	• **Section 2.0 Study Summary**
		  • Updated definition and title of secondary endpoints #1 and #2, in line with statisticians' recommendation.
		• **Section 3.1 Background**
		  • Updated Table 1 and 2 AJCC 8th edition; pT2b-pT4b
		• **Section 4.5 Endpoints**
		  • Updated definition and title of secondary endpoints #1 and #2, in line with statisticians' recommendation.
		• **Section 5.1 Study Summary**
		  • Updated inclusion criterion #1 in line with the Breslow thickness of AJCC 8th edition.
		  • Updated exclusion criterion #4 and #5 to clarify the definition of perineural invasion or neurotropic melanoma and desmoplastic melanoma.
		  • Added table 3; a summary of the eligibility criteria
		• **Section 5.2 Exclusion criterion exceptions**
		  • Added 2 scenarios where meeting exclusion criterion #4, #5 and or #6 will allow the participant to remain on trial.
		  • Reminder for sites that discovery of perineural invasion or neurotropic melanoma and desmoplastic melanoma and /or Microsatellites porst randomisation and before intervention requires participants to be withdrawn.

		• **Section 6.1 Diagnosis of Primary Tumours**
		  • GDPR compliance restrictions- uploading primary source documentation.
		• **Section 6.2 Wide Local Excision Procedure**
		  • Updated Figure 2, with clearer image.
		• **Section 8.3 Follow Up Visit Assessments: Maximum of 10 Years in Duration**
		  • Introduction of sub headings 8.3.2 Years 3 to 5 follow-up and 8.3.3 Years 6 to 10 follow-up.
		• **Section 8.6 Withdrawal and Lost to Follow Up**
		  • Clarification of withdrawal/change in participation level of a participant and LTFU provided to assist sites.
		• **Section 8.8 Health Economics and System Resource Use**
		  • Completion requirements for participating countries added for all questionnaires.
		• **Section 11.2 Serious Adverse Events (SAEs)**
		  • Clarification of SAE reporting provided: Please note: Deaths resulting from disease progression or immunotherapy should not be reported as an SAE.
		• **Section 11.3 Suspected Unexpected Serious Adverse Events**
		  • Definition provided as per (NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods [EH59], November 2016)
		• **Section 11.3 Significant Safety Issues**
		  • Definition provided as per (NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods [EH59], November 2016)
		• **Section 11.3 Urgent Safety Measures**
		  • Definition provided as per (NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods [EH59], November 2016)
		• **Section 12.1 Sample size**
		  • Update to indicate statistical analysis plan has been developed.

5.0	Date	• **Section 6.1 Diagnosis of Primary Tumours**
		  • Added sentence stating clarifying - GDPR compliance restrictions- uploading primary source documentation
		• **Section 8.4 Melanoma Recurrence / Progression or New Primary Melanoma: Diagnosis & Classification**
		  • Clarified recurrence definitions to assist in recurrence reporting
		• ***Section 12.3.2.2 QoL***
		  • Provide outline of the planned statistical analysis for the quality-of-life data being collected.

Contents

1. Abbreviations & Definitions

AE	Adverse Event
AJCC	American Joint Committee on Cancer
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CLND	Completion Lymph Node Dissection
CPMP	Committee for Proprietary Medicinal Products (these are UK specific regulations)
CREST	Cancer Research Economics Support Team
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-Free Survival
DDFS	Distant Disease-Free Survival
DRG	Diagnostic Related Group
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylene Diamine Tetraacetic Acid (an anticoagulant used for blood sampling)
H&E	Haematoxylin & Eosin Staining
HES	Hospital Episode Statistics
HMB-45	Human Melanoma Black (an antigen often present in melanocytic tumours)
HR	Hazard Ratio
HREC	Human Research Ethics Committee
HRQoL	Health-related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
IHC	Immunohistochemistry
LN	Lymph Node
LR	Local Recurrence
MASC Trials	Melanoma and Skin Cancer Trials
Melan A/MART-1	Protein Melan A or melanoma antigen recognized by T-cells 1; often present in melanocytic tumours
MSS	Melanoma-Specific Survival
MRI	Magnetic Resonance Imaging
NHMRC	National Health and Medical Research Council (this is an Australian research entity)
NHS	National Health Service (this is an UK research entity)
ONS	Office of National Statistics (this is an UK research entity)
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression Free Survival
PICF	Patient Information & Consent Form
QALY	Quality Adjusted Life Year
QoL	Quality of Life
S-100	A family of cellular antigens proteins, often present in melanocytic tumours
RCT	Randomised Controlled Trial
RGO	Research Governance Officer
SAE	Serious Adverse Event
SD	Standard Deviation
SN	Sentinel Node
SLNB	Sentinel Lymph Node Biopsy
SrAEs	Surgery-related Adverse Events
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMC	Trial Management Committee
TSC	Trial Steering Committee
UK	United Kingdom

US	Ultrasound
USA	United States of America
WLE	Wide Local Excision

2. Study Summary

2.1 Study Title

Melanoma Margins Trial (MelMarT)

2.2 Background and Rationale

A wide, radical excision to remove the entire primary tumour, to prevent spread and local recurrence (LR) is a classic surgical teaching. In primary melanoma, a secondary wider excision around the original biopsy scar is advocated to reduce risk of LR and improve patient outcomes. Surprisingly, the detail of the wide excision is still highly controversial. Surgical margins vary significantly worldwide, from 1cm to 3cm, translating into large excision defects from 2cm to 6cm across. The management of patients with intermediate and high-risk primaries is particularly speculative. There is a growing concern internationally amongst surgeons that the excess morbidity caused by the larger excision defects, including increased hospital stay, complications and need for reconstructive surgery, coupled with prolonged rehabilitation and increased risk of chronic pain is not justifiable. Many surgeons suspect that 1cm is ample. An appropriately designed trial of adequate size is clearly needed to unify international guidance and to benefit the large and increasing numbers of melanoma patients worldwide.

2.3 Study Objectives

This study will determine whether there is a difference in disease free survival (DFS) for patients treated with either a 1cm excision margin or 2cm margin for clinical Stage II (pT2b-pT4b) primary cutaneous melanoma (AJCC 8th edition, Table 1). The study is designed to be able to prove or disprove that there is no difference in risk of melanoma recurrence between the two groups of patients. This study is designed to show that the risk of long-term pain associated with surgery can be reduced. If the study achieves its primary objective and demonstrates safety with a narrower margin, then we will also be able to determine how much of an impact the narrower excision has on patients in terms of improved quality of life (QoL) and reduced side effects from the surgery and melanoma disease. This trial will also evaluate and determine the economic impact of narrower excision margins on the health services and society in general.

It is expected that successful completion of this study will define the appropriate management of Stage II primary cutaneous melanoma (pT2b-pT4b) for Australia and the international melanoma community.

A patient-facing advertisement approved by the Human Research Ethics Committee (HREC) has been developed to promote the trial within existing investigator networks or in the local healthcare setting for doctors referring patients for trial eligibility assessment. The advertisement may also be shared within patient community forums via social media and on the MASC Trials website.

2.4 Study Hypothesis

There is no difference in DFS for patients treated with either a 1cm or 2cm excision margin for clinical Stage II (pT2b-pT4b) primary cutaneous melanoma. A 1cm excision margin will reduce the risk of long-term pain and will reduce surgical complication rates. A 1cm excision margin will have an impact on improved QoL for patients and change the use of local healthcare resources.

2.5 Study Population

In order to assess the protocol feasibility and recruitment strategies, the study is split into 2 phases; the first is a pilot study and the second is the full study. Pilot study patients who meet full study eligibility criteria will be included in the final analysis.

2.6 Phase I: Pilot study (03.12 MelMarT-I)

400 patients were recruited from January 2015 – June 2016, who fit the following criteria:

1. 18 years or older
2. Histologically confirmed, primary invasive cutaneous melanoma of Breslow thickness >1mm: AJCC 7th edition Stage IB-IIC (pT2-4/N0/M0)
3. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 (See Appendix II) at randomisation
4. Patients were able to give informed consent, and comply with protocol treatment and follow up
5. Randomisation and treatment were performed within 120 days of diagnosis
6. Patients must have had no previous malignancy or primary except low-risk non-melanoma skin cancer, unless in remission and >5 years since diagnosis.

2.7 Phase II: Full Study (02.18 MelMarT-II)

The aim is to recruit a total of 2,998 patients who fit the following criteria:

1. 18 years or older
2. Histologically confirmed, primary invasive cutaneous melanoma: AJCC 8th edition Stage IIA-IIC (pT2b-pT4b)
3. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 (See Appendix II) at randomisation
4. Patients must be able to give informed consent, and comply with protocol treatment and follow up
5. Randomisation and treatment must be performed within 120 days of diagnosis
6. Patients must have no previous malignancy or primary except low-risk non-melanoma skin cancer, unless in remission and >5 years since diagnosis.

2.8 Study Treatments

Once determined as being eligible, patients will be randomised 1:1 to either a 1 cm excision margin or a 2 cm excision margin, in combination with a staging sentinel lymph node biopsy (SLNB).

2.9 Study Design

This is a randomised, controlled, multi-centre, non-inferiority, internationally recruiting, phase III clinical trial.

2.10 Study Endpoints

2.10.1 Primary Endpoint:

1. **Disease-free survival (DFS)**: Time from randomisation until the first clinically, histologically or radiologically confirmed recurrence of melanoma at any body site, or death from any cause.

2.10.2 Secondary Endpoints:

1. **Local recurrence free survival (LRFS)**: Time from randomisation to any clinically, histologically or radiologically confirmed LR of melanoma including satellite lesions and in transit metastases between the primary site and the regional draining lymph nodes or death from any cause.
2. **Distant disease-free survival (DDFS)**: Time from randomisation to any clinically, histologically or radiologically confirmed distant recurrence of melanoma or death from any cause
3. **Melanoma specific survival (MSS)**: Time from randomisation to death due to melanoma
4. **Overall survival (OS)**: Time from randomisation to death from any cause.
5. **QoL and neuropathic pain assessments** at baseline, 3, 6, 12 and 24 and at melanoma recurrence.
6. **Surgery related adverse events** up to 12-months from the date of surgery.
7. **Serious Adverse events** within 1 year
8. **Health economic evaluation** resource utilisation and cost-utility analysis

2.11 Summary of Statistical Methods

2.11.1 Power analysis and sample size

The sample size is based upon a single primary outcome DFS which typically includes the events of recurrence (local, regional, or distant) and death from any cause. We assumed a hazard ratio (HR) of no more than 1.25 will be deemed to be the limit of non-inferiority margin, and a 3-year DFS rate of 85% in the 2cm excision margin arm. These assumptions translate into a 3-year DFS rate of 81.6% in the 1cm excision margin arm and therefore a maximum absolute difference in DFS rates of 3.4%. A non-inferiority log rank test with an overall sample size of 2,998 patients (1,499 in each arm) will achieve 90% power at a 0.05 significance level to detect a non-inferiority HR of 1.25. The sample size allows for 10 percent of patients lost to follow up. The study lasts for a period of 10 years of which participant accrual (entry) occurs in the first 5 years. A smaller sample size (total 2,012) will suffice for the patient-reported outcomes (QoL and pain): this sample will achieve 90% power to detect an effect size of 0.20 (considered a small but clinically relevant difference) at a significance level of 0.0025 (allowing for testing of 20 QoL/pain hypotheses, given 5 key QoL/pain variables at each of three assessment times and over all times), and allowing for 20% missing data at 12 months.

