

**Melanoma Margins Trial  
 MelMarT (ANZMTG 03.12)**

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

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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.

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## 1 Abbreviations & Definitions

AE	Adverse Event
AJCC	American Joint Committee on Cancer
ANZMTG	Australia and New Zealand Melanoma Trials Group
BMI	Body Mass Index
BSA	Body Surface Area
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
DSMC	Data Safety Monitoring Committee
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylene Diamine Tetraacetic Acid (an anticoagulant used for blood sampling)
H&E	Heamatoxylin & 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
HRG	High Risk Group: Patients with cutaneous melanoma TNM stage pT3b, pT4a or pT4b (AJCC stage IIB-IIC)
HRQoL	Health-related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
IHC	Immunohistochemistry
IRG	Intermediate Risk Group: Patients with cutaneous melanoma TNM stage pT2a, pT2b or pT3a (AJCC stage IB-IIA)
IVRS	Interactive Voice Randomisation System
LN	Lymph Node
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
PH	(Cox's) Proportional Hazards (Model)
PI	Principal Investigator
PICF	Patient Information Consent Form
QALY	Quality Adjusted Life Year

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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
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMC	Trial Management Committee
TSC	Trial Steering Committee
UK	United Kingdom
US	Ultrasound
USA	United States of America

## 2 Study Summary

### Study Title

Melanoma Margins Trial (MelMarT)

### Background and Rationale

A wide, radical excision to remove the entire primary tumour, to prevent spread and local recurrence is a classic surgical teaching. In primary melanoma, a secondary wider excision around the original biopsy scar is advocated to reduce risk of local recurrence 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 (see Table 1, Section 3.1 for definitions) 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. In the UK, approximately 45% of all melanoma patients (6,400 cases per annum) with intermediate to high-risk primaries are subject to 2-3cm excision margins. However, 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.

### Study Objectives

This study will determine whether there is a difference in local recurrence rates and melanoma survival rates for patients treated with either a 1cm excision margin or 2cm margin for both intermediate & high risk melanomas. The study is designed to be able to prove or disprove that there is no difference in risk of the tumour recurring around the scar or anywhere else in the body between the two groups of patients. This study is designed to show that the risk of long-term pain associated with surgery can be halved. If the study shows no risk of the tumour recurrence 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 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.

### Study Hypothesis

There is no difference in local recurrence rates or melanoma-specific survival for patients treated with either a 1cm or 2cm excision margin for intermediate and high risk primary melanoma. A 1cm excision margin will halve the risk of long-term pain and will improve surgical complication rates. A 1cm excision margin will have an impact on improved quality of life for patients and change the use of local healthcare resources.

### 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. The patient populations for both phases are identical. All patients who participated in the pilot study will be included in the final full analysis.

### Phase I: Pilot study

The aim is to recruit 400 patients; who fit the following requirements:

- 18 years or older
- histologically confirmed, primary invasive cutaneous melanoma of Breslow thickness >1mm: AJCC Stage IB-IIIC (pT2-4/N0/M0)
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1 (See Appendix II) at randomisation
- Patients must be able to give informed consent, and comply with protocol treatment and follow up

- Randomisation and treatment must be performed within 120 days of diagnosis
- Patients must have no previous malignancy or primary except low-risk non-melanoma skin cancer, unless in remission and >5 years since diagnosis.

### **Phase II: Full Study**

The aim is to recruit a total of 9,684 patients (6,968 in the intermediate risk group and 2,896 in the high risk group) who fit the following requirements:

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

### **Study Treatments**

Once determined as being within the intermediate risk or high risk group, 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.

### **Study 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 first the study has been split into 2 phases; the first is a pilot study and the second is the full study. A limited number of sites will participate in the pilot study which will expand once the full study commences.

### **Study endpoints**

#### ***Primary Endpoints:***

#### **Co -Primary:**

1. Time to local recurrence: Time from randomisation to clinically, histologically or radiologically confirmed local recurrence of melanoma including satellite lesions and in transit metastases to regional draining lymph nodes.
2. Melanoma specific survival: Time from randomisation to death due to melanoma

#### ***Secondary Endpoints:***

1. Recurrence-free survival: time from randomisation to any clinical, histological or radiologically confirmed melanoma recurrence or death from any cause.
2. Overall Survival: time from randomisation to death from any cause.
3. QoL and neuropathic pain assessments at baseline, 3, 6, 12, 24 & 60 months and at melanoma recurrence.
4. Adverse events within 1 year.
5. Surgery related adverse events up to 3 months from randomisation.
6. Health Economics: QALY analysis.

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## Summary of Statistical Methods

The trial sample size is based upon the two primary outcomes, local recurrence and disease specific survival (DSS). For local recurrence, a hazard ratio (HR) of no more than 1.33 was deemed to be the limit of non-inferiority, and for DSS, 1.25. Based upon existing data, the estimated DSS at 5 years in the intermediate risk group is 91.7%; for the high risk group 76.5%. A HR of 1.25 translates into an absolute difference in 5-year survival of 2% and 4.9% for the IRG and HRG respectively. The sample size required for 90% power to detect such a difference, based upon the upper limit of a 95% confidence interval, was determined for both outcomes and the higher of the two values taken as the required sample size. Assuming the loss to analysis will be no more than 10%, 3,484 participants per arm will be required in the intermediate risk group and 1,448 per arm in the high risk group, i.e. a total target sample size of 9,864. The QoL substudy is powered to detect a significant difference in QoL (small effect size (0.3 of a standard deviation (SD)) assessed with FACT-M melanoma combined subscales) and incidence of neuropathic pain (from 8% to 4%) at 12 months. Allowing for a 20% loss to follow up, the larger of the two values gives a total sample size of 988 patients per risk group per arm and an overall total of 3,960 patients.



