Rational treatment selection for Merkel Cell Carcinoma (MCC): A randomised phase III multi-centre trial comparing radical surgery and radical radiotherapy as first definitive treatment for primary MCC with an observational study for patients ineligible for the randomised trial

Protocol Version 2.0 15th January 2016

Sponsor:	University of Birmingham
Funders:	Efficacy and Mechanism Evaluation Programme (EME)
ISRCTN:TBC	
Research Ethics Committee:	West Midlands - Solihull Research Ethics Committee
REC Reference Number:	15/WM/0454
Sponsor Protocol Number:	RG_14-019
CRCTU Reference Number:	SK3008

Cancer Research UK Clinical Trials Unit @CRCTU

UNIVERSITY OF BIRMINGHAM

NHS National Institute for Health Research

This trial will be conducted in facilities funded through Birmingham Science City: Translational Medicine Clinical Research Infrastructure and Trials Platform, an Advantage West Midlands (AWM) funded project which forms part of the Science City University of Warwick and University of Birmingham Research Alliance.

TRIAL PERSONNEL

Chief Investigator	
Dr Neil Steven	Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham. B15 2TT ✉ n.m.steven@bham.ac.uk
Co-Investigators	
Clinicians	
Dr Pat Lawton	Department of Oncology, City Hospital Campus, Nottingham University Hospital Trust. ✉ pat.lawton@nuh.nhs.uk
Dr Carie Corner	Mount Vernon Cancer Centre, Middlesex. HA6 2RN. ✉ cariecorner@nhs.net
Prof Catherine Harwood	Queen Mary University of London, London. ✉ caharwood@doctors.org.uk
Mr Oliver Cassell	Blenheim Head and Neck, Oxford University Hospitals NHS Trust, Oxford. ✉ oliver.cassell@ouh.nhs.uk
Lead Statistician	
Dr Christina Yap	CRCTU, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham. B15 2TT ✉ c.yap@bham.ac.uk
CRCTU Direction of Operations	
Dr Sarah Bowden	CRCTU, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham. B15 2TT ✉ s.j.bowden@bham.ac.uk
Virology	
Dr Philippe Taniere	Department of Cellular Pathology, University of Birmingham, Birmingham. ✉ phillipe.taniere@uhb.nhs.uk
Pathology	
Dr Claudia Roberts	Department of Cellular Pathology, University Hospitals Birmingham NHS Foundation Trust, Birmingham. ✉ claudia.roberts@uhb.nhs.uk
Imaging	
Dr Ian Zealley	NHS Tayside, Ninewells Hospital, Dundee. DD1 9SY ✉ ian.zealley@nhs.net

PPI Coordinator	
Ms Clair Mcgarr	University Hospitals Birmingham NHS Foundation Trust, Birmingham. ✉ clair.mcgarr@uhb.nhs.uk
PPI Representative	
Mr Simon Rodwell	Melanoma Focus, Queen Anne House, Gonville Place, Cambridge. CB1 1ND ✉ rodwell@melanomafocus.com

Key Contacts

Trial Management Team Leader	
Miss Claire Gaunt	CRCTU, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham. B15 2TT ☎ 0121 414 3057 ✉ c.h.gaunt@bham.ac.uk
Trial Statistician	
Mr Kristian Brock	CRCTU, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham. B15 2TT ✉ k.brock@bham.ac.uk
Senior Trial Co-ordinator	
Dr Rachel Blundred	CRCTU, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham. B15 2TT ☎ 0121 414 3792 ✉ r.m.blundred@bham.ac.uk
Trial Co-ordinator	
TBC	
Clinical Immunology Service	
Tim Plant	Department of Clinical Immunology Service, University of Birmingham. ✉ t.plant.1@bham.ac.uk

Translational Coordinating Centres

HBRC (Blood samples and Tumour Blocks)	NHS Tayside (Scans)
Dr Jane Steele (Rational MCC Trial) Human Biomaterials Resource Centre C/O Institute of Biomedical Research Stores Hospital Drive University of Birmingham Edgbaston Birmingham B15 2TT	Dr Ian Zealley Department of Radiology Level 6 Ninewells Hospital Dundee DD1 9SY

Trial Contact Details	
Rational MCC Trial Office	CRCTU, Institute of Cancer and Genomic Sciences, University of Birmingham, Edgbaston, Birmingham. B15 2TT ☎ 0121 414 3792 🖷 0121 414 8392 or 0121 414 7989 ✉ rationalmcc@trials.bham.ac.uk
Registration/Randomisation	☎ 0800 371 969 (9.00 am till 5.00 pm Monday to Friday)
Serious Adverse Event Reporting	🖷 0121 414 8392 or 0121 414 7989

SIGNATURE PAGE

Rational MCC Trial Protocol v2.0 15th January 2016

This protocol has been approved by:

Name:	Neil Steven	**Trial Role:**	Chief Investigator
Signature:		**Date:**	15 JAN 2016

This protocol describes the Rational MCC trial and provides information about procedures for patients taking part in the Rational MCC trial. The protocol should not be used as a guide for treatment of patients not taking part in the Rational MCC trial.

TRIAL SYNOPSIS

Rational MCC	Rational treatment selection for Merkel Cell Carcinoma (MCC): A randomised phase III multi-centre trial comparing radical surgery and radical radiotherapy as first definitive treatment for primary MCC with an observational study for patients ineligible for the randomised trial.		
Chief Investigator	Dr Neil Steven		
ISRCTN	tbc	**Sponsor**	University of Birmingham
Rational MCC Design:	All patients newly diagnosed with MCC suitable for radical treatment are able to contribute to the UK-wide Rational MCC clinical study. It is made up of two components: • **Rational Compare:** A national, multicentre, two arm, randomised phase III trial comparing radiotherapy with surgery as a first treatment for newly diagnosed primary MCC. Rational Compare has an adaptive design and an initial integrated feasibility phase will inform operational adaptations to the trial. • **Rational Review:** A prospective multicentre observational study over 3 years which will collect patient, tumour and treatment data from patients with new presentation of MCC, including those ineligible for randomisation in the Rational Compare trial. Rational Review, including patients ineligible for Rational Compare.		
Rational MCC Duration:	**Rational Compare** - recruitment is over 5 years (with analysis of data from initial feasibility phase at 3 years). Patients will be followed up for a minimum of 2 years. **Rational Review** – recruitment is for 3 years.		
Treatment: Rational Compare	**Arm A: Prioritise surgery –** Wide Local Excision (WLE), aiming for complete excision of all MCC, plus a wide margin **Arm B: Prioritise radiotherapy -** Radical radiotherapy to macroscopic tumour and/or to the tumour bed if already excised, plus a wide margin.		
Treatment: Rational Review	Treatment will be according to the decision of the Specialist Skin Cancer Multi-Disciplinary Team (SSMDT)		
Quality of Life	QLQC30 and EQ-5L-5D questionnaires will be completed prior to trial entry, post randomisation but prior to the start of treatment and at each 3 month clinical assessment visit		
Translational Research Samples	• Tumour blocks from primary MCC tissue • Blood samples before treatment and 3-months after treatment		
Objectives			
Primary Objectives: (Rational Compare)	To determine if radical surgery or radical radiotherapy as first definitive treatment for the primary MCC results in better control of loco-regional disease		
Secondary Objectives: (Rational Compare)	To compare between the trial arms: • Survival with current loco-regional control • Local, in-field, in-transit and regional nodal treatment failure and distant progression • Progression free survival • Overall survival • Quality of life		
Feasibility Phase Objectives: (years 1-3)	• To determine whether Rational Compare is likely to deliver on the trial objectives such that the results will influence individual treatment decisions and international clinical practice • To determine operational adaptations to Rational Compare design to reduce variation between patients and in non-randomised components of the management pathway		

Exploratory Objectives: **(Rational Compare and Rational Review)**	• To determine the additional value of routine Fludeoxyglucose (FDG) Computed Tomography-Positron Emission Tomography (CT-PET) at one and two years in identifying recurrence in patients undergoing clinical assessment and symptom-directed imaging • To identify clinical, pathological and treatment variables associated with good outcome from MCC and select for further investigation variables at presentation as possible prognostic and predictive biomarkers of MCC

Outcome Measures

Primary Outcome Measure:	Time to loco-regional failure: the time to loco regional failure for all patients is the time from randomisation to loco-regional treatment failure
Secondary Outcome Measures:	• The proportion of patients alive and free of loco-regional disease (irrespective of whether loco-regional failure has been previously demonstrated) • Time to local failure (including in-field and in transit metastases) • Time to regional nodal failure • Time to distant progression • Progression free survival • Survival • Quality of life

Trial Design

Patient Population:	Patients newly presenting with histologically proven MCC and who are being considered for radical loco-regional control
Sample Size:	Up to 400 patients in Rational Compare and Rational Review combined. **Rational Compare** –expected at least 250 randomised patients in total after 5 years accrual. **Rational Review** – up to 150 patients across years 1-3. At least 20 patients must be randomised into Rational Compare after 24 months accrual and at least 40 patients randomised after 30 months accrual for the whole Rational MCC trial to continue.

Eligibility Criteria

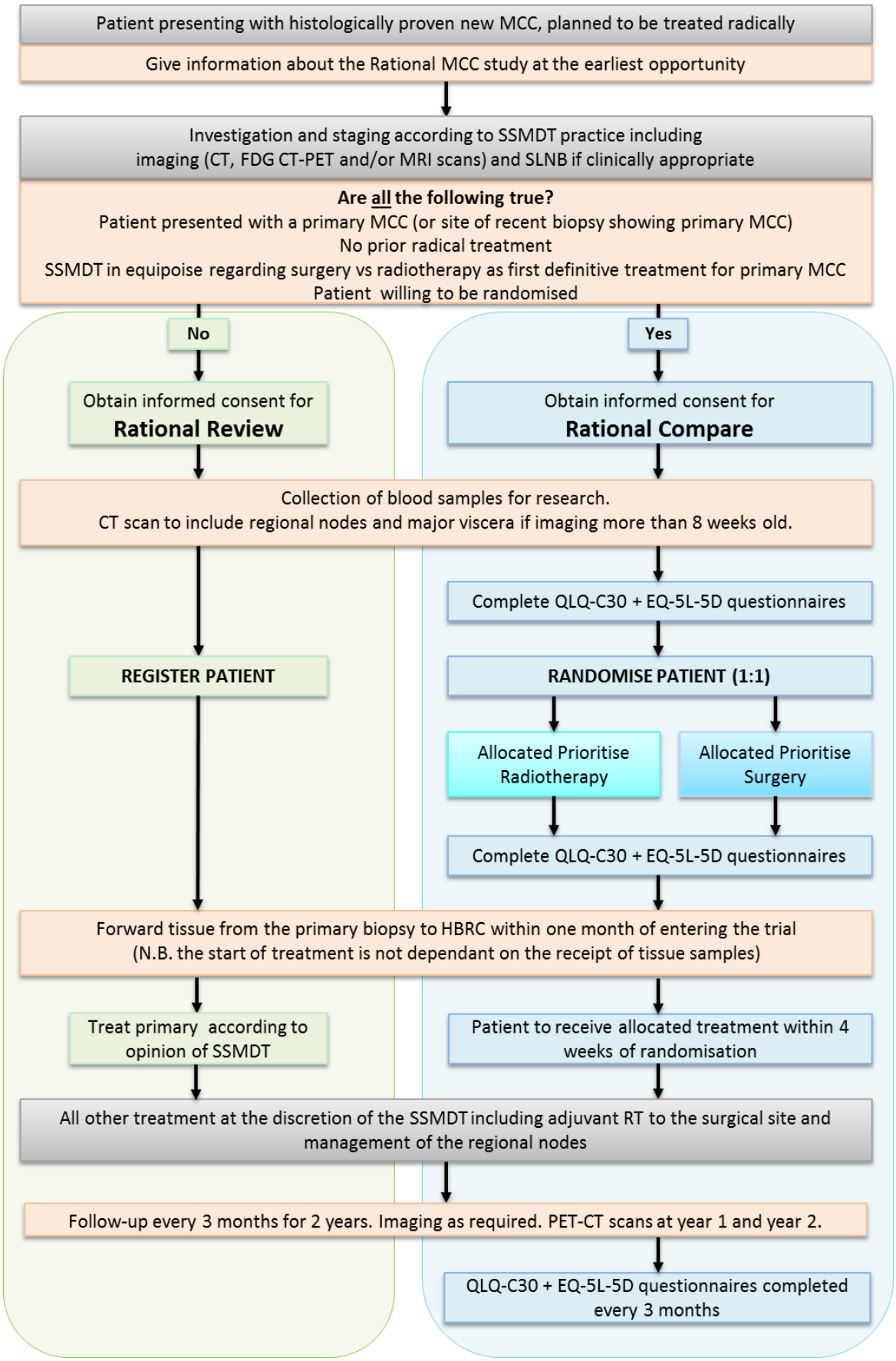
Inclusion Criteria: **All patients**	1. Patients newly diagnosed with histologically-proven MCC 2. Completion of clinical and radiological staging investigations 3. No distant metastases beyond the regional nodal basin 4. Being considered for radical treatment to achieve disease control 5. Able to give valid informed consent 6. Consent for collection of data and tissue samples and follow up 7. Life expectancy six months or greater in relation to general fitness and co-morbidities
Additional Inclusion Criteria for Rational Compare	1. Patients newly presenting with histologically proven *primary* MCC 2. The SSMDT is in equipoise regarding WLE or radiotherapy as first treatment for the primary MCC 3. Consent for randomisation into the trial
Exclusion Criteria for Rational Compare only	1. The primary MCC has already been treated radically with WLE (surgical margins >10 mm) or radiotherapy 2. Intended use of regional or systemic chemotherapy (including molecularly targeted agents and immunotherapy)

Trial Office Contact Details

Rational MCC Trial Office, CRCTU, Institute of Cancer and Genomic Sciences, University of Birmingham, Edgbaston, Birmingham. B15 2TT

☎ 0121 414 3792 🖷 0121 414 8392 or 0121 414 7989

PROJECT SCHEMA



SCHEDULE OF EVENTS

	Screening (1)	Pre-treatment	Treatment	Follow-up (2) Months post enrolment							
				3	6	9	12	15	18	21	24
Informed consent	X										
Cross-sectional imaging	X (3)				X (4)		X (5)		X (4)		X (5)
Clinical history and data collection	X										
Clinical assessment (6)	X			X	X	X	X	X	X	X	X
Full blood count (FBC) (7)	X			X	Results reported if routine bloods are taken						
Review of eligibility	X										
Quality of Life questionnaires (8)	X	X		X	X	X	X	X	X	X	X
Randomisation/ Registration	X										
Blood samples for research	X (9)			X (10)							
Pathological tissue collection		X									
Start of definitive treatment			X (11)								
Concomitant medication reporting (12)				X	X	X	X	X	X	X	X
Adverse Event Reporting (13)			X	X							