2.11.2 Statistical analysis

The primary endpoint of DFS will be analysed using Cox's Proportional Hazards model and graphically described using the Kaplan-Meier method. The endpoint will be defined as the time from surgery until disease progression (first clinically, histologically or radiologically confirmed recurrence of melanoma at any body site) or death from any cause, or a censoring event (end of study, withdrawal). The 95% confidence intervals (CI) around the HR will be examined to assess non-inferiority. Non-inferiority of 1cm excision margin will be claimed if the upper limit of the 95% CI is lower 1.25. An intention-to-treat approach will be adopted but given the non-inferiority nature of the study this will be supplemented by a per-protocol analysis. This test for non-inferiority will only be performed for the primary efficacy outcome; all other secondary outcomes will be tested for superiority of 1cm versus 2cm excision margin. The secondary survival endpoints of distant disease-free survival (DDFS), LR, and OS will also be analysed using a Cox's Proportional Hazards model and graphically described using the Kaplan-Meier method. A sub-group analysis will be performed using pre-specified factors: 1) AJCC Stage (IIA-IIC), 2) Age (<45, 45-65, >65), Gender and 3) Country. Generalisability will be assessed, as far as possible, by comparing the characteristics of those participants participating in the study with those who were eligible but declined.

3. Introduction

3.1 Background

Wide excision to remove the entire primary tumour and to prevent spread is classical surgical oncology teaching. In primary melanoma, a secondary wider excision around the original biopsy scar is advocated to reduce risk of LR and improve patient outcomes. While this 2-stage procedure is the accepted international standard of care for all primary melanomas, surprisingly the detail of the wide excision is still highly controversial.

To date, six randomised controlled trials (RCTs) [1-6] have investigated the effect of wider excision margins on LR and survival from melanoma. Diverse margins, hybrid endpoints, lack of accurate initial staging, small sample sizes and limited stratification have led to inconclusive results. Accordingly, national guidelines regarding the recommended width of surgical excision margins vary significantly worldwide, from 1cm to 3cm, depending on perceived risk of recurrence as determined by depth of invasion from the skin surface. The management of patients with Stage II primaries (see Table 1 and 2 below) is particularly speculative amongst the major international guidelines. There is a growing concern amongst surgical oncologists that the excess morbidity caused by the larger excision defects, including increased hospital stay, complications and need for prolonged rehabilitation[7], increased risk of chronic pain and loss of function in critical anatomic sites, may no longer be justifiable. In most countries where melanoma is prevalent, approximately 45% of all melanoma patients with Stage II primaries are subject to 2-3 cm excision margins. However, many surgeons suspect that 1cm is ample and perform this for lower risk Stage II melanomas wherever national guidance allows, particularly in North America & Australasia, even though evidence for this is lacking.

Table 1 – Categorisation of Stage II (pT2b-pT4b) primary melanoma according to depth of invasion*, histopathological presence of ulceration and prognostic staging groups[8]**

BRESLOW THICKNESS*	ULCERATION**	PATHOLOGICAL STAGING (TNM)	AJCC STAGING[8]
>1.0 – 2.0mm	YES	pT2b	IIA
>2.0 – 4.0mm	NO	pT3a	
>2.0 – 4.0mm	YES	pT3b	IIB
> 4.0mm	NO	pT4a	
> 4.0mm	YES	pT4b	IIC

Table 2 – Current international guidelines for excision margins for primary cutaneous melanomas[9-14]

Tumour Breslow Thickness	UK 2010	USA 2017	Canada 2017	Aus / NZ 2017	Netherlands 2013	Germany 2013
≤ 1mm	1cm	1cm	1cm	1cm	1cm	1cm
1.0 – 2.0mm	1- 2cm	1- 2cm	1- 2cm	1-2cm	1cm	1cm
2.0 – 4.0mm	2 – 3cm	2cm	2cm	1- 2cm	2cm	2cm
> 4.0mm	3cm	2cm	2cm	2cm	2cm	2cm

Two systematic reviews[15-16] and one Cochrane review[17] of these RCTs have shown no benefit of wider excision margins (3-5cm) in changing disease outcome. They have also failed to produce definite guidance on the optimal minimum margins (1 vs. 2 cm) for Stage II melanoma. In 2009, the Cochrane review concluded:

"...Further randomised trials would be needed to clarify optimal excision margins for primary cutaneous melanoma...Current data suggest that 'narrow' margins produce similar outcomes to 'wider' margins so perhaps trials should compare...for example 1 versus 2 cm."

Internationally, the most commonly recommended excision margins for Stage II melanoma patients is 2cm. A 1cm excision margin does not appear to be detrimental to patients' survival or LR rates, but has not previously been directly compared with 2cm in any properly-powered randomised trial. Our aim is to undertake such a comparison, evaluating outcomes including recurrence, survival, QoL and health economics across multiple countries worldwide.

The incidence of melanoma is one of the most rapidly rising of all malignancies. Melanoma tends to affect younger patients (over 45% are <65 years). This international epidemic has major socio-economic implications for many countries. The adoption of wider excision margins after primary melanoma surgery may be creating significant morbidity and reduced QoL for patients, an extra burden on healthcare resources and finances and an important impact on the economy in terms of loss of productivity due to morbidity. An answer to the optimal excision margin is long overdue.

3.2 Quality of Life (QoL)

With optimal surgery, over 80% of melanoma patients survive beyond ten years. Since the overwhelming majority of melanoma patients have surgery and no other treatment, QoL after surgery is a key survivorship issue. Analysis of data from the UK estimates that 59,000 patients are currently alive with a diagnosis of melanoma (0.1% of the population). QoL data[18] revealed significant post-operative morbidity overall in follow up. Those with melanomas located on the extremities and those who required reconstructions had significantly poorer QoL. The prevalence of chronic, moderate-severe neuropathic pain was 8%. We predict that QoL could be significantly improved with the adoption of narrower surgical excision margins, in addition to benefits for the wider health economy, in terms of retaining people in the workplace.

3.3 Cost Effectiveness

The biggest change in clinical management would stem from those patients whose reconstruction would change from complex repair, such as skin graft or local flap, to simple, direct side-to-side closure. Analysis of the feasibility data from the first phase of the study, 03.12 MelMarT-I, showed that more patients in the 2-cm margin group required reconstruction (34.9 vs. 13.6%; $p < 0.0001$). There was an increased wound necrosis rate in the 2-cm arm (3.6 vs. 0.5%; $p = 0.036$). The data demonstrates that the need for reconstruction (local flap or skin graft) more than halved in the narrower excision margin group[19].

An analysis performed in the UK has estimated that narrower excision margins for melanoma could generate savings to the NHS in the order of £1.35 million per annum as a consequence of reduced number of reconstruction procedures, fewer bed days required and fewer surgery-related complications. Similar, proportionate savings can be expected internationally across many modern health-care systems where melanoma is a significant health problem.

4. Trial Objectives and Design

4.1 Objectives

4.1.1 Primary Objective

The primary objective of the trial is to assess whether there is no difference in DFS for patients treated with a 1cm excision margin when compared to a 2cm margin for Stage II primary melanomas (AJCC 8th edition; pT2b-pT4b).

4.1.2 Secondary Objectives

We hope to show that we can reduce the risk of long-term pain. If the study shows no difference in the risk of tumour recurrence, then we will also be able to determine how much of an impact the narrower excision makes to patients in terms of improving QoL and reducing side effects. We will also have enough to data to determine the economic impact of narrower excision margins on the health services and society in general.

4.2 Hypotheses

The trial design has been informed by the following assumptions that there is no difference in melanoma recurrence rates, as measured by DFS, for patients treated with either a 1cm or 2cm excision margin for Stage II melanoma, that a 1cm excision margin will reduce the number of reported surgical complication rates, reduce the risk of long-term pain, as well as improve patients reported QoL and change how local healthcare resources are utilised. There are several study questions which inform the trial design:

- Could a narrower excision margin of 1cm be safely performed without an increase in the risk of **DFS** when compared to a 2cm excision margin in patients at risk of recurrence?
- Does the narrower excision margin improve the patient's **quality of life**?
- Does the narrower excision margin change the use of **local healthcare resources and improve the surgical complication rate**?

4.3 Trial Design

This is a randomised, controlled, multi-centre, non-inferiority, internationally recruiting, phase III clinical trial.
In order to assess the protocol feasibility and recruitment strategies the study has been split into 2 phases; the first phase pilot study 03.12 MelMarT-I, which recruited 400 patients, and the second phase full study 02.18 MelMarT-II, with the aim of recruiting 2,998 patients. A limited number of sites participated in the pilot study which will be expanded once the full study commences.

4.4 Stratification and Randomisation

Patients will be stratified by the following factors:

- AJCC 8th edition Stage (IIA, IIB, IIC)
- Age (<45; 45-65; >65)
- Sex (Male; Female)
- Country

Patients will be randomised 1:1 taking into account the above listed stratification factors using a randomisation system to one of two study arms:

1. **Treatment Arm A**: Wider excision with a 1cm radial margin in combination with a sentinel lymph node biopsy
2. **Treatment Arm B**: Wider excision with a 2cm radial margin in combination with a sentinel lymph node biopsy

Full instructions on how to randomise patients are described in the Operations Manual.

Figure 1 – MelMarT-II-trial schema

MELMART-II TRIAL SCHEMA		TRIAL PHASE	TIME
Diagnosis of Primary Cutaneous Melanoma pT2b-pT4b (N0M0) AJCC Stage IIA-IIC		Screening	Date of diagnosis up to Day 0 (Day 0 = randomisation)
Confirmation of Diagnosis by recruiting institution's designated pathologist **Informed Consent**			
RANDOMISATION **(Stratification Factors: AJCC Stage (IIA, IIB, IIC); Age; Sex; Country)**		Total patients = 2,998	
AJCC IIA-IIC (pT2b, pT3a, pT3b, pT4a, pT4b) **N=2,998**		Stratification & Randomisation	Day 0
At participating sites: **QoL component (FACT-M, EQ-5D-5L and Neuropathic Pain (Pain Detect)) & Health economic component**			Day 0
ARM A: Experimental Arm **Wide Local Excision = 1cm Margin** **+ Sentinel Lymph Node Biopsy** **+/- Reconstruction** **N=1,499**	**ARM B: Control Arm** **Wide Local Excision = 2cm Margin** **+ Sentinel Lymph Node Biopsy** **+/- Reconstruction** **N=1,499**	Surgical Intervention	Surgery no more than 120 days from date of diagnosis
FOLLOW UP			
Clinical Information & Health Status	**Years 1-2:** Baseline, 3, 6, 12, 18 and 24 months **Years 3-5**: Annually **Years 6-10**: Annually (optional based on local standard of care or clinician's discretion) 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	Follow Up	Day 0 - Trial Completion (max. 120 months)
At participating sites: FACT-M, EQ-5D-5L, Pain Detect (Neuropathic pain), Follow Up Employment* and Cost Questionnaire completion			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
Serious Adverse Events			Day 0 – 12 Months
Quality of Life **Health Economics**			Day 0, Month 3,6,12 and 24

4.5 Endpoints

4.5.1 Primary Endpoints

The primary endpoint of the study is:

1. **Disease-free survival (DFS)**: Time from randomisation until the first clinically, histologically or radiologically confirmed recurrence of melanoma of any site or death from any cause.

4.5.2 Secondary Endpoints

Additional endpoints assessed during the study will include:

1. **Local recurrence free survival (LRFS)**: Time from randomisation to any clinically, histologically or radiologically confirmed LR of melanoma including satellite lesions and in transit metastases between the primary site and the regional draining lymph nodes or death from any cause.
2. **Distant disease-free survival (DDFS)**: Time from randomisation to any clinically, histologically or radiologically confirmed distant recurrence of melanoma or death from any cause
3. **Melanoma-specific survival (MSS):** Time from randomisation to death due to melanoma
4. **Overall survival (OS):** time from randomisation to death from any cause.
5. **QoL and neuropathic pain assessments** at baseline, 3, 6, 12, 24 months and at melanoma recurrence.
6. **Surgery related adverse events** up to 12-months from the date of surgery.
7. **Serious Adverse events** within 1 year
8. **Health economic evaluation:** Resource utilisation and cost-utility analysis from hospital notes, MBS and PBS data and patient reported outcomes, at baseline, 3, 6, 12, and 24 months and at melanoma recurrence.