### 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 local recurrence and improve patient outcomes. While this 2-stage procedure is the fundamental international standard of care for all melanomas, surprisingly the detail of the wide excision is still highly controversial.

To date, six randomised controlled trials (RCTs) <sup>1-6</sup> have investigated the effect of wider excision margins on local recurrence 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 intermediate and high-risk primaries (see Table 1 and 2 below) is particularly speculative in the international guidance. 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<sup>7</sup>, 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 intermediate to high-risk primaries are subject to 2-3cm excision margins. However, many surgeons suspect that 1cm is ample and perform this routinely for intermediate risk melanomas wherever national guidance allows, particularly in North America & Australasia, even though evidence for this is lacking.

**Table 1 – Categorisation of primary melanoma according to depth of invasion\*, histopathological presence of ulceration\*\* and prognostic staging groups<sup>8</sup>**

BRESLOW THICKNESS*	ULCERATION**	PATHOLOGICAL STAGING (TNM)	AJCC STAGING <sup>8</sup>	RISK GROUP
1.01 – 2mm	NO	pT2a	IB	<b>INTERMEDIATE</b>
1.01 – 2mm	YES	pT2b	IIA	
2.01 – 4mm	NO	pT3a	IIB	
2.01 – 4mm	YES	pT3b		
> 4mm	NO	pT4a	IIC	<b>HIGH</b>
> 4mm	YES	pT4b		

**Table 2 – Current national guidelines for excision margins for primary cutaneous melanomas<sup>9-13</sup>**

THICKNESS	UK (2010)	USA - NCCN (2014)	AUSTRALIA & NEW ZEALAND (2008)	CANADIAN (2010)	DUTCH (2008)
<= 1mm	1cm	1cm	1cm	1cm	1cm
1.01 – 2mm	1-2cm	1-2cm	1-2cm	1-2cm	1cm
2.01 – 4mm	2-3cm	2cm	1-2cm	1-2cm	2cm
> 4mm	3cm	2cm	2cm	2cm	2cm

Two systematic reviews<sup>14-15</sup> and one Cochrane review<sup>16</sup> 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. 2cm) for intermediate to high-risk 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 2cm."

Internationally, the most commonly recommended excision margins for intermediate to high-risk melanoma patients is 2cm. A 1cm excision margin does not appear to be detrimental to patients' survival or local recurrence 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, quality of life 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 quality of life 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<sup>17</sup> 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 an international database from UK & Australia<sup>18</sup> of 3,213 patients showed excision margins of 1cm, when compared to 2cm, have a significantly reduced requirement for skin grafting in the head & neck region from 30.1% to 9.5% and in the extremities from 18.5% to 6.4% ( $p < 0.0001$ , both). It was also demonstrated that the overall requirement for reconstruction in the UK for the 1cm margin group was 16.4% compared with 32.2% in the wider excision margin group (15.8% absolute difference,  $p = 0.0001$ ). Similar results were found with the Australian data (absolute difference = 14.7%,  $p = 0.0001$ ). The data demonstrates that the overall requirement is halved in the narrower excision margin group<sup>9</sup>. Patients achieved a far superior cosmetic result, decreased morbidity, improved function and QOL when a reconstruction, especially a skin graft, was avoided.<sup>9</sup>

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.

A proportion of reconstructions, particularly on the lower limb, require patients to remain in hospital to convalesce. Our data indicates that the reduction in reconstructions performed would free up a median of 28 beds per week nationally, which is 1% of the total UK daily capacity for plastic surgery (Statistics from Department of Health Website: latest quarter, June 2012). Given the relative lack of access to plastic surgery in the UK, the increasing demand for this expertise and the diversity of conditions treated by this specialty, 1% represents a significant liberation and reallocation of capacity. Narrower margins have major implications for planning melanoma services nationally, where nearly all patients could be managed in a day-case institution, or an independent treatment institution, relieving capacity on the inpatient services of the treating hospital or cancer institution. This would serve to reduce the surgical costs of managing melanoma further still, though current data quantifying the magnitude of the savings are lacking.

## 4 Trial Objectives and Design

### 4.1 Objectives

#### Primary Objective:

The primary objective of the trial is to assess whether there is a difference in local recurrence rates and/or melanoma-specific survival for patients treated with either a 1cm excision margin or 2cm margin for intermediate & high risk melanomas (greater than 1mm in thickness).