(1) Complete screening and trial entry within 14 days of consent. It is possible to consent, screen and register/randomise patients in one day if the data required for the Baseline Form has already been collected as part of routine practice

(2) All assessment points are +/- 2 weeks

(3) A CT scan is required of major sites of metastases, i.e. chest, abdomen and pelvis and relevant regional nodal basins. This can be omitted during screening if appropriate cross sectional imaging covering these sites has been completed within 8 weeks of trial entry

(4) Clinically-directed imaging should be undertaken if recurrence, persistence or progression is suspected, as standard care

(5) FDG CT-PET (or CT scan if FDG CT-PET is unavailable) to be performed up to one month following the clinical assessment at 12 and 24 months

(6) Clinical assessment should confirm fitness prior to treatment and include examination for loco-regional and visceral dissemination

(7) Blood tests to assess fitness for treatment should be undertaken as per local policy and individual clinical need. For the trial, FBC is required to provide an absolute lymphocyte count reading

(8) Rational Compare patients only. Patients should complete a questionnaire before and after randomisation

(9) 5 ml clotted blood, 2 x 4 ml EDTA, up to 50 ml Li-hep. To be taken after consent but prior to the start of definitive treatment

(10) 5 ml clotted blood, 4 ml EDTA

(11) Treatment should begin within 4 weeks of randomisation for Rational Compare patients and as soon as possible in all patients

(12) Any new use of immunosuppressant medication or corticosteroids should be recorded

(13) From first day of treatment to 90 days after last treatment

ABBREVIATIONS

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
AJCC	American Joint Committee on Cancer
CHI	Community Health Index
CI	Chief Investigator
CLL	Chronic Lymphocytic Leukaemia
CRCTU	Cancer Research UK Clinical Trials Unit
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CT-PET	Computed Tomography-Positron Emission Tomography
CTV	Clinical Target Volume
CV	Curriculum Vitae
DMC	Data Monitoring Committee
DVT	Deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
EME	Efficacy and Mechanism Evaluation Programme
FBC	Full Blood Count
FDG	Fludeoxyglucose
GA	General Anaesthetic
GCP	Good Clinical Practice
GHSS	Global Health Status Score
GP	General Practitioner
GTV	Gross Tumour volume
H&E	Haemotoxylin And Eosin
HBRC	Human Biomaterials Resource Centre
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ISF	Investigator Site File
MCC	Merkel Cell Carcinoma
MCPyV	Merkel Cell Polyomavirus
MHRA	Medicines & Healthcare Products Regulatory Agency
MRC	Medical Research Council
NHS	National Health Service
NIHR	National Institute for Health Research
NRES	National Research Ethics Service
PBMC	Peripheral Blood Mononuclear Cells
PET	Positron Emission Tomography
PPI	Patient And Public Involvement
PTV	Planning Target Volume
QA	Quality Assurance
REC	Research Ethics Committee
RFS	Relapse-Free Survival
RT	Radiotherapy
RTTQA	NCRI Radiotherapy Trials QA
SAE	Serious Adverse Events
SLNB	Sentinel Lymph Node Biopsy
SSMDT	Specialist Skin Cancer Multi-Disciplinary Team
TLS	Tumour Infiltrating Lymphocytes
TMG	Trial Management Group
TNO	Trial Number
TSC	Trial Steering Committee
UHBFT	University Hospital Birmingham NHS Foundation Trust
WLE	Wide Local Excision
WMA	World Medical Association

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

1.1. Background

1.1.1. The natural history of Merkel Cell Carcinoma

MCC is a high grade, locally invasive, highly metastatic neuroendocrine skin cancer generally diagnosed in older people (median age 76 years with 62% between 50-80 years and 34% >80 years) (1). It is very rare: 1515 cases reported centrally in England in the decade to 2008 but with incidence rising from 0.1 to 0.2/100,000 across that time (2).

MCC typically presents on sun-exposed skin and ultraviolet light exposure is a risk factor. MCC associates with immune suppression (3), including coincidental chronic lymphocytic leukaemia (CLL) (4), organ transplantation (5), human immunodeficiency virus (HIV) infection (6) and auto-immune disease (7). Immune suppression or leukaemia/lymphoma also appear to predict a more aggressive clinical course (5, 8, 9). Most MCC have the skin commensal, Merkel cell polyomavirus (MCPyV), integrated in the malignant cell genome (10, 11).

Two-thirds of patients present with primary lesions only (stage I and II), one-quarter have clinical or radiological evidence of regional nodal involvement (stage III), and fewer than 10% present with disseminated disease (stage IV). Primary MCC can be controlled with surgery and there is evidence that it is also a radio-responsive tumour. Recurrence rates are high, with relapse-free survival at 5 years for stage I-III patients reported as 48%, median time to recurrence 9 months and >90% recurrences manifest within 2 years (12).

1.1.2. The management of loco-regional MCC in the UK

Diagnosis of MCC is often unsuspected and commonly only made after biopsy or excision in a non-specialist centre. Patients should be rapidly referred to a Skin Specialist Multi-Disciplinary Teams (SSMDT) for definitive management. Currently, treatment of the primary is diverse including wide local excision (WLE), WLE plus adjuvant radiotherapy or radiotherapy without prior wide surgical margins (13-15).

1.1.3. The management of patients presenting with primary MCC

Evidence for the treatment of primary MCC is confounded by there being few prospective or randomised trials. Scanty data are offered on attempted surgical margins. The consistent use of defined WLE, e.g. 20 mm margins with clearance to the next fascial plane, has not been tested. Lewis (2006) undertook a systematic review of case series and reports, comprising 418 patients stage I-IV undergoing various surgical modalities with 1 and 5-year local relapse-free survival (RFS) 70.5% and 60.5% respectively (16). This is supported in more recent case series, e.g. a 64% local RFS reported for 49 surgically-treated cases treated in 17 centres 1988-2009 (17).

MCC is known to be a radio-responsive tumour. Radical radiotherapy for primary MCC is variably defined and may include treatment after either limited local resection or just a biopsy, but in any case without prior extensive surgical intervention to obtain wide margins. Most reports of radical radiotherapy are of patients who had been deemed medically or surgically unfit for surgery or those in relapse, i.e. a poorer prognosis group. There is a signal that high rates of disease control can be achieved. Parvathaneni reported on just 26 patients receiving radiotherapy alone from a retrospective review of 547 MCC cases, with median tumour size 25 mm (range 3-110 mm) and 92.3% local control rate (18). Other series report a local control in 25/25 patients with median primary size 20 mm (19) and in 17/18 patients (20). Veness reported results of radiotherapy as definitive management resulting in in-field control rates of 75% in a mixed group including inoperable primary MCC on initial diagnosis or relapse (21) and 85% in the extended dataset including both macroscopically present primary lesions and primaries excised with narrow margins (22). Harrington reported on 42 patients given definitive radiotherapy for macroscopic primary MCC, 37 after biopsy only and 5 after failed excision, with 90% local RFS at 5 years similar to that for the 122 who had at least resection of local macroscopic disease (23). Field margins were generally ≥3 cm round the tumour and the importance of doses exceeding 50 Gray to achieve local control was emphasised (23).

The use of surgery and adjuvant radiotherapy is associated with high reported local disease control rates. The largest prospective trial of MCC to date (for a randomised comparison of adjuvant regional radiotherapy) used as inclusion criteria completion of WLE to defined standards, local radiotherapy starting within 6 weeks of surgery, good performance status, no immune suppression and no other cancers. This trial population included people with MCC on the lower limbs and on the head and neck and an excellent local disease control rate of 96.4% was observed(24). While giving a signal of

efficacy for WLE plus adjuvant radiotherapy, it does not tell us both modalities are required for all patients and the applicability is questionable because the eligibility criteria may have selected a population with favourable prognosis. A systemic review of retrospective series reported 1 and 5-year local RFS of 90.5% and 87.9% respectively for 169 patients undergoing mixed surgical modalities plus adjuvant radiotherapy to the tumour bed (16), with similarly high local control rates in more recent series (19, 25). One retrospective series included patients undergoing radical radiotherapy after either surgical excision (n=105) or biopsy (n=13) with a 93% local RFS (17). This paper distinguished between patients with uninvolved (R0) or involved (R1) margins including those not undergoing excisional surgery (R2) and reported outcomes for surgery with or without adjuvant radiotherapy. Local disease control was 96% (R0, radiotherapy), 71% (R0, no radiotherapy), 87% (R1 or R2, radiotherapy) and 47% (R1 or R2, no radiotherapy). Both margin status and radiotherapy independently associated with local recurrence risk in multivariable analysis. Although outcome is worse for patients whose primary has not been cleared surgically prior to radiotherapy, it is unclear whether requiring further surgical clearance prior to radiotherapy for such patients would improve or worsen outcome. There is a risk that local disease may progress post-surgery in patients awaiting adjuvant radiotherapy (26).

In summary, it is uncertain (i) whether, if radiotherapy is also given, simple excision is as good as or better than WLE; (ii) whether primary radiotherapy without prior excision (i.e. biopsy only) is as effective as with excision; (iii) conversely, whether the consistent use of quality controlled WLE, e.g. surgical margin 20 mm and to the next fascial layer and with clear pathological margins, is sufficient treatment without adjuvant radiotherapy, in particular, for patients with smaller primary tumours.

Given the uncertainties about optimal management at multiple steps in the treatment pathway, this trial compares treatments for the primary, while collecting additional data on patient, tumour and other treatment variables to inform the design of successor trials.

1.2. Trial Rationale

1.2.1. Justification for patient population

The primary question in the Rational Compare component of the Rational MCC trial tests two radical first-line strategies for newly presenting primary MCC. MCC is a rare cancer, which has compromised the development of clinical evidence underpinning treatment decisions. Selecting a question that is broadly applicable across the population maximises the probability of an informative result. The integrated Rational Review observational component, which broadly will recruit patient ineligible for or declining entry into the Rational Compare randomised trial, maximised data collection from this rare cancer population. This means that the combined data from Rational Compare and Rational Review can be analysed to investigate putative prognostic factors detectable at presentation and the value of routine imaging in follow-up. This will generate a bank of clinical data, fixed tissue, viable peripheral blood mononuclear cells (PBMC), serum and plasma coupled to clinical baseline, treatment and outcome data for future research to be funded separately.

In designing a randomised trial for a rare cancer population, there is a tension between conflicting imperatives, maximising accrual versus minimising heterogeneity in the randomised population to ensure the trial results can be interpreted for defined treatments in a defined group of patients. In the Rational MCC study, accrual is prioritised and a pragmatic approach is adopted to minimise restrictive eligibility criteria and permit flexibility in non-randomised components of the treatment pathway. These areas of expected diversity include (i) the completeness of excision in initial biopsy prior to radical treatment, (ii) the presence of immune compromise or other malignancies (iii) whether staging investigations prior to study entry include Sentinel Lymph Node Biopsy (SLNB) (iv) whether adjuvant radiotherapy is planned for the primary or to clinically uninvolved regional nodes following definitive treatment for the primary (v) the planned management of clinically involved regional nodes. The permissive approach to recruitment is intended to avoid the unintended consequence of slowing existing treatment pathways which might otherwise arise by the trial constraining clinical decision-making in the absence of high quality evidence or national consensus on best practice. The trial incorporates a feasibility phase to determine operational adaptations to design that will address the variation between patients and in non-randomised elements of treatment, based on data on UK practice and outcomes.

1.2.2. Justification for design

This is a pragmatic trial for a rare cancer population. The aim is to maximise the information collected so as to inform rational clinical decision-making for patients first presenting with MCC for whom the intent is to achieve loco-regional disease control. In the Rational Compare randomised trial, it is not feasible to falsify a hypothesis because of the expected low trial numbers. This trial is designed statistically to enable clinical interpretation that either radical radiotherapy or surgery has a high probability of being better than or at least as good as the alternative and, conversely, that the probability is very low of making a disastrously wrong choice. This approach, offering varying probabilities for a range of effect sizes, can be achieved with a sample size of a few hundred patients.

1.2.3. Rationale for the interventions

The primary question of Rational Compare compares two radical first-line strategies to achieve clearance of biopsy-proven primary MCC and adjacent microscopic satellites.

The first strategy is termed “prioritise surgery”, i.e. radical surgery is used as the first and principal treatment modality to achieve pathological marginal clearance of the primary. The trial requires a consistent surgical policy of including clearance to the next fascial layer and a planned margin on the skin that generally exceeds 2 cm or, if limited by specified anatomical considerations, must at least exceed 1 cm. In many or most patients, healing requires a skin flap or graft.

The alternative strategy is termed “prioritise radiotherapy”, i.e. radical radiotherapy is used as the early and principal treatment, aiming to eliminate malignant cells within the primary tumour bed without delay for radical surgery and healing. This represents a wholly different radiotherapy strategy compared to its delayed adjuvant use after healing following radical surgery.

The management pathway should be structured to start definitive local treatment as rapidly as possible because MCC is known to be an aggressive cancer. Screening procedures between consent and randomisation have been kept to a minimum, mainly using data already collected upstream in the management pathway. It is intended that the SSMDT begin mapping the pathways to surgery and to radiotherapy early, even before consent, so that treatment-time targets can be achieved.

Patients randomised to prioritise WLE can subsequently be offered adjuvant radiotherapy to the primary site at the discretion of the SSMDT. This reflects the uncertainty and variation in practice around this issue and published guidance elsewhere supporting adjuvant radiotherapy after WLE but sparing patients with small primary MCC (27). Note that risk factors guiding the selection of patients for adjuvant radiotherapy have not been validated. This issue will be addressed by adapting the trial design following the review of data collected in the feasibility phase.

SLNB is not a study procedure nor a requirement for eligibility. SLNB should be made available for patients for whom the SSMDT considers this to be appropriate, providing this does not slow the pathway to starting definitive treatment. The use of SLNB offers prognostic data: most but not all studies show patients with negative nodes on SLNB have better outcomes than those staged clinically as node negative or with positive operative staging (1, 8, 9, 28, 29). SLNB can bring forward the time of detection of regional recurrence (9, 29, 30). Studies of retrospective incomplete datasets show an association between undergoing SLNB and better disease specific survival, though it is uncertain whether this is a direct causal link (30, 31). SLNB requires general anaesthetic (GA). It therefore puts patients at risk and some patients may be suitable for radical treatment but not for GA. Regional nodal adjuvant radiotherapy can be offered to patients without clinical or radiological evidence of regional nodal involvement and who do not undergo SLNB. During the feasibility phase, Rational Compare offers no recommendation on this issue because although adjuvant radiotherapy might plausibly result in a gain in progression free survival, there is no evidence suggesting a survival gain (24). Both issues will be addressed by adapting the trial design following the review of data collected in the feasibility phase.