5. Eligibility Criteria

5.1 Study Eligibility Criteria

Patient Population

It is expected that patients will be recruited from treatment centres specialising in the surgical care of melanoma patients. Recruiting institutions will be required to demonstrate an adequate annual caseload of primary melanoma and will need to be performing a minimum of 30 -SLNBs per annum. Patients eligible for the trial should be assessed by the specialist multidisciplinary teams (or tumour board) including pathology slide review to confirm the diagnosis of primary melanoma. The following patients would be eligible for the trial:

5.1.1 Inclusion Criteria

Patients may be included in the study if they meet **ALL** of the following criteria:

1. Patients must have a Stage II primary invasive cutaneous melanoma (pT2b-pT4b, AJCC 8th edition) with Breslow thickness >1.0mm to 2.0mm; >2.0mm to 4.0mm or >4.0mm with ulceration, or >2.0mm to 4.0mm; or >4.0mm without ulceration (Table 1) as determined by diagnostic biopsy (narrow excision, incision, shave or punch biopsy) and subsequent histopathological analysis.
2. Must have a primary melanoma that is cutaneous (including head, neck, trunk, extremity, scalp, palm or sole).
3. An uninterrupted 2cm margin must be technically feasible around biopsy scar or primary melanoma.
4. Surgical intervention (which refers to the staging -SLNB and WLE as these are both to be done on the same day) must be completed within 120 days of the original diagnosis. Surgical intervention must also be performed within 28 days of randomisation.
5. Patients must be 18 years or older at time of consent.
6. Patient must be able to give informed consent and comply with the treatment protocol and follow up plan.
7. Life expectancy of at least 5 years from the time of diagnosis, not considering the melanoma in question, as determined by the PI.
8. Patients must have an ECOG performance score between 0 and 1 at screening.
9. A survivor of prior cancer is eligible provided that **ALL** of the following criteria are met and documented:
    - The patient has undergone potentially curative therapy for all prior malignancies,
    - There has been no evidence of recurrence of any prior malignancies for at least FIVE years *(with the exception of successfully treated uterine/cervical or non-melanoma skin cancers (SCCs/BCCs) with no evidence of recurrence*), **and**
    - The patient is deemed by their treating physician to be at low risk of recurrence from previous malignancies.

5.1.2 Exclusion Criteria

Patients will be excluded from the study for **ANY** of the following reasons:

1. Uncertain diagnosis of melanoma i.e., so-called 'melanocytic lesion of unknown malignant potential'.
2. Patient has already undergone WLE at the site of the primary index lesion.
3. Patient unable or ineligible to undergo staging SLNB of the primary index lesion.
4. Perineural invasion or neurotropic melanoma: Neurotropism or perineural invasion in any type of melanoma is an exclusion. Perineural invasion does not include entrapment of nerves within the main primary tumour mass.
5. Desmoplastic melanoma: with any patient where pathology determines melanoma as PURE desmoplastic (as per WHO definition of >90% desmoplasia), they are not eligible for this study. However melanomas with less than 90% desmoplasia or mixed desmoplastic subtypes are eligible unless there is neurotropism present (perineural invasion)
6. Microsatellitosis (a nest of metastatic tumour cells found to be growing away from the primary tumour) as per AJCC 8th edition definition is an exclusion.
7. Subungual melanoma.
8. Patient has already undergone a local flap reconstruction of the defect after excision of the primary and determination of an accurate excision margin is impossible.
9. History of previous or concurrent (i.e., >1 primary melanoma) invasive melanoma.
10. Melanoma located distal to the metacarpophalangeal joint; on the tip of the nose; the eyelids or on the ear; genitalia, perineum or anus; mucous membranes or internal viscera.
11. Physical, clinical, radiographic or pathologic evidence of satellite, in-transit, regional, or distant metastatic melanoma.
12. Patient has undergone surgery on a separate occasion to clear the lymph nodes of the probable draining lymphatic field, including -SLNB, of the index melanoma.
13. Any additional solid tumour or hematologic malignancy during the past 5 years (*with exception of non- melanoma skin cancers (T1 skin lesions of squamous cell carcinoma (SCCs), basal cell carcinoma (BCCs)), or uterine/cervical cancer*).
14. Melanoma-related operative procedures not corresponding to criteria described in the protocol.
15. Planned adjuvant radiotherapy to the primary melanoma site after wide local excision is not permitted as part of the protocol and any patients given this treatment would be excluded from the study.
16. History of organ transplantation.
17. Oral or parenteral immunosuppressive agents (not topical or inhaled steroids) at enrolment or within 6 months prior to enrolment.

Please note:

- Pregnancy is not a specific exclusion criterion for this trial, though it may not be clinically appropriate to perform a wide excision and SLNB until the pregnancy has been completed, which may exclude the patient due to violation of inclusion criterion 4.
- We would advise careful counselling of the patient prior to enrolment, which would include a discussion at the treating centre's multidisciplinary team meeting or tumour board and the central trial office.

Table 3: Summary of Inclusion/Exclusion criteria

Inclusion criteria	**Ineligible**	**Eligible**
Stage II primary invasive cutaneous melanoma as per pT2b-pT4b, AJCC 8th edition see table 1		X
Cutaneous primary melanoma		X
An uninterrupted 2cm margin must be feasible around biopsy scar or primary melanoma		X
Surgical intervention must be completed within 120 days of the original diagnosis and within 28 days of randomisation.		X
Patients must be 18 years or older at time of consent		X
Patient must be able to give informed consent		X
Life expectancy of at least 5 years from the time of diagnosis		X
ECOG performance score between 0 and 1 at screening.		X
A survivor of prior cancer is eligible provided that ALL of the following criteria are met and documented		
* patient has undergone potentially curative therapy for all prior malignancies		X
* no evidence of recurrence of any prior malignancies for at least FIVE years		X
* patient is deemed by their treating physician to be at low risk of recurrence from previous malignancies.		X

Exclusion criteria	Ineligible	Eligible
Uncertain diagnosis	X	
Prior WLE at primary index lesion site	X	
Unable or ineligible to undergo staging SLNB of the primary index lesion	X	
Perineural invasion or neurotropic melanoma: Neurotropism or perineural invasion in any type of melanoma	X	
Desmoplasia >90%	X	
Desmoplasia <90%		X
Desmoplasia mixed subtype		X
Desmoplasia <90% plus Neurotropism or perineural invasion	X	
Desmoplasia mixed subtype plus Neurotropism or perineural invasion	X	
Satellitosis/Microsatellites	X	
Subungual melanoma	X	
Prior local flap reconstruction of the defect after excision of the primary lesion and determination of an accurate excision margin is impossible	X	
History of previous or concurrent invasive melanoma	X	
Melanoma located distal to the metacarpophalangeal joint; on the tip of the nose; the eyelids or on the ear; genitalia, perineum or anus; mucous membranes or internal viscera	X	
Prior surgery to clear the lymph nodes of the probable draining lymphatic field, including -SLNB, of the index melanoma	X	
Any additional solid tumour or hematologic malignancy during the past 5 years (excl. SCC/BCC or uterine/cervical cancer)	X	
Melanoma-related operative procedures not corresponding to criteria described in the protocol	X	
Planned adjuvant radiotherapy to the primary melanoma site after wide local excision is not permitted as part of the protocol and any patients given this treatment would be excluded from the study.	X	
Organ transplantation recipient	X	
Oral or parenteral immunosuppressive agents (not topical or inhaled steroids) at enrolment or within 6 months prior to enrolment	X	

5.2 Exclusion criterion exceptions

The screening process is critical for both patient safety and the integrity of the MelMarT-II trial, however as this trial is a pragmatic in design it is understood that some eligibility exceptions must be allowed for. Below are two scenarios where participants meeting exclusion criterion 4, 5 and or 6 may remain on trial.

1. Participants randomised in good faith and deemed eligible at point of randomisation and intervention. Exclusion criterion 4, 5 and or 6 (e.g. microsatellites/PNI) discovered in wide local excision or discovered after post-hoc review of primary melanoma and/or patient.
   Outcome: Participant to stay on trial. No other action. Included in final analysis.

2. Participants randomised in error (ineligible meets exclusion criterion 4, 5 and or 6 (eg microsatellites/PNI)), undergoes trial intervention then error discovered.
   Outcome: Participant stays on study and follow-up data only (not PROMs) to be collected. Included in a sensitivity analysis, specifically for this group, but not included in main analysis. Serious breach notification to sponsor and ethics.
   In the UK, de-identified patient data will also be sent to the British ethics committee. Historic patients have been withdrawn in the UK but will be reconsented.

Please note: *Participants randomised in error (ineligible meets exclusion criterion 4, 5 and or 6 (eg microsatellites/PNI)), where the ineligibility is discovered before the intervention (WLE surgery).*

Outcome: Participant **withdrawn**. Protocol breach/deviation to be reported in REDCap. No other action.

6. Trial Treatment

6.1 Diagnosis of Primary Tumours

The primary melanoma should be biopsied by excision or rarely by incisional methods for large lesions, attempting to biopsy the apparently thickest portion of the lesion. Although an excision biopsy is the preferred method, incision, punch or shave biopsy is acceptable if the biopsy and subsequent re-excision make it possible to gauge the melanoma's complete thickness. The tumour thickness and staging results will help determine initial stratification. For further information on shave biopsies see appendix VI.

An anonymised copy of the primary diagnosis pathology report is required to be submitted to the Trial Coordinating Centre unless restricted by GDPR compliance.

6.2 Wide Local Excision Procedure

To ensure quality assurance and maintain protocol integrity, each participating institution is required to perform the WLE in strict adherence with the procedure described in this protocol. The flowchart below (figure 2) and appendices IVa and b depicts the WLE process.

6.2.1 Calculating WLE

1. Wider excision margins will be measured as accurately as possible with a ruler and marked with a pen prior to injection of local anaesthetic in the operative field. The measurements and markings will be made using an operating light with the operating field fully exposed. If the *peripheral* margin has been completely excised according to the primary biopsy report, proceed to section 6.2a, even if the deep margin has not been completely excised. If the *peripheral* margin has NOT been completely excised according to the primary biopsy report, then proceed to section 6.2b, even if the deep margin has been completely excised.
2. The excision margin will be calculated in the following manner (figure 2):
    a. *Where the primary has been completely excised at diagnostic excision biopsy (see Appendix IVa):*
        i. The excision margin will be calculated ***without*** reference to the previous margins of the diagnostic excision biopsy. If the patient is randomised to the 1cm arm of the trial then the excision margin from the biopsy scar will be 1cm. If the patient is randomised to the 2cm arm of the trial then the excision margin from the biopsy scar will be 2cm.
        ii. Where there is a linear scar after closure of an elliptical defect, the central half of the scar will have a radial margin measured perpendicularly along its length as determined by the randomisation of the patient. At each end of the central half of the scar, a semicircle will be marked out with a radius equal to the predetermined excision margin so as to ensure that the resecting surgeon does not compromise the margin by tapering the ends of the ellipse prematurely (see Appendix IV).
        iii. If the primary excision biopsy was left to heal by secondary intention, or a complete shave excision has been performed, then the radial excision margin is measured from the edge of the wound.
    b. *Where the primary has not been completely excised at the peripheral margin at diagnostic excision biopsy or there is residual pigmentation clinically consistent with residual melanoma (see appendix IVb)::*
        i. a 2mm margin is marked out around the residual macroscopic tumour and then the randomised margin of either 10 or 20mm is marked from this line. The standard photograph of the lesion with marked margins is the performed.
        ii. intra-operatively the marked 2mm margin is scored with a scalpel as a reference for the reporting histopathologist. The lesion is then removed using the marked randomised margin.
3. A digital photograph will be taken of the marked excision site(s), prior to injection of local anaesthetic, and will be saved in high quality Jpeg format and the filename will be the patient's unique study number. A graduated scale reference, almost always the ruler used to mark the excision margin, will be included in the photograph. The entire area of excision should make up at least half the area of the photograph. The photograph will contain no identifying data or this should be subsequently removed digitally, but not in a way that obscures assessment of the excision margin or the graduated scale.