#### Secondary objectives:

We hope to show that we can halve the risk of long-term pain. If the study shows no risk of the tumour coming back then we will also be able to determine how much of an impact the narrower excision makes to patients in terms of improved QOL and reduced side effects. We will also have enough 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 local recurrence rates for patients treated with either a 1cm or 2cm excision margin for intermediate and high risk melanoma (greater than 1mm thick), that a 1cm excision margin will reduce the number of reported surgical complication rates, halve the risk of long-term pain, as well as improving patients reported QOL and change how local healthcare resources are utilised. There are several study questions which inform the trial design:

1. Could a narrower excision margin of 1cm be safely performed without an increase in the risk of **local recurrence and/or melanoma-specific survival** when compared to a 2cm excision margin in patients at intermediate and at high risk of recurrence?
2. Does the narrower excision margin improve the patient's **quality of life**?
3. Does the narrower excision margin change the use of **local healthcare resources and improve 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 is a pilot study (with the aim of recruiting 400 patients) and the second phase is the full study (with the aim of recruiting 9,684 patients). A limited number of sites will participate 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:

- Risk Group (Intermediate; High) - (see Table 1, Section 3.1 for 2009 AJCC staging system)
- Age (<45; 45-65; >65)
- Sex (Male; Female)
- Site (institution)

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

- **Treatment Arm A:** Wider excision with a 1cm radial margin in combination with a sentinel lymph node biopsy
- **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 is described in the Operations Manual.

**Figure 1 – Trial Schema**

MELMART TRIAL SCHEMA				TRIAL PHASE	TIME
Diagnosis of Primary Cutaneous Melanoma pT2-pT4 (N0M0) AJCC Stage IB-IIC				Screening	No more than 120 days prior to randomisation
Confirmation of Diagnosis – Pathology review at Specialist MDT (Trial Centre) Informed Consent					
RANDOMISATION (Stratification Factors: Risk Group; Age; Sex; Site)				Total patients = 9,684	
Intermediate Risk Group (IRG) AJCC IB-IIA (pT2a, pT2b, pT3a) N=6,968		High Risk Group (HRG) AJCC IIB-IIC (pT3b, pT4a, pT4b) N=2,896		Randomisation & Stratification	Day 0
<b>ARM A: Experimental Arm</b>	<b>ARM B: Control Arm</b>	<b>ARM A: Experimental Arm</b>	<b>ARM B: Control Arm</b>	Intervention (ie: 1 or 2 cm wide local excision)	Day 0 + <14 days
Wide Local Excision = 1cm Margin	Wide Local Excision = 2cm Margin	Wide Local Excision = 1cm Margin	Wide Local Excision = 2cm Margin		
+ Sentinel Lymph Node Biopsy +/- Reconstruction N=3,484	+ Sentinel Lymph Node Biopsy +/- Reconstruction N=3,484	+ Sentinel Lymph Node Biopsy +/- Reconstruction N=1,448	+ Sentinel Lymph Node Biopsy +/- Reconstruction N=1,448		
At participating sites: QOL component (FACT-M, EQ-5D-5L and Neuropathic Pain (PainDetect)) & Health economic component (Form BE)					Day 0

FOLLOW UP		Follow Up	Day 0 +
Clinical Information & Health Status	Annually after 12 months according to National Guidelines of Trial Centre		From 12 months until Trial Completion (max. 120 months)
At participating sites: Follow Up Employment Questionnaires	At 3,6 and 12 months		Day 0 to 12 months
At participating sites: FACT-M, EQ-5D-5L, PainDetect (Neuropathic pain) and Follow Up Cost Questionnaire completion	At 3,6,12, 24 & 60 months		Day 0 – Month 60 (Year 5)
Melanoma Recurrence(s)		At the time of Recurrence	
Death		At the time of Death	
ENDPOINTS			
Local Melanoma Recurrence Melanoma Specific Survival		Primary Endpoints	Day 0 until Trial Completion (max. 120 months)
Recurrence-Free Survival Overall Survival		Secondary Endpoints	Day 0-12 months & 60 months
FACT-M, EQ-5D-5L and Neuropathic Pain (PainDetect) Questionnaires, Health economics (Employment and Cost Questionnaires) and Surgical Complication Rate			

## 4.5 Endpoints

### *Primary endpoints*

The co-primary endpoint of the study will be:

- Time to local recurrence:** Time from randomisation to clinically, histologically or radiologically confirmed local recurrence of melanoma including satellite lesions and in transit metastases to regional draining lymph nodes.
- Melanoma-specific survival:** Time from randomisation to death due to melanoma

### *Secondary endpoints*

Additional endpoints assessed during the study will include:

- Recurrence-free survival:** time from randomisation to any clinical, histological or radiologically confirmed melanoma recurrence or death from any cause.
- Overall Survival:** time from randomisation to death from any cause.
- QoL and neuropathic pain assessments** at baseline, 3, 6, 12, 24 & 60 months and at melanoma recurrence.
- Adverse events** within 1 year
- Surgery related adverse events** up to 30 days from randomisation.
- Health System Resource Use:** from hospital notes and patient reported outcomes at baseline, 3, 6, 12, 24 and 60 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 sentinel lymph node biopsies 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:

#### ***Inclusion criteria***

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

1. Patients must have a primary invasive cutaneous melanoma of Breslow thickness greater than 1 millimetre as determined by diagnostic biopsy (narrow excision, incision or punch biopsy) and subsequent histopathological analysis.
2. Patients must have had the invasive primary completely excised, including any in situ component but excluding melanocytic atypia, with a narrow margin, either in one stage or more than one stage in the case where an incision or punch biopsy has previously been performed. This information, including measured margins of lateral and deep clearance must be documented on the pathology report.
3. Must have a primary melanoma that is cutaneous (including head, neck, trunk, extremity, scalp, palm, sole).
4. An uninterrupted 2cm margin must be technically feasible around biopsy scar or primary melanoma.
5. Randomisation and the primary study intervention, including staging sentinel node biopsy, must be completed by 120 days of original diagnosis.
6. Patients must be 18 years or older at time of consent.
7. Patient must be able to give informed consent and comply with the treatment protocol and follow-up plan.
8. Life expectancy of at least 10 years from the time of diagnosis, not considering the melanoma in question, as determined by the PI.
9. Patients must have an ECOG performance score between 0 and 1.
10. 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 (except for successfully treated cervical or non-melanoma skin cancer with no evidence of recurrence), **and**
  - The patient is deemed by their treating physician to be at low risk of recurrence from previous malignancies.

#### ***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 wide local excision at the site of the primary index lesion.
3. Patient unable or ineligible to undergo staging sentinel lymph node biopsy of the primary index lesion.
4. Desmoplastic or neurotropic melanoma.
5. Microsatellitosis as per AJCC 2009 definition
6. Subungual melanoma
7. 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.

8. History of previous or concurrent (i.e., second primary) invasive melanoma.
9. Melanoma located distal to the metacarpophalangeal joint, on the tip of the nose, the eyelids or on the ear, mucous membranes or internal viscera.
10. Physical, clinical, radiographic or pathologic evidence of satellite, in-transit, regional, or distant metastatic melanoma.
11. Patient has undergone surgery on a separate occasion to clear the lymph nodes of the probable draining lymphatic field, including sentinel lymph node biopsy, of the index melanoma.
12. Any additional solid tumour or hematologic malignancy during the past 5 years except T1 skin lesions of squamous cell carcinoma, basal cell carcinoma, or uterine/cervical cancer.
13. Melanoma-related operative procedures not corresponding to criteria described in the protocol.
14. 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.
15. History of organ transplantation.
16. Oral or parenteral immunosuppressive agents (not topical or inhaled steroids) at any time during study participation or within 6 months prior to enrolment.

## 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 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 determine the tumour risk category for the initial stratification.

A copy of the primary diagnosis pathology report is required to be submitted to the Trial Coordinating Centre.

### 6.2 Wide Local Excision Procedure

*In order to ensure appropriate quality assurance and ensure the integrity of the protocol, each participating institution is required to perform the wide local excision in strict adherence to the procedure described in this protocol.*

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.
2. The excision margin will be calculated in the following manner:
  - 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 pre-determined 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, then the radial excision margin is measured from the edge of the wound.
3. A digital photograph will be taken of the marked excision site, 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.
4. The wide local excision 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.
5. The specimen should be correctly orientated with one or more marking sutures to allow pathological assessment of margins.
6. The surgeon may reconstruct the defect as is deemed appropriate for the patient but this information must be recorded in the protocol for documentation on the MelMarT Case Report Forms (CRF).
7. The specimen will be sent off for histological analysis at the local pathology service to determine the presence or absence of residual tumour and lateral excision margins must be recorded in millimetres on the pathology report.
8. A copy of the wide local excision pathology report is required to be submitted to the Trial Coordinating Centre.

### **6.3 Sentinel Lymph Node Biopsy**

A staging sentinel lymph node biopsy (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). 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 TMC.

## **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 CRFs 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 study is permissive in design. Enrolment into systemic adjuvant therapy trials is permitted during the study subject to appropriate ethical approval. In order to ensure any and all information is available, we request that the participating investigators and institutions enrolling patients on to any such studies agree to collaborate with the MelMarT Trial Coordination Centre to provide sufficient information to determine the treatment administered (placebo, investigation medicinal product, otherwise). Depending on the project, patients may be blinded to the study intervention, if "un-blinding" is necessary, the Study Investigators will undertake to inform the MelMarT Trial Coordinating Centre as soon as possible after the "un-blinding" has occurred. Any treatment that a MelMarT patient receives will be recorded on the CRFs 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
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 CRFs. No pre-operative imaging is necessary for enrolment onto this trial, except for pre-operative mapping lymphoscintigraphy as part of a staging sentinel lymph node biopsy
6. Full medical history
7. ECOG performance score (must be between 0 and 1)
8. Physical exam (including height, weight) 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

Copies of the primary melanoma histopathology report(s) should be provided to the Trial Coordinating Centre as source documentation. All reports must be issued and signed by a pathologist who is member of the specialist multidisciplinary team at the recruiting institution. If necessary, melanomas diagnosed at an outside 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, patient's medical history and eligibility criteria have been checked the patient is ready to be randomised on to the study.

Instructions on how to randomise a patient using the randomisation system are explained in the Operations Manual.

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 were the case, it would be considered unnecessary to repeat any assessments.

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

1. Physical examination (including height and weight)
2. Review of pre-operative mapping lymphoscintigraphy to ensure a staging sentinel lymph node biopsy can be performed.
3. ECOG performance score is to be assessed
4. Sentinel node status needs to be confirmed using pre-operative mapping lymphoscintigraphy followed by a staging SLNB (see section 6.3)
5. For participating sites: The patient will need to complete the following questionnaires including:
  - FACT-M QOL questionnaire
  - PainDetect 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 CRFs. In the case of the patient being diagnosed with a positive sentinel node biopsy for metastatic melanoma, details of the subsequent completion lymph node dissection, operation and pathology reports will be recorded in the CRF and forwarded to the Trial Coordinating Centre, along with the completed CRFs.