Treatment for patients registered on Rational Review is wholly at the discretion of the SSMDT.

1.2.4. Routine imaging in follow-up

The primary outcome for the trial, loco-regional failure, is based on 3-monthly clinical review and clinically directed imaging as appropriate.

It is reasonable to undertake cross-sectional imaging at the end of the first year after primary treatment as a standard part of routine follow-up in patients in whom loco-regional or distant recurrence has not already occurred, because more than half of recurrences will occur in that time. The Rational MCC trial requires routine imaging, at the end of both the first and second years to maximise the timely detection of treatment failure.

Computed tomography positron emission tomography scanning using the glucose analogue 18F-fluorodeoxyglucose (FDG) Computed Tomography-Positron Emission Tomography (CT-PET) will be employed as the principal routine modality to detect regional and distant metastases at one and two years. FDG CT-PET is sensitive in MCC and can detect dissemination missed by conventional CT scanning and SLNB (reviewed in 32), though does not replace SLNB in detection of microscopic regional nodal disease (33). FDG CT-PET scanning is increasingly recognised as contributing to decision-making in MCC(27) but at this stage there is no evidence that FDG CT-PET surveillance is associated with improved outcomes in patients with MCC.

Conventional CT scanning is widely available but access to FDG CT-PET scanning may be more limited. Therefore SSMDTs will be allowed to use conventional CT scanning rather than FDG CT-PET, at least during the trial feasibility phase. At the end of the feasibility phase, the routine annual imaging will be re-evaluated centrally to provide a consistent, standardised report to a template, in order to explore the additional contribution of annual imaging to detection of loco-regional progression in the context of a clinically-driven follow up strategy.

1.2.5. Biological profiling of patients with MCC

Variables related to the primary MCC tumour are already components of the Royal College of Pathologists core dataset (34). Irradiation and cancer immunity may interact (reviewed in 35). MCC is a virus and immune-associated malignancy and both factors appear to interact with outcome. Therefore, immune variables in the history and on analysis of peripheral blood, intra-tumoural infiltration by CD3+ and CD8+ T lymphocytes and detection of MCPyV genomes will be assessed to provide a profile of patients to be factored into interpretation of outcomes (36-40). Note that these are all factors which might feasibly assessed during the initial assessment of a patient newly presenting with MCC.

Future work is likely to include examination of circulating immune responses and further dissection of functional immune and inflammatory components within MCC tumours, to understand mechanisms of immune effect and evasion and identify targets for immune therapeutic intervention.

2. TRIAL DESIGN

Rational MCC is a pragmatic trial. It aims to allow every patient newly diagnosed with MCC and suitable for radical treatment to contribute to a prospective dataset. The overall ambition of this trial is to establish a national framework to deliver research to improve outcomes for patients with this rare aggressive cancer. Rational MCC has an adaptive design and operational adaptations will be informed by the results of the initial integrated feasibility phase.

2.1. The Randomised Trial – Rational Compare

The main aim of the trial is to compare surgery and radiotherapy as definitive treatments for the primary MCC tumour. This phase III, multi-centre, randomised two arm component of the Rational MCC trial is referred to as Rational Compare. The two arms are:

Arm A - Prioritise surgery – WLE of the primary site with radiotherapy reserved for later adjuvant treatment in selected patients

Arm B - Prioritise radiotherapy – early use of radical radiotherapy to the primary site without prior radical surgery

During the first three years of the trial, data from the feasibility phase of Rational Compare will be used to monitor, inform and adapt the design of the trial. Patients randomised during the feasibility phase will be included in the final efficacy analysis.

2.2. The Prospective Observational Study – Rational Review

Patients suitable for radical treatment for newly presenting primary MCC can instead be registered onto the observational study referred to as Rational Review. Reasons for entry to Rational Review rather than Rational Compare may be:

- there were no primary tumours at presentation
- the SSMDT was not in equipoise between radical radiotherapy versus surgery as definitive first treatment for the primary
- the patient declined randomisation

Patients on Rational Review will receive treatment determined by the SSMDT and the same follow up schedule as participants in Rational Compare. Rational Review will run for 3 years.

2.3. Sample Size

Up to 400 patients will be recruited to the Rational MCC trial as a whole.

Rational Compare is expected to recruit at least 250 randomised patients after 5 years accrual.

The sample size for Rational Review is up to 150 patients across years 1-3.

At least 20 patients must be randomised after 24 months accrual and at least 40 patients must be randomised after 30 months accrual otherwise the DMC and TSC will have to review continuation of the Rational MCC trial.

3. AIMS, OBJECTIVES AND OUTCOME MEASURES

3.1. Trial Aims

- Provide evidence from a multi-centre, randomised, two arm, phase III trial that will enable clinicians and patients to select rationally between two currently used interventions to treat the primary MCC
- Provide evidence from a multi-centre prospective study including of patient, tumour, and treatment variables in relation to outcomes to improve the quality of clinical practice and support the development of future clinical trials
- To establish a UK-wide data and tissue bank supporting future research in MCC
- The aim of the Feasibility Phase is to demonstrate that a sufficient number of eligible patients can be identified and recruited over the course of the randomised trial and to monitor and inform the design of the randomised trial

3.2. Rational Compare Objectives

3.2.1. Primary objective

To determine if radical surgery or radical radiotherapy as first definitive treatment for the primary MCC results in better control of loco-regional disease.

3.2.2. Secondary objectives

To compare between the trial arms:

- Survival with current loco-regional control
- Local, in-field, in-transit and regional nodal treatment failure and distant progression
- Progression free survival
- Overall survival
- Quality of life

3.3. Feasibility Phase Objectives

Using data from patients recruited during the first 3 years:

- To determine whether Rational Compare is likely to deliver on the trial objectives such that the results will influence individual treatment decisions and international clinical practice
- To determine operational adaptations to Rational Compare design to reduce variation between patients and in non-randomised components of the management pathway

3.4. Exploratory Objectives

Using data from all patients in Rational Compare and Rational Review studies:

- To determine the additional value of routine FDG CT-PET at one and two years in identifying recurrence in patients undergoing clinical assessment and symptom-directed imaging
- To identify clinical, pathological and treatment variables associated with good outcome from MCC and select for further investigation variables at presentation as possible prognostic and predictive biomarkers of MCC

3.5. Rational Compare Outcome Measurements

3.5.1. Primary outcome measurement

Time to loco-regional failure: the time to loco-regional failure for all patients is the time from randomisation to loco-regional treatment failure.

Loco-regional failure is defined as macroscopic progressing or recurrent MCC between and including the tumour site and regional nodes during or after initiation of definitive loco-regional treatment. Persistence of macroscopic disease at a treated site such that additional treatment is required also counts as progression.

Loco-regional failure should be confirmed by cytology or histology if possible as standard clinical practice.

3.5.1.1. Patient undergoing radical surgery

For patients undergoing radical surgery, loco-regional failure includes but is not limited to:

- Failure to resect all macroscopic disease
- Macroscopic recurrence after WLE but before adjuvant radiotherapy
- Any pattern that requires additional treatment after surgery to control macroscopic disease at the surgical site.

It does not include demonstration of disease only on pathological examination, such as involved margins on the WLE pathological specimen or detection of microscopic nodal involvement on SLNB, if this is carried out during WLE.

3.5.1.2. Patients undergoing radical radiotherapy

For patients undergoing radical radiotherapy, loco-regional failure includes but is not limited to:

- Recurrence or progression during the radiotherapy course
- Persistence of disease after radiotherapy
- Any pattern that requires additional treatment to control macroscopic disease at the site treated with radiotherapy

It does not include detection of microscopic nodal involvement on SLNB if this was carried out after randomisation but prior to radiotherapy.

3.5.1.3. Additional treatment for local disease

It may occur that patients receive separate treatments for the disease at different sites i.e. the local disease (the primary and adjacent satellites) and regional disease (in transit metastases or regional nodes). If there is a delay between local and regional treatments, documented new disease or increase in disease volume would count as failure whereas the fact that macroscopic disease persisted before treatment was initiated at that specific site would not count as progression.

3.5.2. Secondary Outcome Measurements

- **The proportion of patients alive and free of loco-regional disease:** Alive and free of loco-regional disease means that at a point in time, the results of clinical evaluation and cross-sectional imaging (usually FDG CT-PET) demonstrate no evidence of persistent, recurrent or progressing macroscopic loco-regional disease and the patient is not currently undergoing loco-regional treatment. This measure is irrespective of whether loco-regional failure has been previously demonstrated, as long as prior failure has been treated with current disease remission.
- **Time to local failure (including in-field and in transit metastases):** This is the time from randomisation to macroscopic persistence, progression or recurrence between the primary site and regional nodal basin(s), during or after completion of treatment to the primary. The distance from the centre of the treated tumour to the nearest and furthest recurrence will be recorded to permit evaluation whether recurrence is within the treated field or is an in-transit metastasis. Local progression should be confirmed by histological or cytological examination if possible. Microscopic evidence of MCC without macroscopic disease does not count as local progression (see Primary outcome measurements).

- **Time to regional nodal failure:** This is the time from randomisation to macroscopic regional nodal persistence, progression or recurrence detected radiologically or by clinical evaluation. Regional nodal progression should be confirmed by histological or cytological examination if possible. Microscopic evidence of MCC without macroscopic disease does not count as local progression (see Primary outcome measurements).
- **Time to distant progression:** This is the time from randomisation to clinical or radiological evidence of MCC at a site distant to the regional nodal basin during or after loco-regional treatment.
- **Progression free survival:** This is the time to MCC progression or death or last known alive and free of progression up to 5 years from randomisation.
- **Survival:** This is the time to death or last known alive up to 5 years from randomisation.
- **Quality of life (Rational Compare only):** This is change in longitudinal QoL data as measured by the EuroQoL EQ-5D-5L and EORTC QLQ-C30 questionnaires completed by patients at baseline, before treatment, and at months 3, 6, 9, 12 and 24 from randomisation.

3.6. Feasibility Phase Outcome Measurements

- Number of recruiting sites
- Rate of registration to Rational Review and rate of randomisation to Rational Compare
- Time from randomisation to start of definitive treatment of the primary (WLE or radiotherapy)
- Proportion of randomised patients undergoing the allocated treatment
- Surgical and pathological margin for WLE
- Clinical treatment volume, planned treatment volume, dose and fractionation for definitive radiotherapy
- Proportion undergoing adjuvant radiotherapy post WLE
- Time from randomisation to start of adjuvant treatment of the primary site post WLE
- Proportion of patients at point of randomisation with macroscopic disease (R2) or involved margins (R1) after initial biopsy

3.7. Exploratory Outcome Measurements

3.7.1. Assessment of the additional value of routine cross-sectional imaging including:

- Loco-regional failure and distant progression first detected by routine FDG CT-PET (or CT scan if PET scan unavailable) at 1 and 2 years

3.7.2. Assessment of prognostic and predictive variables for:

- Loco-regional failure-free survival time from date of randomisation (or study entry for patients in Rational Review study)
- The proportion of patients alive and free of loco-regional disease
- Overall survival

4. ELIGIBILITY

4.1. Population

It is intended that all patients newly presenting with histologically proven MCC and who are being considered for radical loco-regional control should be eligible for entry to the Rational MCC trial.

4.2. General Inclusion Criteria for All Patients

1. Patients newly diagnosed with histologically-proven MCC (either primary and/or regional nodal disease)
2. Completion of clinical and radiological staging investigations, including CT imaging (or other modality) of regional nodal basin(s) and major viscera (and SLNB if clinically appropriate) to identify regional and distant metastases
3. No distant metastases beyond the regional nodal basin (i.e. not stage IV disease)
4. Being considered for radical treatment to achieve disease control
5. Able to give valid informed consent
6. Consent for collection of data and tissue samples and follow up
7. Life expectancy six months or greater in relation to general fitness and co-morbidities

4.3. Additional Inclusion Criteria for Rational Compare

1. Patients newly diagnosed with histologically-proven *primary* MCC
2. In the opinion of the SSMDT, the primary MCC can be encompassed both within a wide surgical margin and within a radiotherapy field, and the SSMDT is in equipoise regarding WLE or radiotherapy as first treatment
3. A minimum margin of 1 cm surrounding the MCC achievable by either radiotherapy or surgery
4. Consent for randomisation into Rational Compare

4.4. Exclusion Criteria for Rational Compare

1. The primary MCC has already been treated radically with WLE (surgical margins >10 mm) or radiotherapy
2. Intended use of regional or systemic chemotherapy (including molecularly targeted agents and immunotherapy)

5. SCREENING AND CONSENT

5.1. Record of Potentially Eligible Patients

Investigators will be expected to maintain a Patient Screening/Enrolment Log of all patients presenting with or being treated for MCC across the trial period. This Log will include limited information about the potential candidate (e.g. date of birth and gender), the date and outcome of the screening process (e.g. enrolled into trial, reason for ineligibility, or refused to participate).

5.2. Informed Consent

All patients that appear to meet the general inclusion criteria should be provided with the Rational MCC Summary Patient Information Sheet at the earliest opportunity. This short document explains the purpose of the research and introduces Rational Compare and Rational review, which each have their own, more comprehensive Information Sheets. When appropriate, patients should be given further information in the form of the appropriate Patient Information Sheet for them. Some patients may receive the Information Sheets for both Rational Review and Rational Compare if it is unclear which aspect of the study is suitable for them. It is important to explain to patients that both information sheets contain the same information in Part 2 which covers the additional information applicable to both Rational Compare and Rational Review. If appropriate, the Summary Patient Information Sheet and detailed Patient Information Sheets can be given to patients on the same day. The combination of the Summary Patient Information Sheet and the relevant detailed Patient Information Sheet will allow patients to make an informed decision regarding their participation.

It is the responsibility of the Investigator to obtain written informed consent for each patient prior to performing any trial related procedures. However, investigations to diagnose and stage the MCC are standard of care and should be undertaken as early as possible, in parallel with the process of informing the patient about the trial. Investigators must ensure that they adequately explain to the patient the aims of Rational MCC and the additional samples and scans that will be required. In addition, investigators must explain the trial treatments and anticipated benefits and potential hazards of taking part in Rational Compare pending confirmation that the SSMDT is in equipoise regarding radical radiotherapy versus surgery as definitive treatment for the primary.

The Investigator should stress that the patient is completely free to refuse to take part or withdraw from the trial at any time.

The patient should be given ample time (e.g. 24 hours) to read the Patient Information Sheets and to discuss their participation with others outside of the site research team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

It is anticipated that consent will take place after completion of standard staging investigations and when the SSMDT has determined whether it is in equipoise regarding definitive treatment for the primary MCC. There are two Informed Consent Forms which are specific for Rational Review or Rational Compare. If the patient is eligible and wishes to participate they should provide consent using the appropriate Informed Consent Form. Patients will also have an option to consent to donate additional tissue from previous surgeries, future surgeries and other routine investigations throughout the trial.