6.2.2 WLE procedure

1. The wide local excision WLE of the tissue will be performed by cutting vertically down along the margins of the excision for its entire length down to the fascia. The specimen is not to be chamfered in any way to reduce the depth of the defect. The fascia may be removed according to the resecting surgeon's practice. Major superficial structures which, if resected might impart unnecessary morbidity to the patient, such as the long saphenous vein or the superficial branch of the peroneal nerve, for example, may be preserved at the surgeon's discretion if not obviously involved with tumour. Areas where there is no obvious fascia such as the face or dorsum of the hand should be resected down to the next anatomical plane, such as

paratenon.

2. The specimen should be correctly orientated with one or more marking sutures to allow pathological assessment of margins.
3. The surgeon may reconstruct the defect as is deemed appropriate for the patient but this information must be recorded on the MelMarT-II electronic Case Report Forms (eCRF).
4. The specimen will be sent off for histological analysis at the local pathology service to determine the presence or absence of residual tumour. If residual tumour is present then the lateral and deep excision margins must be recorded in millimetres on the pathology report.
5. A copy of the wide local excision WLE pathology report is required to be uploaded in the MelMarT-II eCRF.
6. If the final pathology, after the wide excision has been performed, demonstrates clinically unacceptable margins the treating clinician may take a further margin as deemed clinically appropriate.

6.3 Sentinel Lymph Node Biopsy

A staging SLNB must be performed at the time of the wider excision. This will be undertaken using a pre-operative mapping lymphoscintigram, followed by an intra-operative dual localisation technique using a gamma probe and a dye tracer agent (usually Patent Blue dye or isosulphan blue). Injection of nuclear contrast material and intra-operative SLN localisation without a pre-operative mapping lymphoscintogram is not acceptable. Other tracer agents can potentially be used if they can be shown to have a proven efficacy similar to the standard dual tracer technique and with the prior agreement of the study lead or Trial Management Committee (TMC). In the rare event that a pregnancy test performed on the day of attendance at the Nuclear Medicine department detects a previously undisclosed or unknown pregnancy, then the patient should be withdrawn from the study and a study withdrawal form completed. From that point on, the patient will be managed according to the treating centre's local policy.

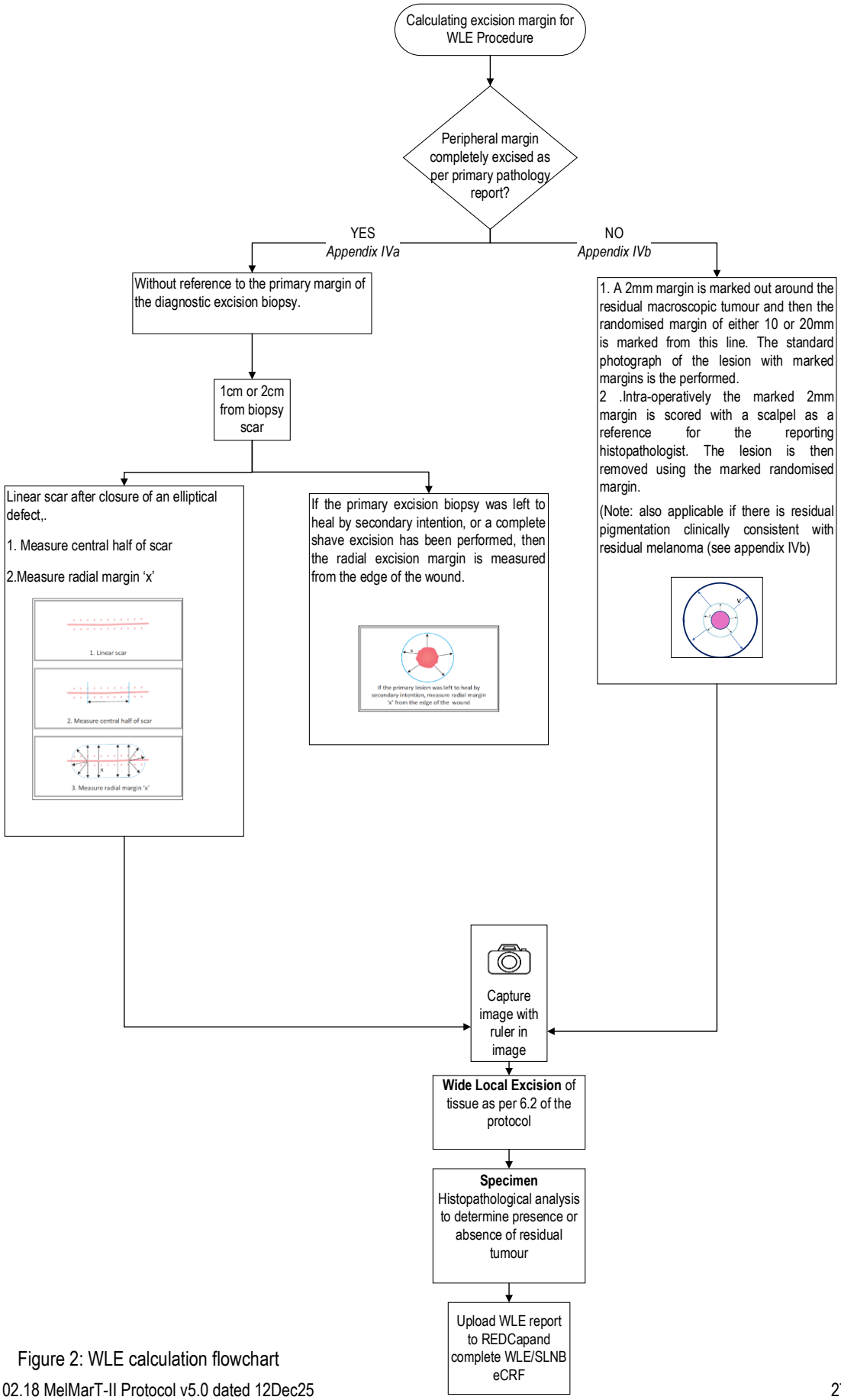

Figure 2: WLE calculation flowchart

7. Acceptable Concurrent Treatments and Participation in Other Clinical Trials

7.1 Adjuvant Radiotherapy

Adjuvant radiotherapy to the primary melanoma site is not permitted as part of the protocol and any patients given this treatment would be excluded from the study. Adjuvant radiotherapy may be provided during the study to treat melanoma recurrence at the discretion of the individual participating institution and reflecting the standard of care at the centre. Adjuvant radiotherapy for melanoma will be recorded on the eCRFs and documented in the source documents.

7.2 Systemic Therapies; Cytotoxic, Immunotherapy and Targeted Therapies

Treatment for local, regional & systemic metastases during the course of follow up is allowable and will be at the discretion of the individual participating institution, including clinical trials. Any treatment will be recorded on the CRFs and documented in the source documents.

7.3 Clinical Trial Participation

The MelMarT-II study is permissive in design. Enrolment into systemic adjuvant therapy trials is permitted during the study, subject to appropriate ethical approval. To ensure that patient information is accurate and current, we request that the participating investigators and institutions enrolling patients in any such studies, agree to collaborate with the MelMarT-II Trial Coordination Centre to provide treatment details (placebo, investigational medicinal product, or other). If a patient is enrolled in a blinded study and an unblinding is required we request that the unblinding information be provided to the MelMarT-II Trial Coordinating Centre as soon as possible. Any treatment received by a MelMarT-II patient during the study must be recorded in the relevant eCRFs and documented in the source documents.

8. Study Assessments

(See Appendix I for the Table of Assessments and Follow Up Visits)

8.1 Screening Assessments

Before patients are randomised on to the study the following procedures must be performed and information obtained to ensure that the patient is eligible for participation:

1. Patient must provide written informed consent (in clinic or remotely as per recruiting institution's own policy)
2. Review eligibility criteria to ensure all conditions are met
3. Confirmation of diagnosis with histopathological evidence of primary cutaneous melanoma and margins of excision
4. Confirmation of anatomical location of the melanoma
5. Imaging as per institution's standard of care. If they are done, they will be documented in the eCRFs. No pre-operative imaging is necessary for enrolment onto this trial, except for pre-operative **mapping lymphoscintigraphy** as part of a staging SLNB
6. Full medical history
7. ECOG performance score (must be between 0 and 1)
8. Physical exam (including height (in metres) and weight (in kilograms)) and confirmation clinically that there is no evidence of AJCC Stage III or Stage IV disease (regional or distant metastases)
9. Review & listing of all existing medical conditions and document use of concomitant medications
10. Review of systemic therapies previously received by the patient and those currently being administered to the patient
11. Blood tests as per recruiting institution's standard of care
12. Review patients' participation in any other clinical trials
13. Confirmation that no more than 120 days have elapsed since the date of original diagnosis, according to the histopathology report.

Copies of the primary melanoma histopathology report(s) should be uploaded to the eCRF as source documentation. All reports must be issued and signed by a pathologist who is a member of the specialist multidisciplinary team at the recruiting institution. If necessary, melanomas diagnosed at a peripheral unit must be reviewed by the recruiting team prior to enrolment on the study.

Once the informed consent procedures have been followed, there has been confirmation of the primary cutaneous melanoma pathology, the patient's medical history and the eligibility criteria have been checked, the patient is ready to be randomised on to the study. The consent process can take place at any point within 120 days of the histological diagnosis of the primary. Randomisation must not take place until the consent process has been completed.

Instructions on how to randomise a patient using the randomisation system (MASC Trials) can be found in the Operations Manual.

The surgical intervention must occur within 28 days (inclusive) of randomisation and within 120 days (inclusive) of the histological diagnosis of the primary. The site investigating team is strongly advised to ensure that the randomisation takes place well within the 28 days before the planned surgical intervention to allow for unforeseen cancellation and rescheduling of the procedure at short notice (for example, if the patient returns a positive covid-19 screening swab at 72 hours prior to surgery). Surgical intervention is not allowed after 120 days from the date histological diagnosis of the primary without exceptional approval from the Trial Coordinating Centre, regardless of the date of randomisation. Once the patient has been randomised, the arm to which the patient has been allocated will be immediately confirmed.

8.2 Baseline Assessments (can occur on the day of the wide local excision)

In some circumstances the screening and the commencement of the baseline assessments (including randomisation) may fall on the same day for the patient. If this is the case, it is unnecessary to repeat any assessments. The patient must complete the baseline patient reported outcome questionnaires prior to the surgical intervention taking place.