Whilst the completion lymph node dissection (CLND) 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, the 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, the baseline assessment will be considered to have been completed on the provision that items 1-4 and 6 have been completed.

## 8.3 Follow Up Visit Assessments: Baseline for a maximum of 10 years in Duration

Patient follow up should be in line with the institution's policy and the following frequency is recommended;

**Years 1:** During the first year patients should attend follow up at 3, 6 and 12 months (+/-2 weeks) including the following assessments

- For participating sites: Health economic questionnaires completed directly by the patient (Baseline and Follow Up Employment Questionnaires) are to be completed during the first year only. Other health economics components (Follow Up Cost Questionnaire) are to be completed during the first year, at Year 2, Year 5 and at any time a melanoma recurrence is diagnosed.
- For participating sites: QOL questionnaires are to be completed during the first year, assessed again at Year 2 and Year 5 and at any time a melanoma recurrence is diagnosed.

**Years 2 to 10:** Annual follow up study visits should be performed.

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

1. Physical examination (including weight)

2. Disease status will be reviewed including any local, in-transit, regional and distant recurrences.
3. ECOG performance score is to be assessed
4. Surgical complications within 30 days of wide excision: surgery-related adverse events (see section 11).
5. 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 on the CRFs. Patients who have a positive sentinel lymph node biopsy 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.
6. Review of any AEs (see section 11)
7. Review of any Serious Adverse Events (SAE) (see section 11)
8. Changes to any systemic therapies being administered to the patient
9. Review of participation in other clinical trials
10. For participating sites: Health system resource use [this component will only be performed at select recruiting institutions at any time melanoma recurrence is diagnosed and at 3, 6, 12, 24 and 60 months post randomisation]
11. For participating sites: The patient will need to complete the following questionnaires any time a melanoma recurrence is diagnosed and at 3, 6, 12, 24 and 60 months post randomisation:
  - FACT-M QOL questionnaire
  - PainDetect Neuropathic Pain questionnaire
  - EQ-5D-5L Utility-based QOL questionnaire
12. In case of patient's death, causality (melanoma related or not) will be recorded

#### 8.4 Melanoma Recurrence / Progression: Diagnosis & Classification

Recurrence is defined as the diagnosis of new sites of melanoma. Disease-free survival will necessarily include local recurrence as a possible first recurrence, even though it is also the primary endpoint (See section 4.5). The time to recurrence is the date at which recurrence is documented. Only the date on which a recurrence was confirmed will be used as a recurrence date. Every recurrence will be sub-classified according to size and location. The exception will be in the case of multiple recurrent episodes of in transit metastases, which need not be reported each time, provided they occur within the same region.

##### Recurrence Classification by Location

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

- 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 CRF.
- 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.
- 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.
- Central nervous system recurrence: Date of a positive CT or MRI of the brain; or spinal fluid cytology
- Distant subcutaneous recurrence: Date of positive excisional, incisional or fine needle aspiration biopsy

**Assessments required when a patient experiences a melanoma recurrence**

The following assessments need to be performed is identical to the follow up visit procedure described above:

1. Physical examination (including weight)
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 on the CRFs. Patients who have a positive sentinel lymph node biopsy 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 [this component will only be performed at select recruiting institutions]
6. For participating sites: QoL questionnaires [this component will only be performed at select recruiting institutions]
7. Review of any AEs (see section 11)
8. Review of any Serious Adverse Events (SAE) (see section 11)
9. Changes to any systemic therapies being administered to the patient
10. Review of participation in other clinical trials

**8.4 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.

**8.5 Withdrawal and Lost to follow up**

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

If a patient withdraws consent to participate the Study Discontinuation Form at the final study visit should be completed. Any other available assessments as described in the follow up visit should be procured from the patient if possible.

If a patient decides to stop their follow-up visits but is willing to keep in contact via telephone, their health status will be periodically ascertained by way of phone contact with their general practitioner or by direct phone contact with the patient. In some circumstances, any other available assessments as described in the follow up visit may be procured from the patient if possible.

For those patients who want to have no further contact, all correspondence regarding the trial will be discontinued. A Study Discontinuation Form is to be completed at the last study visit the patient attends and this is to be submitted to the Trial Coordinating Centre.

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.

## 8.6 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, regularly throughout the first year of the study and at Months 24 and 60, 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)) 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.
- PainDetect (neuropathic pain)

The FACT-M will be scored centrally according to the FACT-M scoring manual ([www.facit.org](http://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 the patient is requested to complete the questionnaires is explained in the in the Operations Manual.

## 8.7 Health 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 of the study and at Months 24 and 60, 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, collected at any time a melanoma recurrence is diagnosed, at baseline, 3, 6, 12, 24 and 60 months, and will be used to estimate QALYs for the economic evaluation.

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

## 9 Pathology

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 confirming the patient's eligibility for the trial.