The Investigator must then sign and date the form. Once the patient is entered into the trial the patient's trial number should be entered on the Informed Consent Form maintained in the Investigator Site File (ISF). A copy of the Informed Consent Form should be given to the patient, a copy should be filed in the hospital notes, and the original placed in the ISF. In addition, if the patient has given explicit consent, a copy of the signed Informed Consent Form must be sent in the post to the Trial Office for review. Details of the informed consent discussions should be recorded in the patient's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the Patient Information Sheet and Informed Consent Form. Throughout the trial the patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient in which case the process above should be followed and the patient's right to withdraw from the trial respected.

Electronic copies of the Patient Information Sheets and Informed Consent Forms are available from the Trial Office and should be printed or photocopied onto the headed paper of the local institution. Details of all patients approached about the trial should be recorded on the Patient

Screening/Enrolment Log and with the patient's prior consent their General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.

Patients on Rational Compare must be randomised within 2 weeks of consent being provided. Note that if the data required for the Baseline Form is available at the point of consent, the consent process, screening and trial entry can in principle be completed on the same day.

5.3. Screening

Potential patients will be identified via SSMDT meetings.

With the exception of the Quality of Life assessment and the blood sample collection for research, the screening requirements defined in this protocol are standard practice and can therefore be commenced prior to obtaining trial consent.

The Patient Screening/Enrolment Log should be completed for all patients considered for the trial. During the Feasibility Study, the Trial Office will request a copy of the Patient Screening/Enrolment Log on a monthly basis.

5.3.1. Screening Assessments

The Baseline Form will collect the following data from assessments conducted during screening for patients on Rational Review and Rational Compare:

- Details of medical history and clinical examination
- Further details about the primary tumour (where applicable) and any metastases
- Pathological diagnosis of MCC
- MCC staging information including results from cross sectional imaging and SLNB (if performed)
- The SSMDTs assessment of how to treat the patients MCC

In addition the following trial specific activities should be performed:

- **Rational Compare patients only:** Quality of Life assessment (note this should be conducted **both** prior to randomisation and post randomisation before the start of the patients treatment
- Sample collection (can be done at any time prior to the start of treatment and should be scheduled to avoid the need for an additional patient visit)
- Pathological tissue and data collection

Further details about these assessments can be found below.

5.3.1.1. Medical history and clinical examination

The medical history and clinical examination should capture the following details required for the Baseline Form:

- Patient demographics including date of birth, gender and patient initials
- Eastern Cooperative Oncology Group (ECOG) performance status
- Other malignancies within 5 years of trial entry, specifically any occurrence of CLL
- Any auto-immune or chronic inflammatory conditions and anti-inflammatory treatment within 5 years of trial entry
- Known HIV infection (testing not required)
- Any prior organ transplantation
- Current immune suppressive medication or corticosteroids

5.3.1.2. Details about the primary tumour and any metastasis

The following details should be captured for the Baseline Form from information gathered during staging:

- History of the primary tumour:
    - Documented clinical size of MCC primary at first presentation to the SSMDT (longest diameter in mm)
    - Location of primary MCC
    - Nature of prior procedure(s) undertaken at the primary site i.e. excision biopsy (narrow surgical margins <10 mm), incisional biopsy, punch biopsy, WLE (resection

with radical intent, margins >10 mm) or other. For any excision, document surgical margins.

- Current status of primary at trial entry:
  - Whether there is current macroscopic disease at the primary site
  - Current size of primary lesion if present (longest diameter in mm)
- Clinical evidence of metastasis including:
  - Local satellite or in transit metastases (number of loco-regional cutaneous metastases and distance of nearest and furthest from centre of primary in mm)
  - Regional nodal metastases (palpable regional nodes and/or regional nodal involvement apparent on imaging)
  - Distant metastases (cutaneous metastases outside regional nodal basin, palpable lymph nodes outside regional nodal basin, evidence of visceral involvement)

5.3.1.3. Pathological diagnosis

The following details should be captured for the Baseline Form from information gathered prior to study entry:

- Confirmation that MCC has been diagnosed by pathological examination (note that the *primary* lesion must be diagnosed by pathological examination as MCC for patients entering Rational Compare)

5.3.1.4. MCC staging

The following details should be captured for the Baseline Form from information gathered prior to study entry:

- Cross-sectional imaging must have been undertaken including the potential regional nodal basins draining the primary site and common sites of distant metastases such as liver and lungs. If imaging was undertaken more than 8 weeks prior to trial entry, an additional CT scan will be required to obtain current staging data. **N.B. a copy of the baseline scan uploaded to CD will be required after trial entry as a comparator for the review of Protocol mandated imaging (see Section 9.3)**
- If SLNB has been performed the following will be required:
  - Date performed
  - Site examined
  - The result, reported as negative (no microscopic nodal disease identified), positive (microscopic nodal disease identified) or indeterminate.
- Patients should be staged according to the MCC section of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. The diagram in Appendix 1 facilitates collection of data from staging investigations. Please note, if there is evidence of distant metastases or stage IV MCC patients are ineligible for the Rational MCC trial.

5.3.1.5. SSMDT assessment

A record of the prior decisions of the SSMDT is required on the Baseline Form (or combined decisions of radiation oncologist and surgeon or dermatologist)

- Is the SSMDT in equipoise regarding offering either radiotherapy or WLE as first definitive treatment for the primary?
- If the SSMDT is not in equipoise regarding offering either radiotherapy or WLE as first definitive treatment for the primary, what is the planned treatment for the primary MCC?
- Does the SSMDT intend to offer adjuvant radiotherapy at the primary site if allocated WLE?
- Does the SSMDT intend to offer treatment at the regional nodal basin and if so what treatment?
- Does the SSMDT intend to offer SLNB after randomisation during WLE or before definitive radiotherapy?

5.3.2. Quality of life (Rational Compare trial participants only)

Patients who have given consent for participation in Rational Compare should be given the Quality of Life booklet containing the EuroQoL EQ-5D-5L and EORTC QLQ-C30 questionnaires to complete

during screening (before randomisation). The screening Quality of Life booklet should be completed while the patient is in clinic, the patient should not be allowed to take it home with them. The original booklet should be sent to the Rational MCC Trial Office and a copy of the booklet should be kept in the Investigator Site File unless local policy dictates otherwise.

5.3.3. Blood samples

The absolute lymphocyte count from a full blood count taken during screening is required on the Baseline Form.

All patients consenting to the Rational MCC trial should have the following baseline blood samples taken after consent but prior to starting treatment:

- 5 ml of clotted blood collected in a red top tube
- 2 tubes containing ≥4 ml of blood in EDTA collected in a purple top tubes
- 1 tube containing up to 40 ml of blood in lithium heparin and 1 tube containing 7-10 ml of blood in lithium heparin collected in a green top tubes

As the research samples can be taken prior to registration or randomisation (meaning that the patient may not have a Trial Number (TNO) at the point of sample collection) specific paired labels have been provided in the Investigator Site File to be used on screening samples which contain a unique sample identifier. A copy of this label should be attached to each of the sample tubes and another should be affixed to the Patient Identification Log to allow the Trials Unit to match up these samples to the three month samples carrying the patients TNO.

Samples should be dispatched using the Safe-boxes® provided and should be sent along with a Sample Collection Form to the Human Biomaterials Resource Centre (HBRC) by first class post. Further details can be found in Section 9.1 and in the Sample Collection Guidelines in the Investigator Site File.

The clotted blood, one of the EDTA samples and the 40 ml lithium heparin sample will be processed and cryo-preserved using standard methods in the HBRC. The other EDTA sample and the smaller lithium heparin sample will be used for real-time immune profiling. The results of these investigations are not required prior to trial entry or treatment.

5.3.4. Pathological tissue and data collection

Pathological data and tissue collected prior to trial entry should be sent within one month after enrolment onto Rational Compare or Rational Review. The following reports and tissues are required for all patients:

- **An anonymised copy of the pathological report of the initial diagnostic biopsy of the primary lesion including details of:**
  - The type of initial diagnostic biopsy undertaken (excision, incision, punch, core, other)
  - The pathological report of the primary lesion should be reported using the Royal College of Pathologists MCC dataset (34) including size of primary lesion, excision margins, whether primary is invading bone, muscle, fascia or cartilage (if these data are available – depending on type of biopsy)
  - This should include a score for Tumour Infiltrating Lymphocytes (TLS) on a standard section stained with haemotoxylin and eosin (H&E) using conventional definitions as for melanoma i.e. brisk (lymphocytes throughout the tumour) non-brisk (foci of infiltration less than the whole of the tumour) and absent (i.e. no lymphocytes in contact with tumour cells).
- **Anonymised copies of all histological and cytological investigations for suspected MCC**
- **A sample of the primary MCC tissue:**
  - A formalin fixed paraffin embedded block from the biopsy of the primary MCC (which is surplus to requirements) or 15-20 standard sections should be dispatched along with a Tissue Collection Form to the HBRC (see Section 9.2). If this is prior to trial entry a unique screening label should be used to identify the samples.

6. TRIAL ENTRY

Patients will either be randomised onto Rational Compare or registered onto Rational Review.

To register a patient onto Rational Review Investigators or designee should complete a Registration Form. To randomise a patient onto Rational Compare Investigators or designee should complete a Randomisation Form. The individual should then call the Rational MCC Trial Office on:

☎: 0800 371 969

Monday to Friday 9am - 5pm

The name of the Investigator directly responsible for the patient's care will be requested. Investigators must be registered with the Rational MCC Trial Office before they are permitted to register or randomise patients into the trial (see Section 13.1).

All of the information requested on the Registration Form or Randomisation Form should be provided. This will include:

- Name of Site and Investigator
- Patient's initials
- Date of birth
- Date of consent

In addition, with the patient's consent, the following details will be requested over the phone and recorded onto the trial entry system but will not be recorded on the Case Report Form (CRF).

- Patients full name
- National Health Service (NHS) number or in Scotland the Community Health Index (CHI)
- Hospital number

The Investigator will be notified of the patient's TNO immediately on completion of the trial entry process. The TNO will be used to identify the patient and should be recorded on the CRF and questionnaires and on any correspondence with the Rational MCC Trial Office. The TNO should also be documented on the original signed Informed Consent Form filed in the ISF.

The following completed and signed documentation should be sent in the post to the Rational MCC Trial Office as soon as possible after the patient has been recruited into the trial:

- Eligibility Checklist
- Registration Form or Randomisation form
- Screening Quality of Life booklet (Rational Compare patients only)
- A copy of the pathological report

In addition, please send a copy of the Informed Consent Form in the post separately to the above documents as this document contains additional patient identifiers.

The Rational MCC Trial Office will send the investigator formal confirmation of the patient's entry into the trial by fax. Please file this confirmation in the Investigator Site File.

Once a patient has been enrolled into the trial, their name should be added to the Patient Identification Log. The Patient Screening/Enrolment Log should also be updated with the patient's TNO. With the patient's prior consent their GP should be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.

Please ensure that the following are sent as soon as possible after the patient has been recruited into the trial:

- A sample of the primary MCC tissue is sent to the HBRC (see Section 9.2)
- A copy of the baseline scan uploaded to disc is sent to NHS Tayside (see Section 9.3)
- The baseline blood samples are sent to the HBRC prior to the start of treatment if they were not sent during screening (see Section 9.1)

6.1. Randomisation Process

Randomisation will be in a 1:1 ratio and will be performed using a bespoke computer randomisation system developed by the Cancer Research UK Clinical Trials Unit (CRCTU) employing a stratified minimisation method.

Patients will be stratified by:

- Clinical, radiological and pathological stage; stage IA, IB, IIA, IIB, IIIA and IIIB/C
- Intent to undertake adjuvant regional radiotherapy for stage I or II disease; no, yes
- Primary status at randomisation; macroscopic disease, locally excised with or without marginal clearance
- Clinical history of current immunosuppressive illness or treatment; no, yes

Patients will be randomised to one of two treatment groups:

- Arm A – Prioritise Radiotherapy
- Arm B – Prioritise Surgery

The Investigator will be notified of the patient treatment allocation immediately on completion of the randomisation process.

Please note that Rational Compare patients are required to complete a further Quality of Life Booklet post Randomisation in addition to the screening Quality of Life Booklet. This can be completed at any time post trial entry so long as it is prior to the start of treatment.

7. TREATMENT DETAILS

7.1. Timing of Treatment

Trial patients should commence definitive treatment as soon as possible following study entry.

It is intended that patients start definitive treatment within 6 weeks of patients providing consent on both Rational Review and Rational Compare and within 4 weeks after randomisation on Rational Compare.

Variation in the management pathway may be driven by perceived clinical need. If treatment cannot be started within this time then a Protocol Deviation Form should be completed. However, patients treated outside the target times will be still be analysed within the trial on an intention to treat basis and other trial procedures should proceed as per protocol. Time to treatment will be monitored and where necessary discussed between the Rational MCC Trial Office and the site research team.

In eligible patients with macroscopic disease or positive margins, serial local excisions should not be undertaken. Rather the pathway to definitive local treatment, WLE or radiotherapy, should be accelerated.

As per the eligibility criteria, a minimum margin of 1 cm must be achievable by either radiotherapy or surgery in order for a patient to enter Rational Compare. Where this is not possible, patients should be entered into Rational Review.

7.2. Trial treatments

7.2.1. Arm A. Prioritise radiotherapy

Patients allocated to Arm A will receive radiotherapy as their definitive treatment for their MCC. The purpose of radical radiotherapy to the primary site is to treat all MCC with confidence that there is no local residual disease.

If macroscopic tumour is present during screening but the SSMDT was in equipoise between radical surgery and radical radiotherapy as definitive treatment for the primary, local radiotherapy should start without delaying for further surgery.

Radiotherapy planning has to be made on an individual basis depending on tumour size and site (before excision if this was undertaken). This will include a photograph with measured rule and/or a tracing of the disease site (scar or macroscopic lesion) with the Clinical Target Volume (CTV) drawn on the skin.

The CTV is the tumour and/or the pre-excision tumour area plus a margin of 3 cm. The margin size can be smaller than 3 cm according to clinical judgement. In exceptional circumstances the margin can be as little as 1 cm provided the SSMDT remains in equipoise between the use of radical radiotherapy versus radical surgery as first definitive treatment for the primary MCC. Participating centres then need to add an appropriate additional margin to allow for set up and penumbra. The CTV may have to be adjusted to avoid irradiation to a critical adjacent structure.

The CTV depth should be down to the underlying aponeurosis of the muscle or periosteum of bone i.e. down to the underlying fascial plane as seen on the planning CT or felt with clinical palpation. The skin lesion should be treated at the 100% isodose line. Appropriate tissue equivalent bolus should be used to ensure the skin surface dose is at 90% of the prescribed dose. The depth of the invasion should be covered by the 90% isodose line. The 90% depth should be prescribed to at least 1 cm.

The intended treatment dose is 60Gy in 30 fractions over 40 days. Treatment will be in 2Gy per fraction, treating usually daily on consecutive days, excluding weekends. Radiotherapy should be delivered without any treatment breaks. Where a break is unavoidable then missed fractions should be compensated for as per individual centres' protocol for Category 1 patients as defined in the Royal College of Radiologists (RCR) guidelines (41).

The following information should be recorded on the Radiotherapy Form following radiotherapy:

- Details of the planning CT and plan assessment form
- The CTV, using photographs or tracings as source data if feasible and documenting the minimum intended margin on the skin
- Reasons for CTV including margins <2 cm on the skin
- Size/depth of the cutaneous lesion
- Anatomical position of the lesion

- Size/shape of the electron field applied
- Details of any bolus/build up used
- Beam energy
- Depth of 50% isodose
- Extent of the deep margin e.g. down to fascia, inclusion of deep fascia, inclusion of muscle
- Dose and fractionation intended and achieved
- Whether radiotherapy completed as planned
- Modality of radiotherapy used (electrons or photons)
- Whether response was clinically complete – i.e. whether there was progression during treatment or residual macroscopic disease present following radiotherapy

7.2.1.1. Radiotherapy Quality Assurance

Radiotherapy Quality Assurance (QA) for the study has been discussed with the NCRI Radiotherapy Trials QA (RTTQA) Group. The QA requirements are minimal and include the following.

- **Pre-study radiotherapy quality assurance -** Centres must successfully complete the pre-trial QA requirements in order to be approved to enter patients into the Rational MCC study. This will be monitored in-house by the Rational MCC Study Office. The full QA process includes:
    - A facility questionnaire
    - A process document
- **Subsequent RTQA for the Rational MCC Study:**
    - Retrospective case review of the first few patients from each centre
    - Collection of full planning data for all Rational MCC patients
    - A copy of the depth dose/isodose curve may be requested on selected patients
- **Non-compliance -** Non-compliance of radiotherapy aspects for the trial will be highlighted to the Chief Investigator (CI), Clinical Oncology members of the Trial Management Group and local Principal Investigators (PIs). Appropriate action will taken.

Further guidance on radiotherapy is given in Appendix 5.

7.2.2. Arm B – Prioritise surgery

Patients allocated to Arm A will receive surgery as their definitive treatment for their MCC. The purpose of WLE is to achieve complete excision of all MCC with confidence that there is no local residual disease.

Surgical planning has to be made on an individual basis depending on tumour size and site. The recommended minimum surgical margin is ≥2 cm and the aim is to achieve an optimal 3 cm surgical margin. In exceptional clinical circumstances the surgical margin can be as little as 1 cm provided the SSMDT remains in equipoise between the use of radical surgery versus radical radiotherapy as first definitive treatment for the primary MCC.

The depth of excision is to the next clear tissue plane. In most primary MCC of the skin this will be down to the next fascial plane (as in melanoma excision). However in tumours that infiltrate more deeply, the fascial plane will need to be removed to ensure deep clearance.

The following information should be recorded on the Surgery Form following surgery:

- The surgical excision margins, using photographs or tracings as source data if feasible
- Reasons for excisions with surgical margins <2 cm on the skin
- Extent of the deep margin e.g. down to fascia, inclusion of deep fascia, inclusion of muscle
- Speciality and grade of surgeon
- Type of anaesthetic e.g. local or general
- Use of a graft or flap or other repair
- Whether excision was clinically complete – i.e. whether there was residual macroscopic disease present following surgery

A copy of the anonymised pathological report of the WLE is required, reported by the SSMDT pathologist using the Royal College of Pathologists MCC dataset (34). The staining results and minimum lateral and deep pathological margins achieved will be recorded.

Adjuvant radiotherapy to the tumour bed may be offered for patients at the discretion of the SSMDT. Typical indications include:

- Tumour size ≥2 cm
- Involved pathological margins
- Satellite or microsatellite tumour nodules
- Lymphovascular invasion
- Chronic immune suppression
- No potential for further surgical management in event of recurrence

7.2.2.1. Surgical Quality Assurance

A Surgical Review Panel will be formed for the purposes of this trial. The purpose of the group will be to ensure that both trial arms are delivered to a comparable quality. The QA requirements are minimal and include the following.

- **Pre-study surgical quality assurance -** Centres must complete a pre-trial facility questionnaire in order to be approved to enter patients into the Rational MCC study. This will be monitored in-house by the Rational MCC Study Office.
- **Subsequent Surgical QA for the Rational MCC Study:**
  - Retrospective case review of the first few patients from each centre
  - Collection of full planning data for all Rational MCC patients
  - A photograph (plus measure rule) or tracing with the centre of the tumour or biopsy scar marked will be collected for all patients where feasible.
- **Non-compliance -** Non-compliance of surgical aspects for the trial will be highlighted to the Chief Investigator (CI), Clinical Oncology members of the Trial Management Group and local Principal Investigators (PIs). Professional feedback and discussed will be provided where appropriate.

7.2.3. Treatment of the primary MCC for patients in Rational Review

Treatment will be determined by the SSMDT in consultation with the patient. The data as described in Section 7.2.1 and 7.2.2 will be collected.

7.3. Additional Treatment at Clinician and SSMDT Discretion

7.3.1. Postoperative (adjuvant radiotherapy to the Primary Tumour site)

If postoperative (adjuvant radiotherapy) is given, the doses recommended are as follows:

- Clear microscopic surgical margins - 50Gy in 25 fractions over 33 days
- Involved positive resection margins - between 60Gy in 30 fractions over 40 days and 66Gy in 33 fractions over 42 days

7.3.2. Management of regional lymph node basin – all patients

For patients with stage I and II disease it is a matter for the SSMDT to decide whether to offer SLNB. For participants on Rational Review, its use must not delay definitive treatment to the primary. If offered, it is expected that this will be undertaken as part of initial staging investigations upstream of trial participation. For consenting patients, data from SLNB will be collected.

On Rational Compare, SLNB can be deferred until after randomisation if this is in the patient's best interests (e.g. to enable it being performed with WLE if randomised to the Prioritise Surgery arm). On either arm, SLNB must be undertaken without delay so that definitive surgery or radiotherapy to the primary starts within 4 weeks of trial entry. The results must be made available in a timely manner to inform decisions regarding the management of the regional nodal basin. The SSMDT and patient must be willing to accept that SLNB is performed without radical surgical treatment to the primary at the same time if the patient is randomised to the Prioritise Radiotherapy arm.

The SSMDT will determine other aspects the management of the regional lymph nodes including adjuvant nodal irradiation or surgery for clinically staged I and II MCC and definitive irradiation and/or nodal dissection for stage III MCC. The decision to offer nodal treatment (or conditional decisions if SLNB is to be undertaken after randomisation) should be made and documented prior to randomisation.

Where it is decided to offer regional nodal irradiation, the radiotherapy dose fractionation should be given as per individual centre protocols and should be recorded. If regional nodal irradiation is given, the doses recommended are as follows:

- Prophylactic (no lymph node dissection) - 50Gy in 25 fractions over 33 days
- Clinically evident lymphadenopathy - 60Gy in 30 fractions over 40 days

8. SCHEDULE OF EVENTS

Please refer to the Schedule of Events table in the introductory pages.

8.1. Clinical Assessment

Patients will undergo clinical assessment every three months for two years. Clinical assessment should include examination for recurrence at and near the primary site, regional nodal basin, skin distant to the region of the primary and major viscera. In the event of cutaneous recurrence between the treated primary and regional nodal basin, the distance on the skin should be measured from the treated primary to the nearest and farthest recurrence. The 12 month and 24 month clinical assessments must be conducted before the patient has had their routine follow up imaging. Details of the assessment should be captured on the Three Month Clinical Assessment Form

8.2. Clinically Directed Imaging

Appropriate imaging should be conducted whenever treatment failure (i.e. recurrence, persistence or progression of MCC) is suspected as per standard care. The SSMDT should use the most appropriate imaging modality to the clinical question. Suspected recurrence should, whenever possible, be confirmed with cytological or histological examination. The date will be recorded on which it first became clinically or radiologically apparent that there was recurrence, persistence or progression at local, regional of distant sites. Location of recurrence and pathological confirmation will be recorded.

8.3. Protocol Mandated Imaging

Follow up FDG CT-PET imaging of viscera and the regional nodal basin(s) should be performed up to one month following the clinical assessment at 12 and 24 months.

During the feasibility stage of the trial (years 1-3 of recruitment), where FDG CT-PET is not available or is considered clinically inappropriate, follow up imaging may be conducted by CT. Radiology will be assessed locally.

During the feasibility study, the baseline scan and follow up scans should be anonymised then uploaded onto a CD and posted along with an Imaging Form to the Department of Radiology, Ninewells Hospital (see Section 9.3)

8.4. Quality of Life – Rational Compare Only

Patients participating in Rational Compare should be given the Quality of Life booklet containing the EuroQoL EQ-5D-5L and EORTC QLQ-C30 questionnaires to complete. These should be completed prior to the start of treatment and at each of the 3 month follow up assessments. The booklet should be completed while the patient is in clinic, the patient should not be allowed to take it home with them. The booklets should be checked to ensure that all questions have been completed. The original booklet should be sent to the Rational MCC trials office and a copy of the booklet should be kept in the Investigator Site File unless local policy dictates otherwise.

8.5. Haematology

A full blood count should be undertaken at the first three month follow up assessment and the absolute lymphocyte count will be recorded. At all subsequent visits the absolute lymphocyte count will be collected if a routine blood test has been conducted.

8.6. Research Blood Sample

The following samples are required at the first three month follow up visit:

- A 5 ml clotted blood sample collected in a red top tube
- ≥4 ml EDTA sample collected in a purple top tube

Samples should be dispatched using the Safeboxes® provided and should be sent along with a Sample Collection Form to the HBRC by first class post. Further details can be found in Section 9.1 and in the Sample Collection Guidelines in the Investigator Site File.

8.7. Concomitant Medication

A record will be made of any new use of immunosuppressant medication or corticosteroids at each three month follow up assessment.

8.8. Patient Follow-Up

Patients will be followed-up for survival data for a minimum of 2 years from the date of trial entry. This information will continue to be collected until the end of the project. Further data from the applicable Cancer Registry on survival and recurrence status may be sought.

8.8.1. Progression

As soon as definite confirmation has been obtained that a patient has progressed or has developed a new second primary cancer a Progression Form should be completed and returned to the Rational MCC Trial Office.

Patients who relapse or develop a new second primary cancer should remain on follow-up.

8.8.2. Death

As soon as possible following notification that a patient has died a Death Form should be completed and returned to the Rational MCC Trial Office. Every effort should be made to obtain a date and cause of death.

8.9. Patient Withdrawal

Patients may withdraw consent at any time during the study.

For the purposes of this study, three types of withdrawal are defined:

- The patient declines the treatment allocated within the study. The patient will continued to be followed per-protocol and patient data will be analysed on an intention to treat basis
- The patient does not wish to attend study visits in accordance with the schedule of assessments but is willing to have data collected and analysed from any routine assessments undertaken
- The patient declines further data collection and only data collected prior to the withdrawal of consent can be used in the study analysis

All patients, including non-compliant subjects, should be followed up according to the protocol unless they withdraw specific consent. All information and blood/tissue samples collected up until point of retraction will be retained and analysed.

If a patient wishes to withdraw consent for additional samples to be collected, the patient should continue in the main trial, but no more additional samples will be collected for that patient from the date of retraction.

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data. A Withdrawal of Consent Form should be completed to notify the Rational MCC Study Office of the patient's withdrawal.

9. SAMPLE COLLECTION

9.1. Blood Samples

9.1.1. Sample collection

Blood samples should be collected prior to the start of treatment (baseline samples) and at the first three monthly assessment (three month samples).

The baseline samples consist of:

- 5 ml of clotted blood collected in a red top tube
- 2 tubes containing ≥4 ml of blood in EDTA collected in a purple top tubes
- 1 tube containing up to 40 ml of blood in lithium heparin and 1 tube containing 7-10 ml of blood in lithium heparin collected in a green top tubes

The three month samples consist of:

- A 5 ml clotted blood sample collected in a red top tube
- ≥4 ml EDTA sample collected in a purple top tube

Samples should be clearly labelled using the labels provided with the patients TNO entered on the label (or a unique screening label prior to TNO allocation). For further details please see the Sample Collection Guidelines in the Investigator Site File.

9.1.2. Sample dispatch

Blood samples should be dispatched using the Safe-boxes® provided and sent along with a Sample Collection Form to:

Dr Jane Steele (Rational MCC Trial)
Human Biomaterials Resource Centre
C/O Institute of Biomedical Research Stores
Hospital Drive
University of Birmingham
Edgbaston
Birmingham B15 2TT

A copy of the Sample Collection Form should be stored in the Investigator Site File and a copy should be sent to the Rational MCC Trials Office. Address labels for the HBRC are provided in the Investigator Site File.

9.1.3. Analysis of immune profile

Investigations are carried out in real-time in the department of Immunology, University Hospital Birmingham NHS Foundation Trust (UHBFT). Standardised flow cytometry of a fresh 4 ml EDTA whole blood sample will be used to provide true counts of circulating immune cells. Functional immune status will be assessed using a 7-10 ml lithium heparin blood sample, characterising the proliferation and cytokine release profile of immune cells in response to standardised stimuli. Results of investigations are not required prior to treatment.

9.2. Pathology

9.2.1. Collection and dispatch of samples

A formalin fixed paraffin embedded block from the biopsy of the primary MCC (which is surplus to requirements) or 15-20 standard sections should be collected for translational research, dispatched using the Safe-boxes® provided and sent along with a Sample Collection Form to:

Dr Jane Steele (Rational MCC Trial)
Human Biomaterials Resource Centre
C/O Institute of Biomedical Research Stores
Hospital Drive
University of Birmingham
Edgbaston
Birmingham B15 2TT

A copy of the Sample Collection Form should be stored in the Investigator Site File and a copy should be sent to the Rational MCC Trials Office. Address labels for the HBRC are provided in the Investigator Site File.

Please be aware that it will be the responsibility of the local site research team to obtain their patient's pathology material if the material is stored at a separate site to the randomising or registering hospital.

It is appreciated that in some instances there may insufficient diagnostic material available for research purposes. If the local pathology team are concerned that there is insufficient tissue available for research, this should be communicated to the Rational MCC Trial Office.

A copy of the associated pathology report will be requested for each patient, this should be anonymised to contain only the patient's unique Rational MCC TNO and returned to the Trial Office.

For further details please see the Sample Collection Guidelines in the Investigator Site File.

9.2.2. Analysis of pathology samples

Nucleic acid will be extracted from the tissue supplied from the biopsy of the primary MCC. Genetic testing will include but is not limited to detecting the presence or absence of MCPyV genomes.

Intra-tumoural infiltration by CD3+ and CD8+ T lymphocytes will be assessed using sections stained by standard immunohistochemistry methods viewed under bright light in the UHBFT pathology department and HBRC. Using digital imaging and automated measurement, CD3+ and CD8+ cells will be counted in the central tumour and at the invasive margin. The trial pathologist will validate cell type, cell location and cell counts performed by digital pathology.

9.3. Central Review of Imaging

For patients recruited within the feasibility stage of the trial (first three years of recruitment), the baseline scan and follow up scans should be anonymised then uploaded onto a CD and posted along with an Imaging Form to:

Dr Ian Zealley
Department of Radiology
Level 6
Ninewells Hospital
Dundee
DD1 9SY

A copy of the Imaging Form should be should be taken and filed in the Investigator Site File and a copy should be sent to the Rational MCC Trial Office.

The uploaded scans will be used to retrospectively evaluate the value of the protocol mandated imaging in detecting recurrence.

10. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the Research Governance Framework for Health and Social Care and the requirements of the National Research Ethics Service (NRES). Definitions of different types of AE are listed in Appendix 2. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the protocol.

10.1. Reporting Requirements

10.1.1. Adverse Events

AEs (see Appendix 2 for definition) are commonly encountered in patients receiving cancer treatment. All AEs experienced by the patient should be recorded in the patient notes. However, these will not be collected by the Rational MCC Trial Office.

10.1.2. Serious Adverse Events

Investigators should report AEs that meet the definition of a Serious Adverse Events (SAE) (see Appendix 2 for definition) following the expedited process set out in Section 10.2. Expected SAEs are excluded from the expedited reporting process and should be recorded on the relevant Treatment CRF. These expected SAEs are set out in the following section.

10.1.2.1. Expected Serious Adverse Events

Patients receiving surgery or radiotherapy may require admission to hospital for appropriate medical intervention following development of some of the more severe known side effects of treatment.

For the purpose of study, the following are regarded as expected SAEs:

Following surgery:

- Admissions for treatment of the following side effects at the site of wide local excision unless the condition is life threatening or proves fatal:
    - Wound separation
    - Seroma
    - Haematoma / bleeding
    - Infection
    - Skin graft failure
    - Flap necrosis
- Admissions to control or treat the following systemic events directly relating to the patients surgery unless the condition is life threatening or proves fatal:
    - Deep vein thrombosis (DVT)
    - Infections

Following radiotherapy:

- Admissions for treatment of the following side effects at the site of radiotherapy that are thought to have occurred as a result of the radiotherapy to the primary within 4 weeks of completing treatment unless the condition is life threatening or proves fatal:
    - Mucositis
    - Skin reaction
    - Dysphagia
    - Pain

This is not an exclusive list and if there is any doubt whether toxicity is expected or not then an SAE Form should be completed.

10.1.2.2. Monitoring pregnancies for potential Serious Adverse Events

For patients receiving radiotherapy to a site on the body which may adversely affect an unborn child, it is important to monitor the outcome of pregnancies in order to provide SAE data on congenital anomalies or birth defects.

In the event that such a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the Rational MCC Trial Office as soon as possible. If it is the patient who is pregnant provide outcome data on a follow-up Pregnancy Notification Form. Where the patient's partner is pregnant consent

must first be obtained and the patient should be given a Release of Medical Information Form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the Release of Medical Information Form. Once consent has been obtained provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form. If appropriate also complete an SAE Form as detailed below.

10.1.3. Reporting period

Details of all SAEs (except those listed above) will be documented and reported from commencement of the treatment of the primary until 28 days after the last protocol-defined treatment. Any SAEs that are thought to be possibly related to the protocol defined treatment should still be reported after this period.

10.2. Reporting Procedure

10.2.1. Site

10.2.1.1. Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in the ISF.

AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 10.1 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the Rational MCC Trial Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form with a SAE Fax Cover Sheet to:

☎: 0121 414 8392 or 0121 414 3700

On receipt, the Rational MCC Trial Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the Rational MCC Trial Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the Rational MCC Trial Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Rational MCC Trial Office in the post and a copy kept in the ISF. Investigators should also report SAEs to their own Trust in accordance with local practice.

10.2.1.2. Provision of follow up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

10.2.2. Rational MCC Trial Office

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial treatment will be regarded as a related SAE. The Clinical Coordinator will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

10.2.3. Reporting to the main Research Ethics Committee

10.2.3.1. Unexpected and Related Serious Adverse Events

The Rational MCC Trial Office will report all events categorised as Unexpected and Related SAEs to the main Research Ethics Committee (REC) within 15 days.

10.2.3.2. Other safety issues identified during course of the trial

The main REC will be notified immediately if a significant safety issue is identified during the course of the trial.

10.2.4. Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

10.2.5. Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

11. DATA HANDLING AND RECORD KEEPING

11.1. Data Collection

The CRF will comprise the following forms:

Form	Summary of data recorded	Schedule for submission
Eligibility	Confirmation of eligibility and satisfactory staging investigations where necessary	Faxed at point of trial entry
Randomisation	Completed for patients on Rational Compare; patient details; details of stratification variables; optional consent issues	As soon as possible after randomisation
Registration	Completed for patients on Rational Review; patient details; optional consent issues	As soon as possible after registration
Radiotherapy	Details of planning CT, size/depth of the cutaneous lesion, anatomical position of the lesion, size/shape of the electron field applied, details of any bolus/build up used, beam energy, depth of 50% isodose	As soon as possible after trial entry
Surgery	Minimum and maximum size of surgical margin on the skin, tissue layer of deep surgical margin, surgical assessment of completeness of excision.	As soon as possible after trial entry
Baseline	Demographics, history, examination, diagnostic and pathology, radiological staging, SLNB, ALC, treatment intentions	Within 1 month of trial entry
3 Month Clinical Assessment	Results current examination and date and site of progressive, persistent or recurrent disease, examination findings, whether confirmed pathologically, any treatment given since last assessment	Within 1 month of assessment
Progression	Details of local and distant progression and new primary cancers	Immediately on discovery that a patient has progressed
Imaging	Date of scan, scanner site, scanner manufacturer, number of detector slices 16/64/128/256/other (please specify), intravenous contrast type, intravenous contrast strength, intravenous contrast volume	Sent along with CD containing uploaded imaging
Death	Date and cause of death	Immediately upon notification of patient's death
Deviation	Completed in the event of a deviation from the protocol	Immediately upon discovering deviation
Withdrawal	Completed in the event of patient withdrawal from the trial	Immediately upon patient withdrawal
Serious Adverse Event	See Section 10	Immediately on discovering that the patient has experienced an SAE
Pregnancy Notification	See Section 10	As soon as possible on discovering that the patient or their partner are pregnant

11.1.1. CRF completion guidance

The CRF must be completed, signed and dated and returned to the Rational MCC Trial Office by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe listed above. The exceptions to this are the SAE Form and Withdrawal Form which must be co-signed by the Investigator.

Entries on the CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

Quality of Life data will not be captured in the source data, it will be recorded directly onto the CRF.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The completed originals should be sent to the Rational MCC Trial Office and a copy filed in the Investigator Site File.

Trial forms may be amended by the Rational MCC Trial Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

11.2. Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years after the end of the trial. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.

12. QUALITY MANAGEMENT

12.1. Site Set-Up and Initiation

All sites will be required to sign a Clinical Trial Site Agreement prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements e.g. registration forms and supply a current CV to the Rational MCC Trial Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the Rational MCC Trial Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Rational MCC Trial Office must be informed immediately of any change in the site research team.

12.2. On-Site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the Rational MCC Quality Management Plan. Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the Rational MCC Trial Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the Rational MCC trial staff access to source documents as requested.

12.3. Central Monitoring

Where a patient has given explicit consent sites are requested to send in copies of signed Informed Consent Forms for in-house review.

Rational MCC Trial staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Rational MCC Trial staff will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or Good Clinical Practice (GCP), and/or poor recruitment. Any major problems identified during monitoring may be reported to Trial Management Group and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the main REC.

12.4. Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the Rational MCC Trial Office of any Medicines & Healthcare products Regulatory Agency (MHRA) inspections.

12.5. Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

Sites are therefore requested to notify the Rational MCC Trial Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Rational MCC Trial Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Rational

MCC Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

13. END OF TRIAL DEFINITION

The end of trial will be 6 months after the last data capture. The Rational MCC Trial Office will notify the main REC that the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.

14. STATISTICAL CONSIDERATIONS

14.1. Definition of Outcome Measures

See Section 3.5.

14.2. Determination of Sample Size

Using conventional frequentist statistics, we estimate that a sample size of nearly 3000 patients would be required to falsify the null hypothesis that neither arm out-performs the other with conventional error rates using a two-sided log-rank test, assuming an event rate of 20% at 2 years (i.e. proportion of patients free of loco-regional failure at 80% at 2 years) and that the true hazard ratio (HR) for loco-regional progression for one arm compared to the other is 0.8 (power 80%, significance 5%). This sample size is not feasible, even with international collaboration.

Table 1: Scenarios used to assess the posterior probability that a treatment is truly much better (true HR<0.8), or better (true HR<1), or worse (true HR>1.2) based on different observed HR, with different number of events and sample sizes, using a non-informative prior.

Total sample size		**100**			**150**			**200**			**250**		
Number of 2-year loco-regional failure events		**20**			**30**			**40**			**50**		
Observed HR		**0.6**	**0.8**	**1.0**	**0.6**	**0.8**	**1.0**	**0.6**	**0.8**	**1.0**	**0.6**	**0.8**	**1.0**
Posterior probability (%) that the true HR is:	**<0.8**	74	50	31	78	50	27	82	50	24	85	50	22
	<1.0	87	69	50	92	73	50	95	76	50	96	79	50
	>1.2	6	18	34	3	13	31	1	10	28	0.7	8	26

The scenarios in Table 1 indicate that if 50 events were observed (with estimated sample size of 250), an observed HR of 0.8 for loco-regional failure comparing the two treatments will inform the clinician that there is a 79% probability that the superior treatment is truly better, a 50% probability that the superior treatment is a much better intervention (true HR<0.8) and only 8% probability of that the treatment is a much worse intervention (true HR>1.2). The SSMDT and patient will be able use these probabilities to make a rational individualised therapeutic decision, alongside the patient's preferences and data on the QoL impact of the two treatments.

Table 1 also shows that even a smaller sample size, for example 150 patients (with 30 events), can still inform decision making for an individual patient, accepting a greater level of uncertainty. An observed HR of 0.8 would still mean a nearly 75% chance that the treatment is truly better, and a less than one in seven chance that it is truly much worse. Of course, if the observed effect size is larger, for example an HR=0.6, there is greater certainty regarding the better treatment, even at lower sample sizes.

In considering the use of the trial in guideline development and in making policy decisions, we should be aware of the limitations of sample size. We can use a decision criterion to aid us in making a decision on the level of certainty required to determine if one treatment is indeed superior to the other. This will be based on the Bayesian posterior probability given the observed data from the trial, $P(HR<\eta^*/ \text{data}) > \pi^*$, where η^* is the upper limit and π^* is the cut-off of the lower level of certainty. The design parameters η^* and π^* will be calibrated on the basis of the operating characteristics of the trial design (and the ease of clinical interpretation), which will be examined in simulation studies. A preliminary simulation of 100,000 replications with $\eta^*=1$, $\pi^*=0.7$ and number of events=50 gives a 77% chance of making a right decision that one treatment is superior than the other when true HR=0.7, and a 30% of incorrectly concluding a treatment is superior when it is not (true HR=1). If an arm is truly very inferior (true HR=1.3), there will be a 7% chance of incorrectly concluding that it is superior.

14.3. Analysis of Outcome Measures

14.3.1. Time-to-events outcomes

Time to event outcomes will be analysed using the Kaplan Meier method. Life tables and plots will be produced. Time to event estimates at 1- and 2-years and, if appropriate, median times will be presented with 95% confidence intervals for each treatment arm and overall, for the primary outcome and other time-to-event outcomes. Cox regression analysis adjusted by the stratification factors will be performed. The observed HR for loco-regional failure, obtained from the Cox model, will be calculated and probabilities for various values of true HR estimated. These will be presented in the context of clear clinical guidance regarding their use in making both policy and individualised treatment decisions.

If there are substantial number of patients who experience a competing risk (e.g. death) without experiencing the outcome of interest (e.g. loco-regional failure), additional competing risk analyses will be conducted to demonstrate that the results are not biased.

14.3.2. Rate outcomes

Rate outcomes will be presented as a numerator (number of events) and a denominator (number of subjects), and as a percentage, for each treatment arm and overall. Confidence intervals will be presented using the Wilson method. To compare the rates between the arms, odds ratios will be presented with confidence intervals.

14.3.3. Quality of life

Data from questionnaires will be used to compare the different impacts of the randomised interventions on QoL. EQ-5D-5L consists of 5 brief questions which provide a simple descriptive profile describing the overall health status of a patient and a single index value for the QoL of the patients. EORTC-QLQ-C30 is a questionnaire developed to assess the QoL of cancer patients. In particular, the Global Health Status Score (GHSS) derived from it provides a descriptive measure of QoL ranging from 0 (the worst score) to 100 (the best score).

An initial report documenting baseline QoL and changes in QoL during and following treatment for all patients contributing to the trial and registration trial will be prepared following the feasibility phase of the project.

Following completion of the trial, the changes in QoL across the period following treatment will be compared between the treatment arms. To model the trend in QoL over time, a linear mixed effects model (taking into account within subject correlation) using linear and quadratic polynomials and more flexible semi-parametric models such as cubic splines, will be considered. Goodness of fit tests will be used to compare the different models. The aim is to obtain the most parsimonious trend of quality of life by considering simple parametric forms (if possible) to facilitate understanding, interpretation and use of the model by clinicians. We will evaluate if QoL changes over time and, if so, what is the pattern of change, as well as if the pattern differs between arm A and B. If the death rate is high (which will result in missing QoL data that are not missing at random and not ignorable), we will assess changes in QoL, taking into account non-random dropout of death (using joint modelling techniques).

14.3.4. Rationale for the analysis of stratification factors

The stratification factors have been chosen because we believe they will affect patient outcomes. Each stratification factor will be summarised and presented by treatment arm.

14.3.5. Operational adaptation of the trial following the Feasibility Phase (year 3)

The decision to adapt the design or develop early stopping rules for the expanded cohort to restrict variations in the non-randomised components of the treatment pathway will be undertaken in consultation with the DMC, informed by data from the feasibility phase: i.e.

- Whether patients with macroscopic disease (R2) or involved margins (R1) after initial biopsy at point of randomisation are a clinically important proportion (>20%) of participants.
- For randomised patients with R1 and R2 primary MCC, whether randomised treatments were delivered per protocol and comparing the time to loco-regional progression between arms, specifically seeking a strong signal that “prioritise radiotherapy” might be inferior to “prioritise surgery”.

- For patients randomised to “prioritise surgery”, whether analysis of time to loco-regional failure offers an early strong signal that WLE without adjuvant radiotherapy to the tumour bed is disadvantageous compared to WLE with adjuvant radiotherapy.
- For all patients, the development of recommendations on the consistent use of SLNB and adjuvant regional nodal irradiation for patients presenting with stage I and II MCC but varying in other parameters, so as to reduce heterogeneity in downstream treatment pathways
- Whether there is a signal that laboratory measurements of immune competence associate with outcome justifying continuing undertaking these real-time measurements in the extended phase of the trial, investigating for interaction with treatment allocation.

Whether there is a signal that laboratory measurements of tumour viral status and intra-tumoural infiltration by CD8+ cells associate with outcome, justifying seeking new research funding to analyse these factors using banked samples from the extended phase of the trial.

14.4. Planned Interim Analysis

The purpose of the initial three year feasibility phase of the randomised trial is to decide whether extending the trial to a total of five years accrual will permit the trial to deliver on its primary and secondary objectives and to determine operational adaptations to reduce the variation in the non-randomised components of the treatment pathway. Simulations will be conducted to evaluate the performance of the resultant adaptive design with potential multiple adaptations at the planning stage.

The feasibility phase and registration study offer an opportunity to measure the proportion of recurrences first detected by FDG-PET imaging at 12 and 24 months in the context of a standard follow-up policy comprising 3-monthly clinical review driving imaging.

14.5. Planned Final Analysis

The first main analysis is planned after 5-years’ accrual and 2-years’ follow-up and a projected sample size >150 patients.

14.5.1. Analysis for factors associated with loco-regional failure, distant metastases and death

This project will result in prospective data from a cohort of patients with primary MCC from Rational Review and Rational Compare: 70-120 patients if the trial closes at the end of the feasibility phase and potentially ≥250 patients if the trial accrues over 5 years. The data will include baseline demographics, staging, immune suppression including CLL, immune suppression at start of treatment based on standard immune assays, components of the pathology dataset in the primary, the viral status of the primary tumour, the presence of intra-tumoural CD8+ cells and treatment of the primary and nodal basin. These markers will be investigated for their prognostic potential and we will explore any possible explanatory role in variation in the efficacy of the randomised interventions.

Analysis will include univariate (log rank test) and, if appropriate (based on number of events per parameter), multivariable (Cox regression) methods. Interpretations based on sample sizes are given in Table 2. Hence, with our planned sample size, it is likely that only important prognostic biomarkers – i.e. ones that provide substantial discrimination in outcome and are present in a reasonable proportion of patients – will be reliably detected; others that appear promising, but do not reach conventional significance, will be prioritised for further validation (while always bearing in mind the likelihood of false positive results with multiple testing).

Table 2: Sample sizes required (alpha=0.05 and power=0.80) to detect differences in event rates for different levels of biomarker presence using a two-sided log rank test, with accrual period of 5 years and follow-up period of 2 years

Sample size		Biomarker expression ratio		
		10-90	25-75	50-50
Clinical event rate by presence versus absence of biomarker at 2 years	10% versus 20%	631	292	203
	5% versus 25%	180	82	54

14.6. Planned Sub-Group Analyses

At the final analysis, we will undertake analyses of the primary outcome, and some of the secondary outcomes, by patient subgroups. Naturally, the levels of the stratification variables will yield subgroups. The definition of subgroups could depend on:

- History of immunosuppressive illness / treatment
- Clinical, radiological and pathological stage (stage IA, IB, IIA, IIB, IIIA and IIIB/C)
- Intent to undertake adjuvant regional radiotherapy for stage I or II disease
- Primary status at randomisation (macroscopic disease, locally excised with or without marginal clearance)
- Lymphocyte count
- Intra-tumoural infiltration by CD3+ and CD8+ T lymphocytes
- Primary treatment
- Other factors

Target trial accrual is not powered for subgroup analyses.

14.7. Stopping Rules

The trial will be reviewed against pre-set targets at four stop/go decision points which the Trial Management Group (TMG), Trial Steering Committee (TSC) and DMC will consider. A summary of the targets that we are required to achieve are include in the table below:

Time-point	Metric
12 months	5 eligible patients identified
18 months	At least 10 centres active
	At least 10 patients registered
24 months	At least 20 patient randomised
30 months	At least 40 patients randomised
	A monthly randomisation accrual rate of >3/month
	Definitive treatment routinely started within 4 weeks of randomisation in both arms
	Suitable margin sizes routinely achieved in both arms

15. TRIAL ORGANISATIONAL STRUCTURE

15.1. Sponsor

The trial is sponsored by the University of Birmingham.

15.2. Coordinating Centre

The trial is being conducted under the auspices of the CRCTU, University of Birmingham according to their local procedures.

15.3. Trial Management Group

The TMG will consist of the Chief Investigator, the Clinical Co-Investigators, the Lead Statistician, the Trial Statistician, the Trial Coordinator and the Trial Management Team Leader. Key personnel will be invited to join the TMG as appropriate to ensure representation from a range of professional groups. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will be responsible for the day-to-day running and management of the trial. The TMG will meet by teleconference or in person every three months.

15.4. Trial Steering Committee

A TSC, with an independent chair, will provide overall supervision for the trial and provide advice through its independent chair. The TSC will consist of independent members with relevant clinical expertise, patient representatives, Efficacy and Mechanism Evaluation (EME) programme observers, the Chief Investigator (CI), Lead Statistician, Trial Statistician and other key members of the TMG and provide independent oversight for the trial and review recruitment and trial progress. The ultimate decision for the continuation of the trial lies with the TSC. The TSC will meet 6 months, 18 months and 36 months post obtaining REC approval, and annually thereafter.

15.5. Data Monitoring Committee

Data analyses will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. During the recruitment phase of the trial the DMC is scheduled to meet approximately one month prior to the TSC. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TMG who will convey the findings of the DMC to Trial Steering Committee, funders, and sponsors. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety. The trial would also stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community.

15.6. Finance

This is a clinician-initiated and clinician-led trial funded by the Medical Research Council (MRC) via the EME Programme.

The Sponsor will pay Research Costs, as defined in the Clinical Site Agreement, to participating sites.

The trial has been adopted by the National Institute for Health Research (NIHR) Cancer Research Network Portfolio.

16. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th World Medical Association (WMA) General Assembly, Somerset West, Republic of South Africa, 1996.
(website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Data Protection Act 1998 and Human Tissue Act 2008") and GCP. The protocol will be submitted to and approved by the main REC prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain written confirmation of local R&D approval. Sites will not be permitted to enrol patients until confirmation of R&D approval is received by the Rational MCC Trial Office and written confirmation from the Trial Office confirms that recruitment may commence.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

17. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998. With the patient's consent, their full name, date of birth, hospital number and NHS number, or in Scotland the CHI, will be collected at trial entry to allow tracing through the Cancer Registries and the NHS Information Centre for Health and Social Care (service formally provided by the Office of National Statistics) and to assist with long-term follow-up via other health care professionals (e.g. patient's GP). Patients will be identified using only their unique trial number (TNO), initials, and date of birth on the Case Report Form and correspondence between the Rational MCC Trial Office and the participating site. However patients are asked to give permission for the Rational MCC Trial Office to be sent a copy of their signed Informed Consent Form which will not be anonymised. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to the Rational MCC Trial Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The Rational MCC Trial Office will maintain the confidentiality of all patient's data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer (e.g. Cancer Registries, laboratory staff). Representatives of the Rational MCC trial team may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

18. INSURANCE AND IDEMNITY

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

19. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the TMG and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham. Intellectual property rights will be addressed in the Clinical Trial Site Agreement between Sponsor and site.

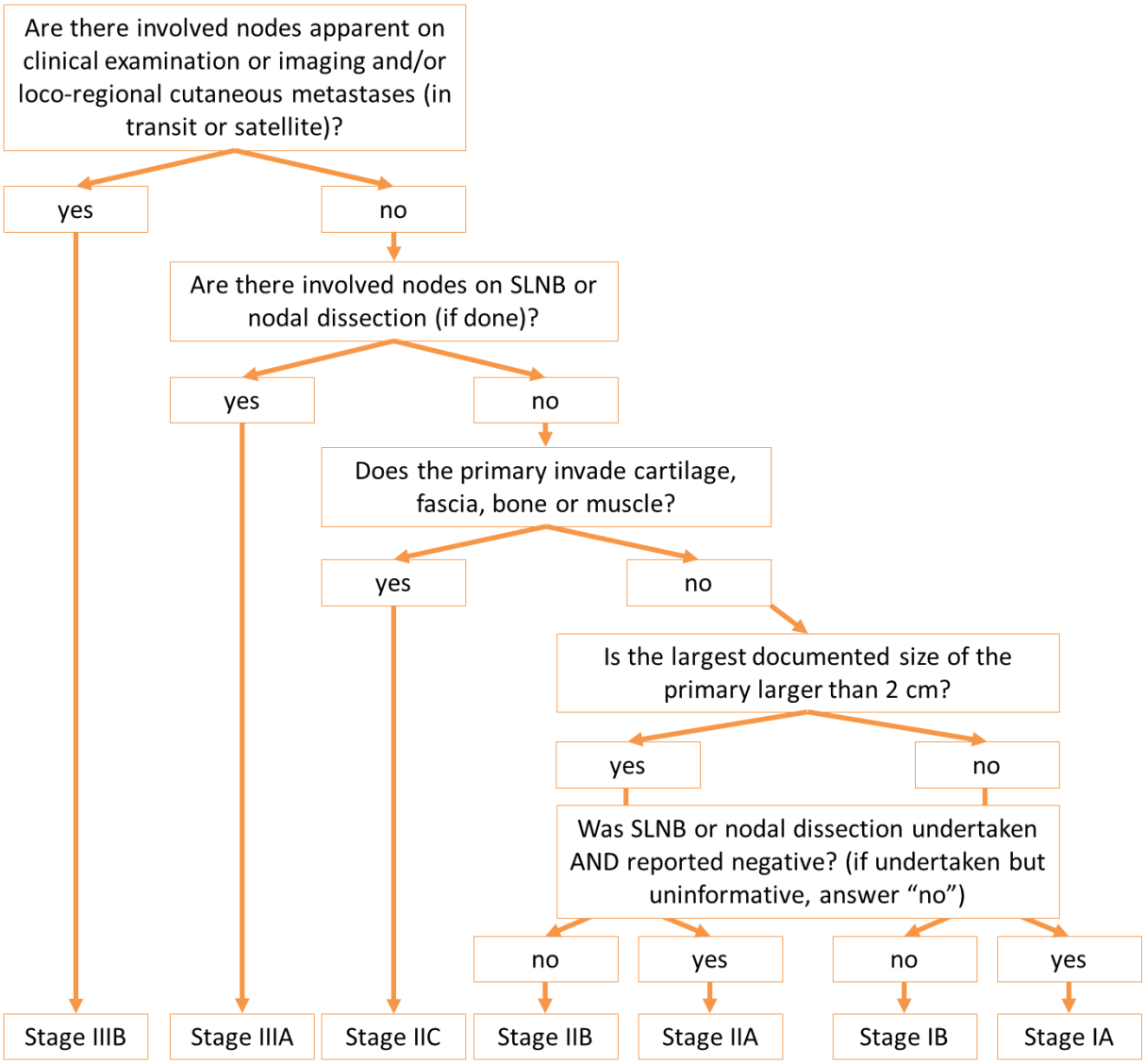
20. REFERENCES

1. Lemos BD, Storer BE, Iyer JG, Phillips JL, Bichakjian CK, Fang LC, et al. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. J Am Acad Dermatol. 2010;63(5):751-61.
2. Rare skin cancer in England: National Cancer Intelligence Network; 2011. Available from: http://www.ncin.org.uk/publications/data_briefings/rareskincancer.
3. Ma JE, Brewer JD. Merkel cell carcinoma in immunosuppressed patients. Cancers. 2014;6(3):1328-50.
4. Koljonen V, Kukko H, Pukkala E, Sankila R, Bohling T, Tukiainen E, et al. Chronic lymphocytic leukaemia patients have a high risk of Merkel-cell polyomavirus DNA-positive Merkel-cell carcinoma. British journal of cancer. 2009;101(8):1444-7.
5. Penn I, First MR. Merkel's cell carcinoma in organ recipients: report of 41 cases. Transplantation. 1999;68(11):1717-21.
6. Engels EA, Frisch M, Goedert JJ, Biggar RJ, Miller RW. Merkel cell carcinoma and HIV infection. Lancet. 2002;359(9305):497-8.
7. Hemminki K, Liu X, Ji J, Sundquist J, Sundquist K. Kaposi sarcoma and Merkel cell carcinoma after autoimmune disease. International journal of cancer Journal international du cancer. 2012;131(3):E326-8.
8. Asgari MM, Sokil MM, Warton EM, Iyer J, Paulson KG, Nghiem P. Effect of host, tumor, diagnostic, and treatment variables on outcomes in a large cohort with Merkel cell carcinoma. JAMA dermatology. 2014;150(7):716-23.
9. Fields RC, Busam KJ, Chou JF, Panageas KS, Pulitzer MP, Allen PJ, et al. Recurrence after complete resection and selective use of adjuvant therapy for stage I through III Merkel cell carcinoma. Cancer. 2012;118(13):3311-20.
10. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science. 2008;319(5866):1096-100.
11. Chang Y, Moore PS. Merkel cell carcinoma: a virus-induced human cancer. Annu Rev Pathol. 2012;7:123-44.
12. Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. J Clin Oncol. 2005;23(10):2300-9.
13. Samuel RJ, Matthews AG, Holme SA. Merkel Cell Carcinoma in Scotland 2000-2010. The British journal of dermatology. 2015.
14. Jackson PC, Wallis K, Allgar V, Lind MJ, Stanley PR. Merkel cell carcinoma in East Yorkshire: A case series and literature review of current management. Journal of plastic, reconstructive & aesthetic surgery : JPRAS. 2015;68(5):667-72.
15. Blythe JN, Macpherson D, Reuther WJ, Ethunandan M, Ilankovan V, Sharma S, et al. Management of early stage cutaneous Merkel cell carcinoma of the head and neck. The British journal of oral & maxillofacial surgery. 2014;52(9):806-9.
16. Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. Arch Dermatol. 2006;142(6):693-700.
17. Ghadjar P, Kaanders JH, Poortmans P, Zaucha R, Krengli M, Lagrange JL, et al. The essential role of radiotherapy in the treatment of Merkel cell carcinoma: a study from the Rare Cancer Network. Int J Radiat Oncol Biol Phys. 2011;81(4):e583-91.
18. Parvathaneni U, Iyer J, Nagase K, Parvathaneni K, Nghiem P. The safety and efficacy of primary radiation therapy without upfront surgery for Merkel cell carcinoma. International Journal of Radiation Oncology, Biology, Physics. 2012;84(3 Suppl 1):S168.
19. Pape E, Rezvoy N, Penel N, Salleron J, Martinot V, Guerreschi P, et al. Radiotherapy alone for Merkel cell carcinoma: a comparative and retrospective study of 25 patients. J Am Acad Dermatol. 2011;65(5):983-90.
20. Sundaresan P, Hruby G, Hamilton A, Hong A, Boyer M, Chatfield M, et al. Definitive radiotherapy or chemoradiotherapy in the treatment of Merkel cell carcinoma. Clin Oncol (R Coll Radiol). 2012;24(9):e131-6.
21. Veness M, Foote M, Gebski V, Poulsen M. The role of radiotherapy alone in patients with merkel cell carcinoma: reporting the Australian experience of 43 patients. Int J Radiat Oncol Biol Phys. 2010;78(3):703-9.
22. Veness M, Howle J. Radiotherapy alone in patients with Merkel cell carcinoma: the Westmead Hospital experience of 41 patients. The Australasian journal of dermatology. 2015;56(1):19-24.
23. Harrington C, Kwan W. Outcomes of Merkel cell carcinoma treated with radiotherapy without radical surgical excision. Annals of surgical oncology. 2014;21(11):3401-5.

24. Jouary T, Leyral C, Dreno B, Doussau A, Sassolas B, Beylot-Barry M, et al. Adjuvant prophylactic regional radiotherapy versus observation in stage I Merkel cell carcinoma: a multicentric prospective randomized study. Ann Oncol. 2012;23(4):1074-80.
25. Senchenkov A, Barnes SA, Moran SL. Predictors of survival and recurrence in the surgical treatment of merkel cell carcinoma of the extremities. J Surg Oncol. 2007;95(3):229-34.
26. Tsang G, O'Brien P, Robertson R, Hamilton C, Wratten C, Denham J. All delays before radiotherapy risk progression of Merkel cell carcinoma. Australas Radiol. 2004;48(3):371-5.
27. NCCN Clinical Practice Guidelines in Oncology: Merkel Cell Carcinoma v.1.2009. National Comprehensive Cancer Network; 2009.
28. Kachare SD, Wong JH, Vohra NA, Zervos EE, Fitzgerald TL. Sentinel lymph node biopsy is associated with improved survival in Merkel cell carcinoma. Annals of surgical oncology. 2014;21(5):1624-30.
29. Fields RC, Busam KJ, Chou JF, Panageas KS, Pulitzer MP, Kraus DH, et al. Recurrence and survival in patients undergoing sentinel lymph node biopsy for merkel cell carcinoma: analysis of 153 patients from a single institution. Annals of surgical oncology. 2011;18(9):2529-37.
30. Sadeghi R. Importance of sentinel node mapping in Merkel cell carcinoma: important new evidence by Tseng et al. American journal of surgery. 2015;209(6):1111.
31. Tseng J, Dhungel B, Mills JK, Diggs BS, Weerasinghe R, Fortino J, et al. Merkel cell carcinoma: what makes a difference? American journal of surgery. 2015;209(2):342-6.
32. Beylergil V, Carrasquillo JA. Molecular imaging and therapy of merkel cell carcinoma. Cancers. 2014;6(2):1020-30.
33. Hawryluk EB, O'Regan KN, Sheehy N, Guo Y, Dorosario A, Sakellis CG, et al. Positron emission tomography/computed tomography imaging in Merkel cell carcinoma: a study of 270 scans in 97 patients at the Dana-Farber/Brigham and Women's Cancer Center. J Am Acad Dermatol. 2013;68(4):592-9.
34. Slater D, Walsh M. Standards and datasets for reporting cancers: Dataset for the histological reporting of primary cutaneous Merkel cell carcinoma and regional lymph nodes: Royal College of Pathologists; 2014. Available from: http://www.rcpath.org/publications-media/publications/datasets/Cutaneous-Merkel.
35. Durante M, Reppingen N, Held KD. Immunologically augmented cancer treatment using modern radiotherapy. Trends in molecular medicine. 2013;19(9):565-82.
36. Angell H, Galon J. From the immune contexture to the Immunoscore: the role of prognostic and predictive immune markers in cancer. Current opinion in immunology. 2013;25(2):261-7.
37. Paulson KG, Iyer JG, Tegeder AR, Thibodeau R, Schelter J, Koba S, et al. Transcriptome-wide studies of merkel cell carcinoma and validation of intratumoral CD8+ lymphocyte invasion as an independent predictor of survival. J Clin Oncol. 2011;29(12):1539-46.
38. Paulson KG, Iyer JG, Simonson WT, Blom A, Thibodeau RM, Schmidt M, et al. CD8+ Lymphocyte Intratumoral Infiltration as a Stage-Independent Predictor of Merkel Cell Carcinoma Survival: A Population-Based Study. American journal of clinical pathology. 2014;142(4):452-8.
39. Sihto H, Bohling T, Kavola H, Koljonen V, Salmi M, Jalkanen S, et al. Tumor infiltrating immune cells and outcome of Merkel cell carcinoma: a population-based study. Clinical cancer research : an official journal of the American Association for Cancer Research. 2012;18(10):2872-81.
40. Pallan L, Hislop A, Birtwhistle J, Blackbourn D, Steven N. Differences in phenotype and function of the immune in Merkel Cell Cancer patients compared with control patient group. 2014 NCRI Cancer Conference; Liverpool2014. p. B255.
41. The timely delivery of radical radiotherapy: standards and guidelines for the management of unscheduled treatment interruptions. The Royal College of Radiologists; 2008.

21. APPENDIX 1 – AJCC CANCER STAGING FORM FOR MCC

Patients should be staged according to the Merkel Cell Carcinoma (MCC) section of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual. The following diagram facilitates staging. Please note, if there is evidence of distant metastases or stage IV MCC patients are ineligible for the Rational MCC trial.



22. APPENDIX 2 – DEFINITION OF ADVERSE EVENTS

Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the treatment received.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Related Event

An event which resulted from the administration of any of the research procedures.

Serious Adverse Event

An untoward occurrence that:

- Results in death
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly/ birth defect
- Or is otherwise considered medically significant by the Investigator***

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Unexpected and Related Event

An event which meets the definition of both an Unexpected Event and a Related Event.

Unexpected Event

The type of event that is not listed in the protocol as an expected occurrence.

24. APPENDIX 3 – COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

The full NCI CTCAE document is available on the NCI website, the following address was correct when this version of the protocol was approved:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

25. APPENDIX 4 – WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians
in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. 4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

26. APPENDIX 5 – RADIOTHERAPY GUIDELINES

Radiotherapy Protocol

Version 1.0

1. OVERVIEW

The Rational MCC study comprises a randomised comparison between radical surgery versus radical radiotherapy (RT) as the first and definitive treatment at the primary site of MCC (termed Rational Compare) and an observational study for patients not eligible for the randomised study (termed Rational Review).

Patients should be entered into Rational Compare only if the Clinical Oncologist believes radical treatment to the primary is feasible and appropriate and if the skin specialist multi-disciplinary tram (SSMDT) is in equipoise between radical RT and radical surgery to treat the primary MCC.

If the Clinical Oncologist considers radical RT to be inappropriate, the patient is not eligible to be randomised onto Rational Compare and will be treated according to the decision of the SSMDT. For example, the MCC might be in a site in which RT is usually avoided such as the anterior lower leg. The patient can still contribute to Rational Review.

Rational Compare permits but does not require the use of subsequent adjuvant RT to the tumour bed for patients randomised to the 'prioritise surgery arm'. This will be offered at the discretion of the skin specialist multi-disciplinary team (SSMDT). Commonly used selection criteria are listed in the trial protocol. These will be formalised in the protocol as requirements following the initial feasibility phase.

Rational Compare permits but does not require the use of adjuvant RT to the regional nodal basin for patients with stage IB or IIB MCC (i.e. patients without macroscopic nodal involvement and without evidence provided by sentinel lymph node biopsy). The use or non-use of adjuvant RT to the regional nodal basin will be formalised in the protocol following the initial feasibility phase.

Patients in Rational Compare with stage III MCC, i.e. with regional nodal involvement, must have treatment for involved nodes. The choice whether to offer surgery or radiotherapy or both is at the discretion of the SSMDT.

2. RADICAL DEFINITIVE RADIOTHERAPY FOR THE PRIMARY MCC

2.1. Radiotherapy timelines

RT should be started within 28 days of the date of randomisation onto Rational Compare. If exceptionally this cannot be achieved, this must be recorded on a Deviation Form.

2.2. Radiotherapy technique

In most cases it is anticipated that single fields using electrons will be used but in some situations with larger or more complex volumes or if the tumour is close to critical structures such as the eye, CT planned photon volumes may be more appropriate and can be used.

2.3. Radiotherapy planning

RT should be delivered to the primary disease site on the skin with a margin of normal skin around it. The aim is that the Clinical Target Volume (CTV) includes the clinically apparent tumour, i.e. the Gross Tumour volume (GTV), or the site of the primary tumour if an excision biopsy has been performed, plus a 3 cm lateral margin of normal skin. If the tumour is close to critical structures then smaller margins can be used, e.g. 2 cm. For a patient to be eligible for Rational Compare, the smallest acceptable planned margin around the GTV or site of the primary tumour is 1 cm.

The CTV depth of RT treatment should be down to the underlying aponeurosis of the muscle or periosteum of bone i.e. down to the underlying fascial plane as seen on the planning CT or felt with clinical palpation. In most cases it is expected this will be at least 10 mm.

Critical organs should be excluded from the CTV and planning target volume (PTV). For example, a Merkel Cell Tumour on the cheek close to the eye may require the margin at the upper border to be less than 3cm to avoid the eye. The CTV might include only a 1 cm margin at one side of the field edge to avoid including the eye within the PTV.

RT planning should be based on clinical assessment of the primary excision site with reference to the operation notes, histopathology report and pre-operative clinical photographs. It is anticipated that radiotherapy planning for the primary or as adjuvant treatment to the primary will mainly be conducted with a direct electron field but the treating clinician may use whatever planning methods are deemed appropriate. Radiotherapy planning for nodal irradiation may involve multi-field conformal photon treatment.

A record of the intended treatment site should be made after randomisation to aid RT planning and for future assessment of local relapse. This includes:

- A photograph with measured rule and/or a tracing of the disease site (scar or mass lesion) with the planned CTV margin of surrounding normal skin and the field edge drawn on the skin.
- Landmarks to accurately define the local area should also be recorded at this time. If there are no stable natural anatomical landmarks, tattoos may be used if necessary to accurately locate the treatment area. These would not be needed if custom lead shielding is being used.
- If appropriate, a CT scan of the primary site to demonstrate the depth of the lesion.

The PTV and field edge are defined by a further margin around the CTV to account for set up variations and penumbra respectively. This margin must ensure that the CTV is encompassed within the 90% isodose.

For all skin lesions, the dose should be prescribed to 100% isodose line. The depth of the CTV should be covered by the 90% isodose line.

Appropriate tissue equivalent bolus should be used to ensure the skin surface dose is at 90% of the prescribed dose. Appropriate shielding of critical organs may require the manufacture of a lead mask; wax block or use of an internal lead eye shield.

The dose variation across the PTV must not exceed +10% and -10% of the prescription point (ICRU reference point) dose. Where an electron beam abuts a photon beam overlying a site that contained disease (such as in cases offered RT to both the primary site (electrons) and draining nodes (photons) there may be overlapping fields. The treating clinician will determine if the degree of overlap is acceptable.

The total dose will be prescribed to the 100% isodose which encompasses the level of invasion by the skin lesion.

Treatment will be in 2Gy per fraction, treating daily on consecutive days but aiming to exclude weekends. RT should be delivered without any treatment breaks. Where a break is unavoidable then missed fractions should be compensated for as per individual centres' protocol for Category 1 patients.

Patients should be treated with 60Gy in 30 fractions over 40 days.

For single electron fields, verification imaging will not be required but visual checks of set-up will be carried out by the treating radiographers. For photon planned radiotherapy, treatments the verification imaging required will depend on the radiotherapy planning technique used and it should be carried out according to local departmental procedure.

2.4. Patient positioning

Patient's positioning and immobilisation will be dependent on the location of the lesion(s) to be irradiated.

3. ADDITIONAL TREATMENT AT CLINICIAN AND SSMDT DISCRETION

3.1. Postoperative (adjuvant radiotherapy to the Primary Tumour site)

If postoperative (adjuvant RT) is given, the doses recommended are as follows:

- Clear microscopic surgical margins - 50Gy in 25 fractions over 33 days
- Involved positive resection margins - between 60Gy in 30 fractions over 40 days and 66Gy in 33 fractions over 42 days

3.2. Regional nodal irradiation

If regional nodal irradiation is given, the doses recommended are as follows:

- Prophylactic (no lymph node dissection) - 50Gy in 25 fractions over 33 days
- Clinically evident lymphadenopathy - 60Gy in 30 fractions over 40 days

4. QUALITY ASSURANCE

Radiotherapy Quality Assurance (QA) for the study has been discussed with the NCRI Radiotherapy Trials QA (RTTQA) Group. The QA requirements are minimal and include the following.

4.1. Pre-study radiotherapy quality assurance

Centres must successfully complete the pre-trial QA requirements in order to be approved to enter patients into the Rational MCC study. This will be monitored in-house by the Rational MCC Study Office. The full QA process includes:

- Facility questionnaire
- Process document

4.2. Subsequent RTQA for the Rational MCC Study

- Prospective case review of the first few patients from each centre
- Collection of full planning data for all Rational MCC patients including
    - planning CT (if performed) and plan assessment form
    - size/depth of the cutaneous lesion
    - anatomical position of the lesion
    - size/shape of the electron field applied
    - details of any bolus/build up used
    - beam energy
    - depth of 50% isodose
- A copy of the depth dose/isodose curve may be requested on selected patients

4.3. Non-compliance

Non-compliance of RT aspects for the trial will be highlighted to the Chief Investigator (CI), Clinical Oncology members of the Trial Management Group and local Principal Investigators (PIs). If required, appropriate action will be taken.

27. NOTES

Trial Office

Cancer Research UK Clinical Trials Unit
University of Birmingham
Edgbaston
Birmingham, B15 2TT

☎ 0121 414 3792 🖷 0121 414 8392

✉ rationalmcc@trials.bham.ac.uk

Registration and Randomisation

☎ 0800 371 969

Monday to Friday 9.00 am to 5.00 pm

Serious Adverse Event Reporting

🖷 0121 414 8392 or 🖷 0121 414 7989