The following assessments need to be performed as part of the initial baseline assessment:

1. Physical examination (including height (in metres) and weight (in kilograms))
2. Review of pre-operative **mapping lymphoscintigraphy** to ensure a staging -SLNB can be performed (see section 6.3)
3. Perform SLNB if clinically indicated. (see section 6.3)
4. ECOG performance score (must be between 0 and 1) is to be assessed
5. For participating sites: The patient will need to complete the following questionnaires including:
    - FACT-M QoL questionnaire
    - Pain Detect Neuropathic Pain questionnaire
    - EQ-5D-5L Utility-based QoL questionnaire
    - Baseline Employment Questionnaire
6. For participating sites: Blood sample (EDTA and whole blood) might be drawn and banked for future biomarker analysis (at the discretion of Institution's own policy]).

The Baseline Assessment will be considered to be complete when the above items have been performed and documented on the eCRFs. In the case of the patient being diagnosed with a positive sentinel node biopsy for metastatic melanoma, details of a subsequent completion lymph node dissection will be recorded and any operation and pathology reports will be uploaded into the eCRF.

Whilst a completion lymph node dissection (CLND), if performed, will certainly be at a later date and during a separate admission, the procedure will be considered part of the baseline assessment for the purposes of the trial. Accordingly, a CLND must be performed before the first follow up trial visit which is scheduled at 3 months.

In the case of the patient being diagnosed with a positive SLNB but a CLND is declined or is not standard practice, the baseline assessment will be considered to have been completed on the provision that items 1-6 have been completed.

8.3 Follow Up Visit Assessments: Maximum of 10 Years in Duration

Patient follow up should be in line with the institution's policy, preferably face to face however telehealth consultations are permitted in the trial. The term telehealth refers to the entire spectrum of activities used to deliver care at a distance without direct physical contact with the patient. Telehealth consultations can be conducted via various methods which include and are not limited to telephone, video, patient portal messages, e-consults, remote monitoring and the use of electronically available patient reported outcome measures.[20]

The following frequency for follow up visit assessments is recommended;

8.3.1 Years 1 to 2 of follow-up

During the first 2 years patients should attend follow up at 3, 6, 12, 18 and 24 months (+/- 2 weeks) after surgery preferably in clinic however telehealth consultations are permitted. If visits cannot be conducted within +/- 2 weeks, participants should receive questionnaires electronically or via post to ensure QoL questionnaires are completed within the visit window. Follow up includes the following assessments:

1. For participating sites: Health economic questionnaires are to be completed as follows: The Follow Up Employment Questionnaire is to be completed directly by the patient, preferably in clinic (paper-and-pen) however it is acceptable to be completed electronically (as per MelMarT-II trial Operations Manual) or at the patient's home and returned either via post or at the next available clinic visit. The questionnaire should be completed at months 3 and 6, and at any time a melanoma recurrence is diagnosed. The follow up Cost Questionnaire is to be completed by the study team at months 3, 6, 12, 24 months and at any time a melanoma recurrence is diagnosed.
2. For participating sites: QoL questionnaires are to be completed at months 3, 6, 12, 24 months and at any time a melanoma recurrence is diagnosed preferably in clinic (paper-and-pen), however it is acceptable to be completed electronically (as per MelMarT-II operations manual) Electronic completion is suitable for telehealth consultations and also for following up for patients who fail to complete by paper-and-pen in clinic. It is also acceptable for patients to complete hard-copy QoL questionnaires at their home and return either via post or at the next available clinic visit.

8.3.2 Years 3 to 5 of follow-up

Annual follow up study visits should be performed (+/- 4 weeks) preferably in clinic however telehealth consultations are permitted.

8.3.3 Years 6 to10 of follow-up

Annual follow up study visits are recommended to be performed (+/- 4 weeks). These visits are optional and are based on local standard practice or clinician decision. The annual follow up visits in years 6-10 can be performed via the patient's regular scheduled study visit or via telehealth consultations with the patient or their treating clinician. If the patient cannot be contacted, survival data will be collected as outlined in section 8.6, Withdrawal and Lost to follow up.

The following assessments need to be performed at each follow up visit (see Appendix I):

1. Physical examination at least annually (including weight in kilograms).
2. Disease status will be reviewed including any local, in-transit, regional and distant recurrences.
3. ECOG performance score is to be assessed.
4. Imaging as required to investigate suspected disease recurrence/progression or as per institution's standard of care. If they are done, they will be documented in the source documents and relevant reports uploaded in the eCRFs. Patients who have a positive SLNB and elect not to have a completion lymph node dissection but serial ultrasound scanning instead should have, as a minimum, a twice-yearly scan of the affected nodal field for the first five years.
5. Collection of **SrAEs** up until the 12-month visit (see section 11).
6. Collect **ALL** Serious Adverse Events (SAE) up until the 12-month visit (see section 11).
7. Changes to any systemic therapies being administered to the patient.
8. Review of participation in other clinical trials.
9. For participating sites: Health system resource use and questionnaire at any time melanoma recurrence is diagnosed and at 3-, 6-, 12-, and 24-months post randomisation. The questionnaires should be completed preferably in clinic (paper-and-pen) however it is acceptable to be completed electronically (as per MelMarT-II operations manual) or at the patient's home and returned either via post or at the next available clinic visit.
10. For participating sites: The patient will need to complete the following questionnaires at any time a melanoma recurrence is diagnosed and at 3-, 6-, 12-, and 24-months post randomisation:
    - FACT-M QoL questionnaire
    - Pain Detect Neuropathic Pain questionnaire
    - EQ-5D-5L Utility-based QoL questionnaire

    The questionnaires should be completed preferably in clinic (paper-and-pen); however, it is acceptable to be completed electronically (as per MelMarT-II operations manual). Electronic completion is suitable for telehealth consultations and also for following up for patients who fail to complete by paper-and-pen in clinic. It is also acceptable for patients to complete hard-copy QoL questionnaires at their home and return either via post or at the next available clinic visit.
11. In case of patient's death, causality (melanoma related or not) will be recorded.

8.4 Melanoma Recurrence / Progression or New Primary Melanoma: Diagnosis & Classification

Recurrence is defined as the development of local, in transit, regional, or distant disease following randomisation and WLE surgery. Ideally, recurrences should be confirmed through histological or cytological evidence. However, in the absence of such confirmation, radiological findings that are clinically unequivocal—particularly when they lead to a decision to initiate melanoma-directed therapy—are also considered acceptable indicators of recurrence. Only the date on which a recurrence was formally confirmed will be recorded as the

recurrence date. Each recurrence will be sub-classified according to size and anatomical location. An exception applies to multiple episodes of in transit metastases: these do not require individual reporting if they occur within the same anatomical region.

Clarification on Recurrence Definition

- **Imaging-Detected Metastatic Disease Post-Randomisation** A patient who is enrolled, randomised, and treated according to protocol may undergo imaging—typically prompted by a decision to initiate adjuvant therapy (often due to a positive sentinel node). If metastatic disease is subsequently identified, this constitutes a recurrence. The recurrence date should be recorded as the earliest of the imaging, cytology, or histology confirmation. Crucially, the patient must have had no known evidence of recurrence at the time of randomisation.
- **Positive Sentinel Node Without Further Disease** A patient with a positive sentinel node, whether managed with or without adjuvant therapy (including radiotherapy), is **not** considered to have a recurrence. Likewise, patients who undergo completion lymphadenectomy following sentinel node biopsy and are found to have additional lymph node involvement are **not** classified as having a recurrence.
- **New Primary Melanoma** The emergence of a new primary melanoma—distinct from the original MelMart lesion—is **not** regarded as a recurrence, even if the patient has positive sentinel node(s).

8.4.1 Recurrence Classification by Location

The date of recurrence is defined as the date at which a diagnosis is confirmed (and documented in the eCRF) by the methods described below:

1. *Local, In-transit or satellite recurrence:* Date of positive excisional, incisional or fine needle aspiration biopsy. In the case of multiple lesions, the distance from the wide excision scar to the nearest, clinically apparent lesion will be noted in the eCRF.
2. *Lymph node recurrence:* Date of positive excisional, incisional or fine needle aspiration biopsy or, in the case of inaccessible/inoperable nodes, the diagnostic appearance of metastatic lymphadenopathy on CT, PET–CT or MRI scan.
3. *Visceral recurrence or effusions:* Date of positive cytology or biopsy, if feasible; or the appearance of a single new lesion; or the appearance of multiple lesions on CT, MRI or PET–CT scan which show increases in size or numbers on serial observations.
4. *Central nervous system recurrence:* Date of a positive CT or MRI of the brain; or spinal fluid cytology
5. *Distant subcutaneous recurrence:* Date of positive excisional, incisional or fine needle aspiration biopsy

8.4.1.1 Assessments required when a participant experiences a Melanoma Recurrence

The following assessments need to be performed if the patient experiences a recurrence. They are identical to the follow up visit procedure described above:

1. Physical examination at least annually (including weight in kilograms).
2. Disease status will be reviewed including any local, in-transit, regional and distant recurrences.
3. ECOG performance score is to be assessed.
4. Imaging as required to investigate suspected disease recurrence/progression or as per institution's standard of care. If they are done, they will be documented in the source documents and relevant reports will be uploaded in the eCRFs. Patients who have a positive -SLNB and elect not to have a completion lymph node dissection but serial ultrasound scanning instead should have, as a minimum, a twice-yearly scan of the affected nodal field for the first five years.
5. For participating sites: Health system resource use and questionnaire.
6. For participating sites: QoL questionnaires.
7. Collection of **SrAEs** up until the 12-month visit (see section 11).
8. Collect **ALL** SAEs (see section 11).
9. Changes to any systemic therapies being administered to the patient.
10. Review of participation in other clinical trials.

8.4.2 New Primary Melanoma

If a patient is diagnosed with a new primary melanoma, details regarding the new primary (including size and location) and how it is treated will be recorded in the 'New Primary Melanoma NP'-eCRF.

8.5 Study Completion

The study is designed as an events-driven analysis. Accordingly, patients will be enrolled and followed up until the requisite number of events occurs to confirm or reject the hypotheses regarding the primary endpoints. It is anticipated that the median follow-up period will be five years. If a patient has completed the schedule of follow up visits for 10 years, no further follow up is necessary. A final study visit will be performed at Month 120 (Year 10) and the Study Discontinuation Form should be completed at that visit.

If a patient dies, please ensure that the Study Discontinuation Form is completed and a copy of the death certificate or discharge summary is provided, if available. Reason for death, melanoma related or not, will be considered in the final analysis.

8.6 Withdrawal and Lost to Follow Up

Participation in this study is voluntary; patients are able to withdraw at any time.

1. Withdrawal/change in participant level: If a patient's level of participation changes throughout the trial, a study discontinuation form must be completed. This form informs MASC Trials of the change in participation level and assists with data monitoring. Please refer to the operations manual for details instructions.

2. Lost to follow-up All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow up with persons authorised by the patient including family members or other medical professionals. Lost to follow up is defined by the inability to contact the patient after a minimum of three documented phone calls, faxes, or emails as well as lack of response by the patient. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use permissible local methods to obtain the date and cause of death. If after all attempts, the patient remains lost to follow up, then the last known alive date as determined by the investigator should be reported and documented in the patient's medical records.

The National Death Index at the Australian Institute of Health and Welfare will be used to collect survival information on patients who have been lost to follow up. Similar systems will be employed in other countries where available.

8.7 Quality of Life Assessments

QoL is an important secondary endpoint for this trial and will be assessed at any time a melanoma recurrence is diagnosed, at Months 3, 6, 12 and 24 or until the participant withdraws consent or death occurs.

The questionnaires used in this study are:

- ***Functional Assessment of Cancer Therapy – Melanoma (FACT-M (version 4)).*** It consists of two subsections: The FACT-G subsection is a 27-item compilation of general questions divided into four primary QoL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. It is considered appropriate for use with patients with any form of cancer. The Melanoma Surgery Subscale evaluates melanoma-specific symptoms such as surgical morbidity and side effects. A trial outcome index allows direct comparison across treatment arms.
- ***The EuroQoL EQ-5D-5L*** a preference-based measure of health status – commonly used in trial-based economic evaluation and is well-matched for cancer-specific instruments. This tool contains 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
- ***Pain Detect questionnaire*** – to assess neuropathic pain.