One of the designated pathologists of each cooperating institution will confirm that a subject'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:

- Breslow thickness

- Melanoma subtype (superficial spreading, nodular etc.)
- The presence and width (measured in millimetres) of ulceration
- The presence of lymphatico-vascular invasion
- The presence of neurotropism spread
- The presence of satellitosis (AJCC 2009 definition)
- Mitotic rate (number per mm<sup>2</sup>)
- The presence and grade/classification of Tumour Infiltrating Lymphocytes as per classification of Azimi et al JCO 2012
- Closest excision margins to both invasive and in situ, deep and peripheral, measured in millimetres

Wide excision specimens will be examined according to the instructions described in the operations manual. Specimens will be examined for any residual tumour and the present of satellites. Measurements from the tumour edge to the surgical margins of the specimen will be recorded in the source documents and on the CRF.

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 CRF and will include the following information:

- Maximum diameter of largest deposit
- Microanatomical location of deposit according to Dewar criteria
- Tumour penetrative depth (Starz thickness) as recommended by Scolyer et al.
- Number of nodes involved
- Site of nodes
- Presence or absence of extracapsular spread (extension)
- Mutation status (if available)

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

- Maximum diameter of largest deposit
- Number of nodes involved
- Site of nodes
- Presence or absence of extracapsular spread (extension)
- Mutation status (if available)

## 10 Data Collection

In the first phase, trial data will be recorded in full on the CRFs provided to each site in hard copy. In a second phase of the trial, data may be collected electronically.

The site is required to complete all appropriate data entry fields as specified on the forms. The investigator will be asked to confirm the accuracy of completed CRFs by signing forms as indicated. Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a subject's medical records, hospital charts, operation reports, the investigator's subject study files, as well as the results of diagnostic tests such as X-rays, PET/CT scans, MRI imaging and laboratory results.

For QOL (FACT-M, PainDetect) and health system resource use (EQ-5D-5L), data entered onto the CRF will be considered as source.

The Trial Management 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 Safety Reporting

### 11.1 Adverse Events

For the purposes of this trial, an Adverse Event (AE) is defined as any untoward medical occurrence in a participant administered a treatment which may have a causal relationship to the patient's melanoma diagnosis and/or with the treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease associated with the patient's melanoma and/or treatment. An AE is any adverse change (developing or worsening) from the participant's pre-treatment condition, including intercurrent illness.

AEs and any pre-existing medical conditions will be recorded at the Baseline assessment and routinely at Follow Up, until the participant completes the study, withdraws or dies.

#### **Surgery-Related Adverse Events (Surgical complications)**

The following surgical adverse events will be recorded from the time of trial treatment to 30 days following the wide excision (inclusive):

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

Surgical adverse events will be graded in severity according to the Clavien-Dindo system<sup>19</sup> (See appendix V)

### 11.2 Serious Adverse Events

#### **SAE Definitions**

A serious adverse event (SAE) is any untoward 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 v4.0) toxicity;
- **and**
- could be related to the wide local excision surgery, including sentinel lymph node biopsy procedure.



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.

### **SAE Reporting**

If any trial patient experiences an SAE all relevant and subsequent information relating to each reported SAE must be submitted on the CRF, along with any available source documentation, to the Trial Coordinating Centre. This must be completed within 24 hours of the site becoming aware of the event. All SAE CRFs require the signature of the Principal Investigator.

### **SAE Reporting Timelines**

<b>Type</b>	<b>Timeframe</b>
Initial SAE Report	The site must submit the original 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. Please use the original SAE Form, and use additional Forms if more space is required. Please provide copies of all relevant source documents if available.
Completed Report	Once the event has resolved or if the participant has died, using the original SAE Form(s), the site should provide the complete report to the Trial Coordinating Centre as soon as possible. This must include relevant source documents.

All SAEs will be reviewed by the Study Chair, also summarised for review by the Data Safety Management Committee and the Trial Management Committee.

SAEs must be reported as per the local Ethics Committee (EC) / Human Research Ethics Committee (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.

## **12 Statistical Considerations**

### **12.1 Sample Size**

The sample size is based upon the two primary outcomes, local recurrence and disease specific survival (DSS). For local recurrence, a hazard ratio (HR) of no more than 1.33 was deemed to be the limit of non-inferiority, and for DSS, 1.25. Based upon existing data, the estimated DSS at 5 years in the intermediate risk group is 91.7%; for the high risk-risk group 76.5%. A HR of 1.33 translates into an absolute difference in local recurrence rates of 2.3% and 3.7% for the intermediate and high risk groups respectively. A HR of 1.25 translates into an absolute difference in 5 year survival of 2% and 4.9% for the intermediate and high risk groups respectively. The sample size required for 90% power to detect such a difference, based upon the upper limit of a 95% confidence interval, was determined for both outcomes and the higher of the two values taken as the required sample size. Assuming the loss to analysis will be no more than 10%, 3,484 participants per arm will be required in the intermediate risk group and 1,448 per arm in the high risk group, i.e. a total target sample size of 9,864. The QoL substudy is powered to detect a significant difference in QoL (small effect size (0.3 of a standard deviation (SD)) assessed with FACT-M melanoma combined subscales) and incidence of neuropathic pain (from 8% to 4%) at 12 months. Allowing for a 20% loss to follow up, the larger of the two values (ie. 8%) gives a total sample size of 988 patients per risk group per arm and an overall total of 3,960 patients.