The FACT-M will be scored centrally according to the FACT-M scoring manual (www.facit.org). The EQ-5D-5L will be scored centrally according to the EuroQoL EQ-5D-5L user guide v 1.0 April 2011 (Rabin, Oemar et al. 2011).

Complete instructions on how the site is to administer, and how the patient is requested to complete the questionnaires is explained in the Operations Manual and eCRF guidelines.

8.8 Health Economics and System Resource Use

Resource use is an important secondary endpoint for this trial and will be assessed at any time a melanoma recurrence is diagnosed, regularly throughout the study for the first year and at Month 24 or until the participant withdraws consent or death occurs. All hospitalisations and other interventions will be captured in order to measure resource use.

- The ***EQ-5D-5L*** will be completed alongside the QoL Questionnaires (by all sites), collected at any time a melanoma recurrence is diagnosed, at baseline, 3, 6, 12, and 24 months, and will be used to estimate quality adjusted life years (QALYs) for the economic evaluation.

- The ***Charity and Community-Based Health and Social Services*** is a survey which will only be administered to the UK sites **only** at any time a melanoma recurrence is diagnosed, at baseline, 3, 6, 12, and 24 months as part of a country specific Health economic analysis.

- The Baseline Employment survey will be completed alongside the QoL Questionnaires (by UK, Australia, New Zealand, Ireland, Netherlands and Slovenia), collected at baseline, and will be used for the economic evaluation.

- The Follow-up Employment survey will be completed alongside the QoL Questionnaires (by UK, Australia, New Zealand, Ireland, Netherlands and Slovenia), collected at any time a melanoma recurrence is diagnosed, at baseline, 3, 6, 12, and 24 months, and will be used to estimate quality adjusted life years (QALYs) for the economic evaluation.

Complete instructions on how to administer the questionnaires is contained in the Operations Manual and eCRF guidelines.

9. Pathology

A. All eligible patients will require histological confirmation of melanoma using Haematoxylin and Eosin (H&E) and usually the addition of immunostains (at least one of S100, Melan-A, MART-1 or HMB45). Copies of the histopathological report will be collected at the Baseline assessment as source documentation and uploaded into the eCRF, confirming the patient's eligibility for the trial.

B. One of the designated pathologists of each cooperating institution will confirm that a participant's tumour is a primary melanoma and measure the thickness to tenths of a millimetre using an ocular micrometer and the technique of Breslow. The pathologist will produce a synoptic report of the melanoma with the following information:

1. Breslow thickness
2. Melanoma subtype (superficial spreading, nodular etc.)
3. The presence and width (measured in millimetres) of ulceration
4. The presence of lymphatico-vascular invasion
5. The presence of neurotropism spread
6. The presence of microsatellitosis (AJCC 8th edition definition)
7. Mitotic rate (number per mm^2)
8. The presence and grade/classification of Tumour Infiltrating Lymphocytes as per classification of Azimi et al JCO 2012[21]
9. Closest excision margins to both invasive and in situ, deep and peripheral, measured in millimetres

C. Wide excision specimens will be examined as per procedures followed by the designated pathologists of each cooperating institution. Please refer to appendix VI for further information on shave biopsies. Specimens will be examined for any residual tumour and the presence of satellites. Measurements from the tumour edge to the surgical margins of the specimen will be recorded in the source documents and on the eCRF.

D. Sentinel node biopsy specimens will be examined according to the recruiting institution's usual practice. Details of nodal metastases will be recorded in the source documents and on the eCRF and will include the following information:

1. Maximum diameter of largest deposit
2. Microanatomical location of deposit according to Dewar criteria[22]
3. Number of nodes involved
4. Site of nodes
5. Presence or absence of extracapsular spread (extension)
6. Mutation status (if available)

E. Completion lymph node dissection specimens will be examined according to the recruiting institution's usual practice. Details of nodal metastases will be recorded in the CRF and will include the following information:

1. Maximum diameter of largest deposit
2. Number of nodes involved
3. Site of nodes
4. Presence or absence of extracapsular spread (extension)
5. Mutation status (if available)

10. Data Collection

1. In the first phase, 03.12 MelMarT, trial data will be recorded in full on the CRFs provided to each site in hard copy.

2. The second phase of the trial, 02.18 MelMarT-II will utilise electronic data capture for data collection. Sites will be required to complete all appropriate fields as specified on the eCRFs. Periodically, the investigator will be asked to confirm the accuracy of completed eCRFs by signing forms as indicated. Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a participant's medical records, hospital charts, operation reports, the investigator's participant study files, as well as the results of diagnostic tests such as X-rays, PET/CT scans, MRI imaging and laboratory results.

3. Electronic administration of QoL and health system resource use questionnaires may be implemented as part of the electronic data capture system. For any QoL (FACT-M, Pain Detect) and health system resource use (EQ-5D-5L and Employment Questionnaires), data entered onto the paper CRF by the patient, this will be considered as source.

4. The Trial Coordinating Centre may request copies of some source documents in support of the CRF as a quality assurance exercise. All study-related documentation is required to be maintained by the site for 15 years following completion of the study.

11. Adverse Event Reporting

11.1 Adverse Events (AEs)

Pre-existing medical conditions that may affect the trial intervention should be recorded at the Baseline Assessment CRF. Adverse Events (AEs) **related** to the surgical intervention will be recorded from randomisation until 12 months post-surgical intervention or until the patient withdraws or dies. The site Principal Investigator or their delegate is responsible for the assessment of causality of AEs. AEs will be classified for type and severity according to the CTCAE criteria, v 5.0 (appendix III).

11.1.1 Surgery-related Adverse Events -SrAEs (Surgical complications)

The wide local excision (WLE) and staging SLNB procedures are referred to as the surgical intervention throughout the protocol. Events related to the surgical intervention (WLE and staging SLNB) are referred to as SrAEs (e.g., surgery-related AEs) throughout the protocol.

The following AEs will be considered related to the intervention and recorded from the time of trial treatment up to 12 months following the study intervention (inclusive):

- wound separation
- seroma/haematoma
- haemorrhage
- infection
- skin graft failure
- necrosis of flap used for reconstruction
- deep venous thrombosis
- urinary tract infection
- pneumonia
- cardiac complications

11.2 Serious Adverse Events (SAEs)

All Serious Adverse events (SAEs), will be recorded from randomisation until 12 months post the surgical intervention or until the patient withdraws or dies. The site Principal Investigator or their delegate is responsible for the assessment of causality of SAEs.

Please note:

- Deaths resulting from disease progression or immunotherapy should **not** be reported as an SAE.
- Deaths related to WLE/SLNB **should** be reported as an SAE

11.2.1 SAE Definitions

A SAE is any **untoward** (unexpected) medical occurrence which:

- is fatal;
- is life-threatening;
- requires unanticipated in-patient hospitalisation or prolongation of hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly/birth defect;
- is a grade 4 (NCI CTCAE v5.0);

The term "life threatening" in the definition of SAE refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which, hypothetically, might have caused death if it were more severe.

11.2.2 SAE Reporting

If any trial patient experiences an SAE all relevant and subsequent information relating to each reported SAE must be submitted on a paper CRF, along with any available source documentation, to the Trial Coordinating Centre. An initial report must be completed within 24 hours of the site becoming aware of the event. Subsequent information should be provided as soon as it is available. All SAE CRFs require the signature of the site Principal Investigator.

11.2.3 SAE Reporting Timelines

Table 4– Serious adverse event reporting timeline

Type	Timeframe
Initial SAE Report	The site must submit the original paper SAE Form to the Trial Coordinating Centre within 24 hours of becoming aware of a trial participant experiencing an SAE. Please provide copies of relevant source documents if available. Should the site have any questions please immediately contact the Trial Coordinating Centre for assistance.
Updated Report	The site should provide any updates to the Trial Coordinating Centre as soon as possible. This data may be entered into the eCRF system. Please provide copies of all relevant source documents if available.
Completed Report	Once the event has resolved or if the participant has died, the site should update the eCRFs as soon as possible. This must include the upload of relevant source documents.

All SAEs will be reviewed by the Study Chair, and also summarised for review by the Data Safety Management Board (DSMB) and the TMC.
SAEs must be reported as per the local Ethics Committee (EC) / HREC / Research Governance Officer (RGO), in accordance with international and local laws and regulations.
Should any trial site have any questions please immediately contact the Trial Coordinating Centre for assistance.

11.3 Suspected Unexpected Serious Adverse Events

A Suspected Unexpected Adverse Reactions (SUSAR) is defined as an adverse reaction that is both serious and unexpected. All SUSARs must be reported to MASC Trials as soon as practical and local HREC.

11.4 Significant Safety Issues

A Significant Safety Issue (SSI) is defined as: "A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial." (NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods EH59, November 2016). All SSI must be reported to MASC Trials as soon as practical and local HREC. As the Sponsor MASC Trials is reposnible for reporting SSIs to the overarching HREC.

11.5 Urgent Safety Measures

An Urgent Safety Measure (USM) is defined as: "A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety." (NHMRC Guidance: Safety monitoring and reporting in clinical trials involving therapeutic goods [EH59], November 2016). All SSI must be reported to MASC Trials as soon as practical and local HREC.

12. Statistical Considerations

12.1 Sample Size

Power Analysis and Sample Size: The sample size is based upon a single primary outcome DFS which typically includes the events of recurrence (local, regional, or distant) and death. We assumed a HR of no more than 1.25 will be deemed to be the limit of non-inferiority margin, and a 3-year DFS rate of 85% in the 2cm excision margin arm. These assumptions translate into a 3-year DFS rate of 81.6% in the 1cm excision margin arm and therefore a maximum absolute difference in DFS rates of 3.4%. A non-inferiority logrank test with an overall sample size of 2,998 patients (1,499 in each arm) will achieve 90% power at a 1-sided 0.05 significance level to detect a non-inferiority HR of 1.25. The sample size conservatively assumes 690 events will occur and allows for 10 percent of patients being lost to follow up. The study lasts for a period of 10 years of which participant accrual (entry) occurs in the first 5 years. The above sample size calculation was performed using the gsDesign (3) package in R, and results were confirmed using simulation with 10,000 iterations using the npsurvSS package (4). A smaller sample size (total 2,012) will suffice for the patient-reported outcomes (QoL and pain): this sample will achieve 90% power to detect an effect size of 0.20 (considered a small but clinically relevant difference) at a significance level of 0.0025 (allowing for testing of 20 QoL/pain hypotheses, given 5 key QoL/pain variables at each of three assessment times and over all times), and allowing for 20% missing data at 12 months.

Statistical Analysis: The primary endpoint of DFS will be analysed using Cox's Proportional Hazards model and graphically described using the Kaplan-Meier method. The endpoint will be defined as the time from surgery until disease progression (first clinically, histologically or radiologically confirmed recurrence of melanoma at any body site) or death from any cause, or a censoring event (end of study, withdrawal). The 95% CIs around the HR will be examined to assess non-inferiority. Non-inferiority of 1cm excision margin will be claimed if the upper limit of the 95% CI is lower 1.25. An intention-to-treat approach will be adopted but given the non-inferiority nature of the study this will be supplemented by a per-protocol analysis. This test for non-inferiority will only be performed for the primary efficacy outcome; all other secondary outcomes will be tested for superiority of 1cm versus 2cm excision margin. The analysis of the primary endpoint will be conducted when the last patient has completed a 5-year follow-up, using all available follow-up data for each patient. The secondary survival endpoints of DDFS, LRFS, and OS will also be analysed using a Cox's Proportional Hazards model and graphically described using the Kaplan-Meier method. A sub-group analysis will be performed using pre-specified factors: 1) AJCC Stage (IIA-IIC), 2) Age (<45, 45-65, >65), Gender and 3) Country. Generalisability will be assessed, as far as possible, by comparing the characteristics of those participants participating in the study with those who were eligible but declined. A statistical analysis plan describing the data synthesis, analysis principles and statistical procedures for the final analysis of the trial data has been developed.

12.2 Feasibility and Early Closure Criteria

This study will closely monitor accrual rates with respect to the feasibility of study completion. Overall and institution specific accrual rates will be assessed as part of routine reporting (at least annually) to the TMC.

The trial is an international collaboration involving patients recruited by experts in melanoma treatment from international sites.

Lost to follow up is estimated as 10% over the course of the trial (20% in QoL sub study). Data on patients lost to follow up will be sought via the National Death Index in Australia, and ONS 'flagging' and HES in the UK and similar systems in countries where they are available.

Consideration will be given to stopping the trial early if accrual is less than expected. The decision to close the study early will be determined by the Study Chair in consultation with the DSMB and TMC. All investigators and sites will be fully informed of any decision to close the trial early and a full and complete explanation will be provided at that time.

Stopping guidelines will be discussed with the DSMB and TMC and incorporated into their charters. The non-inferiority and multi-stage design means that stopping rules for efficacy and futility are implicit. Adverse outcomes assessing any evidence of lower DFS in the in the narrow margin group will be considered by the DSMB at annual meetings. Point estimates and 95% CIs for the incidence of serious adverse events, LR and MSS will be presented.

12.3 Planned Statistical Analyses

12.3.1 Statistical Analyses of Primary endpoint

The primary analysis will be based upon Cox's Proportional Hazards model, stratified by recruiting country and include pre-specified prognostic variables within the PH model. Overall non-inferiority will be declared if non-inferiority can be concluded for the primary endpoint. This analysis will be carried out after the final database lock. The study team, with the exception of the trial statistician will be kept blind to

these analyses, which will be reviewed only by the DSMB. A report will be prepared by the DSMB, shared with the Study Chair and members of the study team including TMC members for consideration.

12.3.2 Statistical Analyses of Secondary Endpoints

12.3.2.1 Survival endpoints

Cox Proportional Hazards models will be used for all secondary time to event endpoints with results presented as HRs with 95% CIs. The stratification and additional pre-specified prognostic factors will be controlled for in multivariable models to give adjusted HRs. The Proportional Hazards assumption will be assessed for appropriateness and accelerated failure time models will be used if the assumption is deemed inappropriate. A sensitivity analysis based on restricted mean survival time (RMST) will also be performed to quatify the absolute treatment effect for time to event endpoints at 3 and 5 year cut-off time t. All secondary time to event outcomes will be described using the Kaplan-Meier method stratified by treatment arm.

12.3.2.2 QoL

The QoL and neuropathic pain data will be analysed at the trial completion and will utilise 3, 6, 12 and 24-month date as per the Pro-specific Statistical analysis plan (MelMarT-II PRO-specificSAP_Final_v1.2_25Sep25). QoL data will be analysed as a continuous outcome using mixed linear models, with surgical group and time included as fixed effects (time as a categorical variable), a random intercept included to account for repeated measures, baseline values and pre-specified prognostic and stratification variables included as covariates, and site considered as a random factor. These models will yield estimates of the average difference in QoL between surgical groups over all time-points, as well as the mean difference at each assessment time point, and associated 95% CI. The presence of neuropathic pain at 12 months will be analysed using logistic regression, again with pre-specified prognostic and stratification variables included in the model. The utility scores from the EQ-5D-5L are required for the calculation of QALYs for the cost-utility analysis, and will be analysed as part of the economic evaluation.

The sample size calculation was based on the primary outcome of DFS being analysed within the non-inferiority framework, with a non-inferiority margin defined as an HR of 1.25. To demonstrate non-inferiority at a one-sided 5% significance level and 90% power and assuming 10% attrition, a total of 2,998 patients (1,499 per arm) will be recruited into the study. Further details of a priori sample size calculations are provided in Section 6 of the Main SAP.
There are 20 QoL hypotheses in total, given 4 key QoL variables at each of four assessment times and overall (over all times). With a sample of 2,998 observations and using a Bonferroni corrected alpha=0.0025 (two-tailed), there is >90% power to detect a standardised effect size of 0.20 (considered a small but clinically meaningful effect size), allowing for 10% attrition per year over the 24 months follow up.
Power sensitivity calculations for the neuropathic pain outcome were conducted separately from the QoL analyses, as pain is assessed using a distinct ordinal scale and modelled using a proportional odds logistic regression model. Assuming a 3-category outcome with a skewed distribution (90% / 8% / 2% (7) and accounting for 10% attrition over the first 12 months (the time point of primary interest for neuropathic pain), there is 95% power to detect a between-group OR of 1.5 (moderate effect size), but only 64% power to detect an OR of 1.3 (small effect size), at a two-sided alpha of 0.05.

Statistical significance of QoL outcomes analyses will be assessed using a Bonferroni-corrected alpha of 0.0025, unless otherwise specified. 95% confidence intervals (CI) will be presented for ease of interpretation, although these do not reflect the more conservative Bonferroni-corrected threshold of statistical significance, which would correspond to 99.75% CI. Statistical analyses of neuropathic pain will be assessed using an alpha of 0.05 and reported with 95% CI.

The analyses of QoL and neuropathic pain endpoints will be based on all registered patients (the full analysis set or FAS) and accordingly will follow the intention-to-treat (ITT) principle.
Analyses of QoL and neuropathic pain at recurrence will be limited to patients with lesion recurrence reported at each follow-up time point.

12.3.2.3 Cost Effectiveness

Resource utilisation, cost-utility and federal health budget impact of using 1cm versus 2cm margins will be determined from a societal and health care system perspective. Improvements in morbidity are anticipated to result in an improvement in patient QoL, hence to result in more QALYs for patients who receive 1cm WLE margins. We will conduct a cost-utility study from a societal perspective, taking into account health service resource use (inpatient and outpatient), productivity loss, patient's time associated with accessing care and any need for domiciliary care. Resource use for both trial arm alternatives will be estimated based on the equipment used, medical supplies, practitioner time, in hospital stay, pharmaceuticals and any outpatient care as required.

Associated hospital and other health care use will be captured on the eCRFs, and Australian patients will be consented for access to their Medicare Benefits Schedule (MBS) and Pharmaceutical Benefits Scheme (PBS) data. The latter data will be used as a proxy to extrapolate to international healthcare systems. Patient costs will include travel and clinic time and will be collected using a brief questionnaire administered at each visit. All health system resource use will be valued according to the relevant Australian-Refined Diagnosis Related Groups (ARDRGs), MBS item numbers and PBS for prescribed medicines. Lost work time (productivity losses) in the first 4 months will be collected by patients using a validated questionnaire at the first visit post-surgery. Analysis of uncertainty will comprise one-way sensitivity analyses conducted around key variables, and a probabilistic sensitivity analysis to estimate the joint uncertainty in all parameters. A cost effectiveness acceptability curve (CEAC) will be plotted, providing information about the probability that the surgical intervention is cost-effective, given the suggested cost effectiveness threshold for a QALY gained in each jurisdiction. Costs will be assessed using local country prices and expressed as a common currency for the final analysis (using purchasing power parities, PPP). Mean estimates of costs will be used and CI will be generated by boot-strapping the data.

12.3.3 Planned Subgroup Analyses

As previously described, the primary and secondary endpoints will be evaluated in the following sub-groups:

- AJCC 8th edition staging (pT2b-3a; pT3b-4a; pT4b)
- Age (<45; 45-65; >65)
- Sex (Male; Female)
- Country

Additionally, these variables will be included in a Cox Proportional Hazards model together with the treatment arm variable in order to assess adjusted HRs and 95% CIIs. Other outcomes assessed for the main study will also be analysed for the subgroups with the acknowledgement that these analyses would be exploratory and hypothesis-generating.

12.3.4 Interim Analyses

An independent DSMB will be established to monitor the occurrence of serious clinical and biological events. Periodic reports of all information that is available on all major events and toxicities will be provided to the Study Chair and TMC members at least annually. The DSMB will monitor the trial for safety outcomes and will particularly review the following:

- Unacceptable surgical mortality / morbidity (any Grade 4 or higher)
- Adverse outcomes assessing any evidence of higher recurrence and lower DFS in the narrow margin group
- Accrual at a rate less than the expected number of patients
- The development and availability of a clearly more effective therapy

Interim monitoring for harm will be conducted at a 33% information fraction (i.e., 230 primary endpoint events). At this time the 1 cm margin arm will be compared with the 2 cm margin arm using a HR from a Cox Proportional Hazards model. If the lower end of a one-sided 95% CI exceeds a HR of 1.25 then a signal for harm will be detected. Should the 1cm margin arm have a worse outcome rate according to this test then consideration will be given by the DSMB to recommend termination of the trial if the committee believes the interim results are sufficiently compelling to change practice. An interim analysis at 50% was considered but deemed unnecessary since simulations indicated that the required number of events would occur close to the time that randomisation (and surgery) of the final participant is due to be completed.

13. Responsibilities of the Principal Investigator at each site

The study will be performed in accordance with the CPMP/ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and the National Statement on Ethical Conduct in Human Research, NHMRC 2007 (Updated 2018) in Australia and applicable guidelines in participating sites overseas.

The study protocol, including the final version of the participant information and informed consent form to be used, must be approved by the TMC and a constituted HREC prior to enrolment of any patients into the study. The opinion of the HREC should be dated and given in writing. It is the responsibility of the Principal Investigator at each site to forward a copy of the approval from the HREC clearly identifying the protocol submitted for review and a copy of the approved participant information sheet and consent form to the Trial Coordinating Centre prior to entry of patients.

The site Principal Investigator is responsible for ensuring that written informed consent by the patient is obtained before study entry. The investigator is responsible for informing the Trial Coordinating centre and the HREC of any SAEs and/or major amendments to the protocol as per local requirements.

The site Principal Investigator is responsible for ensuring that all regulatory requirements are followed.

The site Principal Investigator is required to ensure compliance with the protocol in its entirety. It is the responsibility of the investigator to maintain adequate and accurate CRFs.

International institutions: International institutions must abide by their own laws and regulations. It is the responsibility of the site Principal Investigator to forward a copy of the necessary approvals for this study to Trial Coordinating Centre ahead of site initiation. Any correspondence relating to the approval of protocol amendments and ongoing study reports must also be provided to the Trial Coordinating Centre on request.

14. Reporting of Results

The Study Chair and TMC will be responsible for decisions regarding presentations and publications arising from this study.

Authorship credit should be based on the Vancouver statement by the International Committee of Medical Journal Editors, i.e., substantial contribution to all three of the following criteria:

- Conception and design OR analysis and interpretation
- Drafting article OR critically revising it for intellectual content
- Final approval of version to be published

Or, a fourth criterion is:

- Contributors who register 2% or more (accrual by institution) of the evaluable cases on the study will be listed as authors. The designated author is the choice of the institution's PI and in most cases would be the investigator with the highest accrual. If an institution places a large number of cases on the study, that institution will get an additional author for every 150 participants accrued, not to exceed a total of three authors (i.e., two authors for > 150 participants and three authors for > 300 participants)
- Contributors who register <2% (accrual by institution) of the evaluable cases on the study will be recognised as Contributing Authors (non-author contributors) and members of the MELMART GROUP and their names will be listed in the Medline citation.