## **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 Trial Management Committee (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 substudy). Data on patients lost to follow up will be sought via 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 Data Safety Monitoring Committee and Trial Management Committee. 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 DSMC and TMC and incorporated into their charters. The non-inferiority and multi-stage design means that stopping rules for efficacy and futility are implicit. Feasibility is the primary outcome measure for the first stage. Feasibility will include an assessment of compliance with randomised treatment group, recruitment rate and reasons for any difficulties. The first feasibility review will be after the completion of phase 1 of the study. This will be at one year after study start when it is expected that 400 patients will have been enrolled from at least 2 countries. Adverse outcomes assessing any evidence of higher recurrence and lower melanoma specific survival in the narrow margin group will be considered by the DSMC at annual meetings. Point estimates and 95% confidence intervals for the incidence of serious adverse events, local recurrence and melanoma specific survival 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 (PH) model, stratified by recruiting country and include pre-specified prognostic variables within the PH model. The analysis will be conducted within each melanoma risk group. A separate model will be constructed for local recurrence and for melanoma specific survival. Overall non-inferiority will be declared if non-inferiority can be concluded for both outcomes. This analysis will be carried out after the final database lock. Interim analyses comparing recurrence rates and melanoma specific survival will be carried out as agreed with the DSMC and TSC prior to commencement of the full trial. The study team, with the exception of the trial statistician will be kept blind to these analyses, which will be reviewed only by the DSMC. A report will be prepared by the DSMC, shared with the Study Chairman and members of the study team including TMC members for consideration. Based on the report recommendations, the TMC will then determine the best course of action in respect to the Full Study protocol.

### **12.3.2 Statistical Analyses of Secondary Endpoints**

#### **QOL**

The quality of life data, assuming a Normal distribution, will be analysed using a General Linear Model, including baseline value and pre-specified prognostic values, plus stratification variables, as well as treatment group. Site will be considered as a random factor. 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.

**Cost-effectiveness**

We will conduct a cost utility study from the perspective of the National Health Service (NHS) and social services. Economic data will be collected in the first year of follow-up. Information obtained from the study will be used to inform a simple model of relative cost-effectiveness of the different treatments. Models will be calculated for the 5 year follow-up of the study as well as for a lifetime model. The economic analysis will initially be carried out for the Australian & UK samples only. Data collected will include a detailed micro-costing of the index surgical procedure in a sample of patients enrolled in the study. Information on length of stay, complications, and recurrence will be collected as part of the study from secondary care data. Resource use on primary care and other contacts will be collected by means of patient completed questionnaires for the first year only. The EQ-5D-5L will be collected at baseline, 3, 6 and 12 months visits, and will be used to estimate QALYs for the economic evaluation.

**12.3.3 Planned subgroup analyses**

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

1. Risk Group (Intermediate; High) - (see Table 1, Section 3.1 for 2009 AJCC staging system)
2. Age (<45; 45-65; >65)
3. Sex (Male; Female)
4. Site (institution)

Additionally, these variables will be included in a Cox proportional hazards model together with the treatment arm variable in order to assess adjusted hazard ratios and 95% confidence intervals. 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 Data Safety Monitoring Committee (DSMC) 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 Trial Management Committee members at least annually. The DSMC will monitor the trial for safety outcomes and will particularly review the following:

- Unacceptable surgical mortality / morbidity (any Grade 4 toxicity or higher)
- Adverse outcomes assessing any evidence of higher recurrence and lower melanoma specific survival in the 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

**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) 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 Trial Management Committee and a constituted Human Research Ethics Committee (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 PI 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 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 investigator is responsible for ensuring that all regulatory requirements are followed.

The 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 local PI 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 5% or more (accrual by institution) of the evaluable cases on a 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 10% of the participants accrued, not to exceed a total of three authors (i.e. two authors for  $\geq 15\%$  accrual and three authors for  $\geq 25\%$  accrual)

Acknowledgement of the collaboration between ANZMTG is 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.

Publications must be reviewed by the TMC and ANZMTG Executive Committee prior to submission.

## 15 Quality Assurance

### 15.1 Data Management and Source Data Verification

Trial sites are expected to regularly provide the completed CRFs reflecting the patient visits to the Trial Coordinating Centre. Copies of relevant documents for source verification and quality assurance will be requested including various imaging scans and reports.

The Trial Coordinating Centre will issue data queries as required to clarify CRF data and will report to the Study Chair regarding CRF submission and query completion 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 CRFs, 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 subjects 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-Randomisation	6 months Post-Randomisation	12 months Post-Randomisation	Year 2 to 10 During annual follow up visits (Month 12-120)	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	-
Prescribed imaging scans <sup>#</sup>	X <sup>#</sup>	-	X <sup>#</sup>	X <sup>#</sup>	X <sup>#</sup>	X <sup>#</sup>	X <sup>#</sup>	-	-
EDTA, whole blood <sup>++ □</sup>	-	X <sup>++ □</sup>	-	-	-	-	-	-	-
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.								
Sentinel node status needs to be confirmed <sup>∞</sup>	-	X	-	-	-	-	-	-	-
QOL questionnaires <sup>+</sup>	X	X	X	X	X	X <sup>+</sup>	X	-	-
Health system resource use questionnaires <sup>**</sup>	X	X	X	X	X	X <sup>**</sup>	X	-	-
Surgery-related AEs	-	-	Ω	-	-	-	-	-	-
AEs and SAEs monitored	-	X	X	X	X	X	X	X	X
Record meds & treatments & other clinical trials	X	X	-	X	X	X	X	X	X