Acknowledgement of the collaboration between MASC Trials and relevant funders are required in all publications, abstracts and presentations. Publications and abstracts must be presented to the Study Chair and TMC for review and approved prior to submission. Draft publications will be presented to the Publications/Writing Committee of each collaborating group for comment prior to submission.

In line with the ICMJE recommendations (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html) and the MASC Trials "Authorship and Publications Policy" standard operating procedure, publications must be reviewed by the TMC and MASC Trials prior to submission.

15. Quality Assurance

15.1 Data Management and Source Data Verification

Trial sites are expected to regularly enter data into the eCRFs, reflecting the patient visits. Copies of relevant documents for source verification and quality assurance will be requested including various imaging scans and reports. Many of these will be uploaded into the eCRF database by sites.

The Trial Coordinating Centre will issue data queries as required to clarify eCRF data and will report to the Study Chair regarding eCRF completion and query resolution rates as well as any issues related to protocol compliance.

15.2 Protocol Amendments

Changes and amendments to the protocol can only be made by the TMC. Approval of amendments by the HREC is required prior to their implementation. In some instances, an amendment may require a change to the participant information sheet and/or consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the eCRFs, if required, will be incorporated in the amendment.

15.3 On Site Monitoring

Site monitoring is scheduled annually for this study (also subject to funding and recruitment rate and at the discretion of the TMC).

15.4 Site Audits

This study is subject to audit by each of the groups involved and could occur at any stage of the study. Sites will be informed in advance in writing, outlining and the scope of the audit should one occur.

15.5 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the Trial Coordinating Centre and will only be available to staff directly involved with the study.

Personal data identifying trial participants will be held securely at the sites according to local institutional requirements for the purpose of follow up after the conclusion of the protocol-specified period. Sites may be asked to submit copies of source documents to the Trial Coordinating Centre e.g., pathology reports, however, all reports must be de-identified prior to sending, with only participant trial number and initials detailed.

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17. Appendices

Appendix I: Table of Assessments and Follow up Visits

Assessment	Pre-Randomisation	Baseline Assessments	3 months Post-Surgical Intervention	6 months Post-Surgical Intervention	12 months Post-Surgical Intervention	18 months Post-Surgical Intervention	24 months Post-Surgical Intervention	Year 3 to 10 During annual follow up visits (Month 36-120)	At recurrence	End of Study	Death
Confirmation of diagnosis of primary cutaneous melanoma (histopathology) and no clinical evidence of AJCC Stage III or Stage IV disease	X	-	-	-	-	-	-	-	-	-	-
Confirmation of anatomical location of the melanoma	X	-	-	-	-	-	-	-	-	-	-
History, physical exam, & ECOG assessment including disease status*	X	X	X	X	X	X	X	X	X	X	-
Prescribed imaging scans#	X#	-	X#	X#	X#	X#	X#	X#	X#	-	-
EDTA, whole blood++ ¤	-	X++ ¤	-	-	-	-	-	-	-	-	-
Review of pre-operative mapping lymphoscintigraphy to ensure a staging sentinel lymph node biopsy can be performed	-	X	-	-	-	-	-	-	-	-	-
Surgical Intervention	Patients will be randomised to undergo wide local excision with either a 1cm or 2cm margin + sentinel lymph node biopsy at the baseline visit. The surgery must be performed within 120 days following original diagnosis and within 28 days of randomisation.										
Sentinel node status needs to be confirmed∞	-	X	-	-	-	-	-	-	-	-	-
QoL questionnaires+	-	X	X	X	X	-	X	-	X	-	-
Health system resource use questionnaires**	-	X	X	X	X	-	X	-	X	-	-
SrAEs monitoring	-	X	X	X	X						
SAEs		X	X	X	X						
Record meds & treatments & other clinical trials	X	X	X	X	X	X	X	X	X	X	X
Date & cause of death, including copy of death cert., if available	-	-	-	-	-	-	-	-	-	-	X

*Disease status is assessed at every indicated visit and includes any local, in-transit, regional and distant recurrences. Any other imaging after randomisation will be as clinically indicated by local protocol or for suspicion of systemic progression. #Pre-operative mapping lymphoscintigraphy has to be performed prior to the surgical intervention. Any other imaging will be as clinically indicated by local protocol.

++EDTA and whole blood might be drawn and banked for future biomarker analysis, as part of individual Institution policy. This is not part of the study protocol

¤Further blood test as per recruiting institution's standard of care.

∞∞When the SLNB proves to be positive for metastatic melanoma, details of the subsequent completion lymph node dissection, operation and pathology reports will be uploaded in the eCRF, along with the completed case report forms. In the case of the patient being diagnosed with a positive sentinel node biopsy but a completion lymph node dissection is declined, then the baseline assessment will be considered to have been completed as long as all other items have been completed.

+ QoL questionnaires (FACT-M, EQ-5D-5L and Pain Detect (neuropathic pain)) completion will be at the discretion of the participating Institution. QoL questionnaires need to be completed at any time a melanoma recurrence is diagnosed and at baseline, 3, 6, 12, and 24 months.

** Health system resource use questionnaires completed by the patient (Baseline and Follow Up Employment Form) will be completed at baseline, 3 and 6 months, and at diagnosis of melanoma recurrence. Other health system resource use questionnaires (Follow Up Cost Questionnaire) will be completed at any time a melanoma recurrence is diagnosed and at 3, 6, 12, and 24 months.

Appendix II: ECOG Performance Status

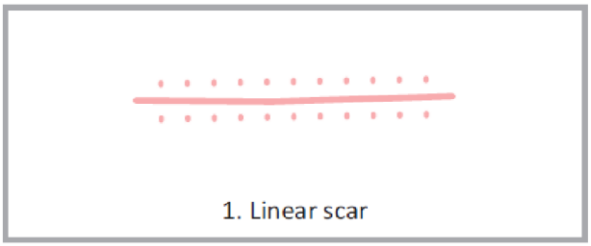
Grade	Definition
0	Able to carry out all normal activity without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to do light work.
2	Ambulatory and capable of all self-care but unable to carry out any work. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.
5	Dead

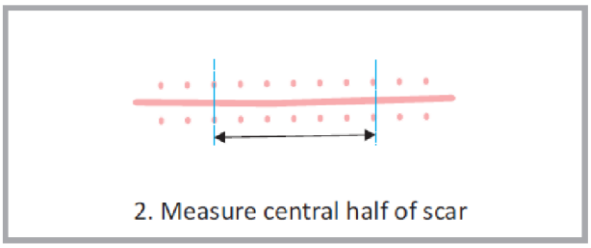
Appendix III: NCI Common Terminology Criteria for Adverse Events version 5.0

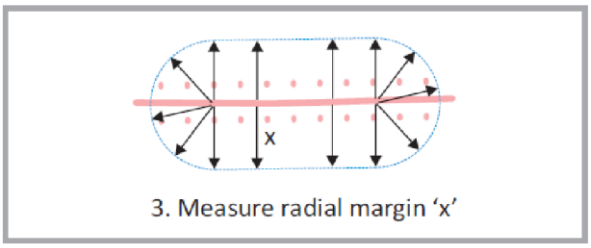
The National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0) can be found at:

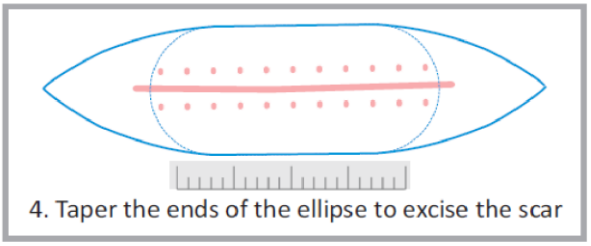
http://evs.nci.nih.gov/ftp1/CTCAE/About.html

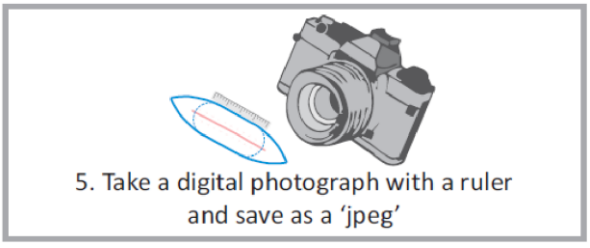
Appendix IVa: Wide Local Excision Procedure

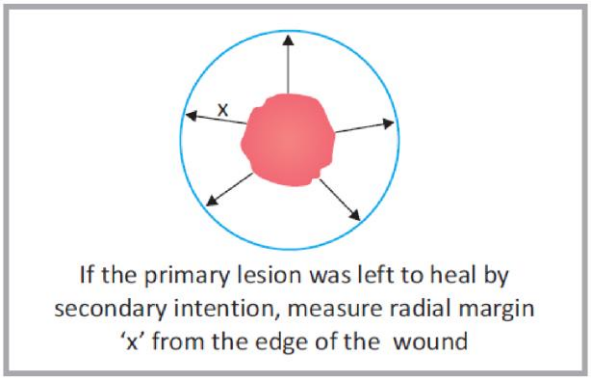




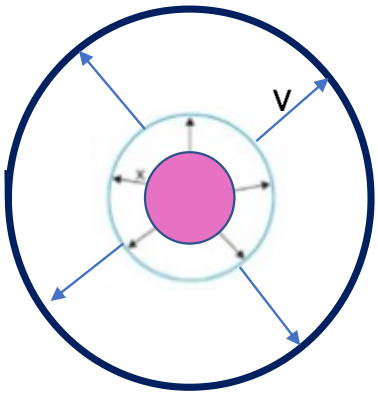




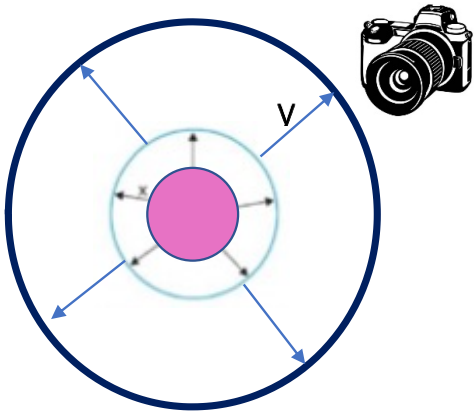




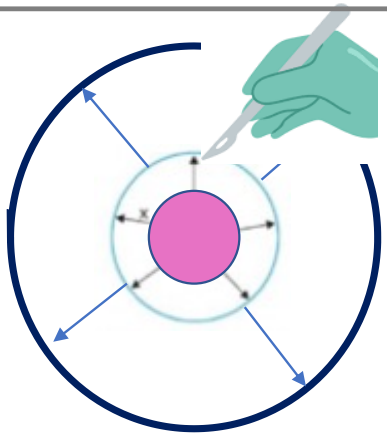
Appendix IVb: Procedure for incompletely excised peripheral margin after shave biopsy



Step 1: If the incomplete shave biopsy was left to heal by secondary intention, then mark 2mm (x) from the edge of the scar or visible tumour (if any). From this margin, mark the radial margin allocated to the patient (y).



Step 2: Photograph the markings, including the ruler and particpant's trial number and save as a 'jpeg'



Step 3: Score the entire circumference of the 2mm margin with a scalpel, deep enough to be obvious to the pathologist assessing the wide excision specimen

Appendix V: Managing Patients with Shave Biopsies

It is preferable to keep the wide excision specimen intact and mark/score the estimated edge of the melanoma with a scalpel that the pathologists can recognise. Scalpel markings will then be interpreted by the Pathologist who has knowledge of the protocol and the reasons for the markings which should be explained in the clinical notes. A sticker should be provided on the path form (ideally the sticker from the photo) to annotate that it is a MelMarT-II trial patient.