Assessment	Pre-Randomisation	Baseline Assessments	3 months Post-Randomisation	6 months Post-Randomisation	12 months Post-Randomisation	Year 2 to 10 During annual follow up visits (Month 12-120)	At recurrence	End of Study	Death
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 pre-randomisation. 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 sentinel lymph node biopsy proves to be positive for metastatic melanoma, details of the subsequent completion lymph node dissection, operation and pathology reports will be recorded in the CRF and forwarded to the Trial Coordinating Centre, 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, 24 and 60 months.

\*\* Health system resource use questionnaires completed by the patient (Baseline and Follow Up Employment Form) will be completed at baseline, 3, 6 and 12 months. 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, 24 and 60 months.

Ω Surgery-related AEs will be collected up to 30 days following the wide local excision.



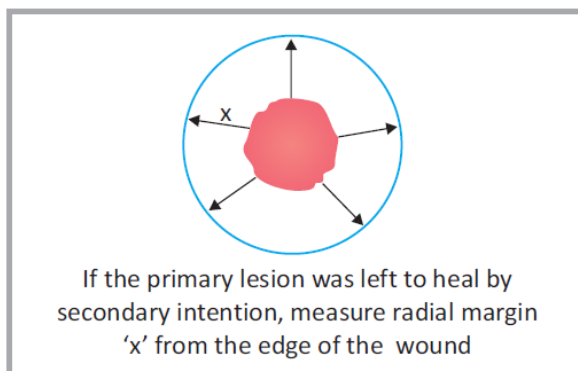
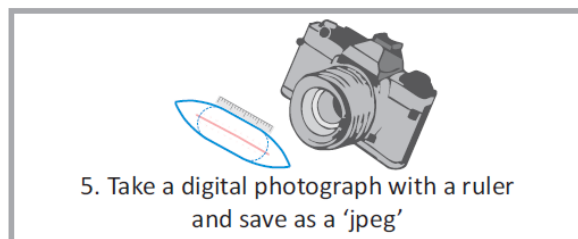
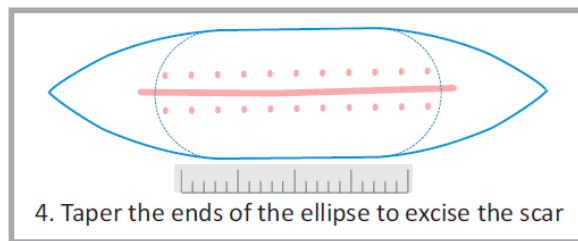
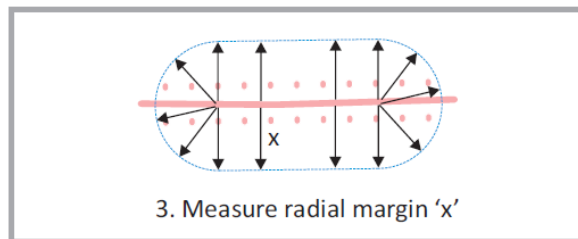
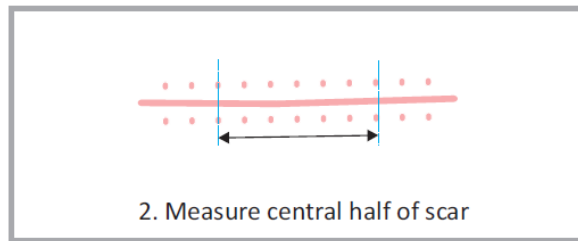
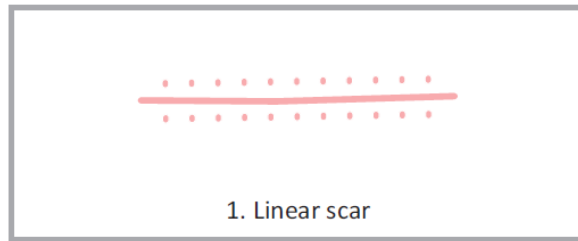
**Appendix II: ECOG Performance Status**

<b>Grade</b>	<b>Definition</b>
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 4.0**

The National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0) can be found at: <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>

### Appendix IV: Wide Local Excision Procedure



**Appendix V: The Clavien-Dindo Scale For Surgical Complications<sup>19</sup>**

<b>The Clavien-Dindo Scale For Surgical Complications</b>	
<b>Grades</b>	<b>Definition</b>
<b>Grade I:</b>	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
<b>Grade II:</b>	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
<b>Grade III:</b>	Requiring surgical, endoscopic or radiological intervention
<b>Grade III-a:</b>	Intervention not under general anaesthesia
<b>Grade III-b:</b>	Intervention under general anaesthesia
<b>Grade IV:</b>	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management
<b>Grade IV-a:</b>	Single organ dysfunction (including dialysis)
<b>Grade IV-b:</b>	Multi-organ dysfunction
<b>Grade V:</b>	Death of a patient
<b>Suffix 'd':</b>	If the patients suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

‡ brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit.