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TIDAL Melanoma Study: Topical Imiquimod or Diphenylcyclopropenone for the Management of Cutaneous In-transit Melanoma Metastases – A Phase II Single Centre Prospective Randomised Study.

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BMJ Open – Study Protocol

TITLE: *TIDAL Melanoma Study*: *Topical Imiquimod or Diphenylcyclopropenone for the Management of Cutaneous In-transit Melanoma Metastases – A Phase II Single Centre Prospective Randomised Study.*

STUDY ACRONYM: *Topical Imiquimod or Diphenylcyclopropenone for Advanced Loco-regional (TIDAL) Melanoma Study*

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CONFLICT OF INTEREST AND FUNDING

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ETHICS AND DISSEMINATION

The submitted study has institutional ethics approval (HREC/15/QPAH/632) and is being conducted in accordance with appropriate human research standards.

ABSTRACT

INTRODUCTION – In-transit melanoma metastases present a complex therapeutic challenge. Complete surgical excision of localized disease is considered the gold standard, however surgery is not always acceptable and alternatives are required. Early treatment results reported using imiquimod and diphenylcyclopropenone (DPCP) suggest that topical immunotherapies can be used to successfully treat select patients with melanoma metastases. A Phase II, randomized, single centre, pilot study was designed assess the clinical efficacy and safety of DPCP and imiquimod for the treatment of superficial, cutaneous in-transit metastases.

METHODS AND ANALYSIS - This in an open-label, non-superiority study with no on-trial treatment cross-over. Eligible patients will be randomized in a 1:1 ratio to receive topical therapy over 52 weeks with a subsequent minimum follow-up duration of 12 months. The primary endpoint is the complete response rate of treated lesions using RECIST criteria. The target sample size is 30, with 15 patients allocated in each treatment arm. The trial incorporates health-related quality of life measures and biological tissue collection for further experimental sub-studies. In addition, the study will facilitate a health economic comparison with the existing local standard of care, isolated limb infusion (ILI).

ETHICS AND DISSEMINATION – Approval was obtained from the Human Research Ethics Committee at the participating centre. and recruitment has commenced. The results of this study will be submitted for formal publication within a peer-reviewed journal.

TRIAL REGISTRATION – Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN 12615001088538 Prospectively registered: 16 October 2015.

Limitations and Strengths of This Study

- This trial will be performed as proof of concept, pilot study with a small sample size and non-comparative, non-blinded design. These factors will reduce the extrapolation of clinical findings to this general patient group and these are limitations to the study design.
- Within this complex patient cohort a potential selection bias may be introduced by including patients whom have failed other treatment modalities with more aggressive disease-types. Additionally, the broad DPCP dosing range compared to imiquimod may create a treatment bias with more individualized regimens 'tailored' to patients within the DPCP treatment arm.
- The prospective design, randomized allocation of participants and strict clinical trials environment will improve the quality of data collected and available evidence for these therapies.
- The provision for titration of dose and frequency of the investigational agents will help establish an evidence-based treatment regimen and the use of standardised clinical outcome measures (evaluated using RECIST) will produce higher quality efficacy data than is currently available; this will assist with power calculations required for a powered comparative study.
- In addition to technical information, the pilot study will assist with evaluating the financial and logistical feasibility (including patient compliance, data collection and costs) of establishing a full-scale study.
- The secondary outcomes including adverse events, patient-rated outcomes and health-related costs will facilitate further health and economic evaluations associated with these novel treatments.

INTRODUCTION

There has been a sustained increase in the incidence of cutaneous melanoma worldwide, with an estimated lifetime risk now of up to 1 in 147 in the UK and 1 in 25 in other Commonwealth nations. [1 - 3] With early detection, the five-year survival rate for melanoma is excellent (> 90%) however, the prognosis remains poor in patients with recurrent, loco-regional disease. [4] In-transit melanoma is an advanced form of disease (≥Stage IIIb) associated with significantly lower quality of life outcomes secondary to disease-related functional impairment and treatment side-effects and a poor prognosis. [4 - 6] Patients have an unpredictable clinical course with variable treatment responses. [7, 8] Currently, the management of these patients is variable with no consensus on the optimal therapeutic approach.

Complete surgical excision is effective for localized disease however, often surgery is not appropriate. Loco-regional treatments may improve quality of life however do not improve melanoma-specific survival. Existing strategies aim to maximize loco-regional disease control, while reducing disease and treatment-related morbidity. Due to the need for less-invasive, targeted non-surgical modalities, immunological-based therapies have recently been investigated for the treatment of melanoma metastases. [9]

Topical immunotherapies may improve disease control without a significant increase in treatment-related adverse events. In selected patients DPCP and imiquimod have been reported to produce response rates of up to 84% and 100% respectively. [10, 11] Lesion morphology may also be an important predictor of treatment response, with higher response rates observed with superficial (epidermotropic) lesions versus nodular or bulky types. [12, 13] Therefore, it appears patients can be rationally selected for treatment based on disease phenotype, while respecting patients' co-morbidities and functional status. [14] The agents appear to be convenient to administer, relatively cheap and generally well-tolerated, although these findings have not be established within a formal trial setting.

Study Rationale

The use of both agents has, to date, been reported in small case series with retrospective study designs. A Phase II, randomized, proof of concept, pilot study was therefore designed to formally evaluate imiquimod and DPCP for the selective management of superficial, cutaneous in-transit melanoma metastases. The aim of this study is to determine if either treatment is a clinically efficacious and well-tolerated alternative to current therapies in patients who cannot undergo, refuse or have failed surgery. The trial will also formally measure patient-rated outcomes, facilitate a health economic evaluation and include biological tissue collection for further experimental sub-studies.

TIDAL Melanoma Study (PICO Format)

Research Question – Can topical imiquimod or DPCP be used to effectively treat patients with superficial cutaneous in-transit melanoma metastases?

Population – Adults ≥ 18 years with stage III / IV melanoma and biopsy confirmed superficial, cutaneous in-transit metastases that have failed, decline or are unsuitable for surgery.

Intervention – Patients will be randomized 1:1 to receive either topical imiquimod or DPCP therapy.

Comparison – While this is a non-superiority, proof of concept, pilot study reference will be made to the local historical standard or care represented by isolated limb infusion (institutional treatment results available) where appropriate.

Outcome – The primary endpoint is the number of patients experiencing a complete response within treated lesions as determined clinically using RECIST. Secondary outcomes include: the proportion of patients experiencing clinical response in target lesions at 12, 18 and 24 months (complete or partial response, stable disease or progressive disease as per RECIST), progression and disease-free survival, time to loco-regional and overall disease progression, rate of treatment-related adverse events and patient-rated outcomes.

Time – The primary outcome will be measured at the time of best response, up to 12 months following treatment commencement. Clinical assessments will be performed regularly during outpatient reviews in addition to radiological surveillance at 12, 18 and 24 months with a planned minimum follow-up duration of 12 months from the time of best response. Patients will be excluded from the trial if they develop progressive loco-regional or systemic disease.

METHODS AND ANALYSIS

Trial Design

This is a Phase II randomized, proof of concept, pilot study to be performed at a single centre in Brisbane, Australia. It is designed as an open-label, dual arm, non-superiority trial without on-trial treatment cross-over. Eligible patients are to be randomised in a ratio of 1:1 to receive either imiquimod ('Treatment Arm A') or DPCP ('Treatment Arm B') therapy over a minimum duration of 52 weeks or until the time of complete response or disease progression. Treatment will be performed by the patient at home allowing for intermittent, scheduled clinical reviews within an outpatient setting. The minimum follow-up duration will be 12 months from the last treatment (best response or up to 12 months after commencement) and this will allow for close clinical and radiological surveillance of disease.

Pilot Study

There is limited data available in the literature describing the use of these investigational agents for this indication. Therefore, 30 subjects will be enrolled within the pilot study. The data collected will provide important information concerning clinical efficacy and improve the accuracy of power calculations required for a full-scale comparative study. This will also help investigators establish a standardized treatment regimen that allows for dosing titration to effect (regarding the dosing frequency and total dose applied). In addition to technical information, the pilot study will assist with evaluating the financial and logistical feasibility (including patient compliance, data collection and costs) of establishing a full-scale study. The revised procedures will be intended for use within a larger trial programme at multiple centres as a Phase II trial. Given this is a non-superiority, proof of concept, pilot study, formal power-calculations have not applied to determine participant allocation numbers.

Allocation

Randomisation is provided by a web-based permuted block system. The randomisation method uses permuted blocks of variable size between two to four participants and stratification factors are: 1. Age <65 OR ≥65 years at time of diagnosis of in-transit metastases; AND 2. Time to develop in-transit metastases <12 months OR ≥12 months from the time of primary melanoma diagnosis. Patients are randomised in a 1:1 ratio and allocated to either treatment arm, thereby receiving one of two possible treatments.

Participants

Adults ≥ 18 years, with AJCC stage III or IV disease and biopsy-confirmed cutaneous in-transit melanoma metastases will be enrolled for treatment. Patients must be willing and able to comply with study requirements and provide valid consent. A minimum of 5 measurable lesions in anatomical locations suitable for topical treatment are required to enable initial and repeat lesion biopsies and the objective assessment of tumour response. Treated lesions will be between 2-15mm in diameter that can be accurately assessed by ruler/caliper. Macular, papular or small nodular morphology types will be included. Patients must be considered un-suitable for surgery by the treating clinician due to anatomical location or prohibitive disease factors, patient refusal or previous treatment failure. There will be a minimum duration of 12 weeks between completing other treatments (such as isolated limb infusion or PV-10 intralesional therapy). Women of child bearing potential must have a confirmed negative blood pregnancy test at study entry and use approved contraception throughout the study. Patients must have adequate renal, haematopoietic and hepatic function, with no clinically significant impairment or uncontrolled haematological, hepatic or renal disease.

Exclusion Criteria

- Considered eligible for concurrent treatment with systemic chemo- or immunotherapies.
- Subjects who have received chemotherapy or other systemic cancer therapy within 12 weeks of study.
- Subjects who have received other local therapy (e.g. surgery, cryotherapy, laser or radiofrequency ablation) to the treatment area within 4 weeks of study treatment.
- Life expectancy of less than 6 months or ECOG performance status ≥3.
- Medical or psychiatric condition that compromises the patient's ability to complete the treatment regimen or follow-up assessments as per protocol.
- Female subjects that are pregnant or lactating.
- Known history of immumodeficiency including HIV positive subjects, uncontrolled central nervous system metastases, concomitant systemic corticosteroid or other immunosuppressive use or previous organ transplant.
- Known severe concurrent or inter-current illness including: cardiovascular, respiratory or immunological) illness, psychiatric disorders, or alcohol or chemical dependence that would, in the opinion of the Investigator, compromise safety or compliance or interfere with interpretation of study results.
- Previous severe adverse or allergic reaction to either treatment agent.

Study Objectives

Primary Endpoint

The primary endpoint is the number of patients experiencing a complete response within treated lesions as determined clinically using the Response Evaluation Criteria in Solid Tumors (RECIST). [15]

Secondary Endpoints

- Proportion of patients experiencing a non-complete response in target lesions (partial response, stable disease and progressive disease as per RECIST) at 12, 18 and 24 months after treatment commencement.
- Length of time patients experience loco-regional disease-free and progression-free survival.
- Proportion of patients experiencing overall disease progression including death following the treatment.
- Patient-rated outcomes (reported quality of life parameters) before, at the time of best response and 12 months following treatment, assessed using the FACT-M subscale.
- Rate of treatment-related adverse events.
- Estimated health-related costs.

Recruitment

Potential subjects are initially assessed through the Melanoma Outpatient Clinic at the Princess Alexandra Hospital, Brisbane, Australia. Enrollment, treatment and follow-up occurs through a multi-disciplinary trial clinic with an emphasis on the treatment of patients with in-transit melanoma. This involves specialist care provided by dermatologists, surgeons, oncologists, trial nurses and other allied health professionals. Each eligible subject is enrolled in the study for 52 weeks of treatment after commencing imiquimod or DPCP. The aim is to achieve a minimum follow-up duration of 12 months and up to 24 months following the best response or progressive disease. The total recruitment window will be open for at least 24 months and the total study length is therefore estimated to be up to 36 months based on recruitment rates.

Investigational Agents

Imiquimod

Patients are treated using 5% topical imiquimod applied as a mixture within an aqueous cream. This concentration remains constant throughout the duration of treatment. A local inflammatory response is produced with application once daily, five days per week, with two rest days. The solution is applied to the treatment area with a 0.5cm margin surrounding lesions and left overnight for an 8 hour duration. The treatment is continued so that a mild to moderate dermatitis is maintained following sequential treatments and this includes the provision to titrate the treatment frequency for individual patients (Table 1).

DPCP

Patients are initially sensitized to DPCP using a 2% solution applied to a clinically accessible point of contact (e.g. medial arm). Two weeks following sensitisation the definitive treatment is commenced. The optimal dose of DPCP is based on an individual's clinical response. Treatments concentrations range from 0.005% to 5% applied as a mixture within an aqueous cream. A contact dermatitis is produced following application once per week for 24-48 hours exposure depending on the intensity of response. The ideal maintenance dose is gradually reached by titrating the dose to effect so that a mild to moderate dermatitis is achieved following sequential treatments.

Treatment Schedule

Eligible patients commence treatment within four weeks of signing informed consent. Both treatments are self-administered by patients or their carer with regular clinical reviews conducted through the outpatient setting.

1. Patients randomised to Treatment Arm A receive topical 5% imiquimod cream applied to target lesions up to 5 times weekly for the first 16 weeks and then second daily thereafter. The total treatment area is recommended as <25 cm^2 with a maximum number of 20 target lesions.

2. Patients randomised to Treatment Arm B receive topical DPCP cream. Patients successfully sensitised with the 2% solution commence the treatment regimen two weeks after initial contact. This involves self-application of 0.005% DPCP once weekly for the first 8 weeks. Regular clinical review as per the treatment schedule enables titration of up to a 5% solution applied once or twice per week (24-48 hours) to achieve the desired therapeutic effect. A maximum number of 20 target lesions are included within the treatment field.

Table 1. Imiquimod and DPCP Treatment Regimens

Week	Imiquimod	DPCP
1 - 8	5% Imiquimod applied to lesions 5 days per week with 2 rest days.	0.005% DPCP applied once weekly
8 - 16	Imiquimod applied to lesions 5 days per week (as tolerated). If a sustained, moderate treatment reaction is noted then frequency modified to every second day (3 days per week).	DPCP concentration titrated to effect (up to 5% concentration) and applied once per week to lesions. DPCP can be used up to twice per week to achieve moderate treatment reaction.
16-52	Imiquimod applied on alternate days (3 days per week) to lesions as tolerated.	DPCP applied at maintenance dose as tolerated in order to achieve moderate erythematous reaction and clinical effect.

End of Trial Review and Continuing Treatment

Following the conclusion of the trial patients will be offered ongoing treatment at the current standard of care. Patients will continue to be reviewed at regular clinical outpatient appointments. During the final visit, a comprehensive clinical assessment of tumour response, medical examination, radiological evaluation and serum biochemical work-up will be performed. Patients with a complete clinical response following treatment will be offered either continuing treatment for the duration of the trial period (up to 24 months) or cessation of treatment until disease recurrence at which time treatment will be re-commenced as per protocol. There is no substantial evidence for one treatment strategy over another, with various regimens previously reported and both treatment options will be explored within this pilot study.

Statistical Analysis

All subjects who are enrolled and receive either therapy for a minimum duration of 4 weeks will be evaluated for the primary and secondary outcomes using an intention to treat analysis. Univariate and bivariate analyses will be conducted to assess for factors significantly associated with treatment response and a multivariate cox-regression model will be used to adjust for significant dependent variables. Progression-free, disease-free and overall-survival will be calculated using a Kaplan Meier Survival Estimate. Treatment-related adverse events will be recorded and treatment failure includes both loco-regional disease recurrence or progression of in-transit melanoma metastases within the treatment field. This will be defined as the presence of malignant melanoma cells identified clinically and using dermoscopy then confirmed on histopathology.

Treatment Response

Based on existing evidence it is expected that most patients will develop a clinical response to both therapies within 1-3 months of commencing treatment and experience clinical regression within 6-12 months. If no clinical response is demonstrated within 3 months, treatment is discontinued. Baseline documentation of target lesions is performed prior to treatment commencement. This is performed using standardized data collection forms and colour photography. Up to a maximum of 20 measurable lesions in total are identified as target lesions, recorded and measured at baseline. The change in the longest diameter for all target lesions is used to assess the objective tumor response following treatment using RECIST. Regular radiological and serum biochemical assessments are also integrated within the treatment and follow-up regimen.

Outcomes Assessments

Treatment response will be determined through clinical and photographic assessment for palpable or visual lesions at baseline and at the time to best response or up to 12 months following the commencement of treatment. Efficacy will be measured using RECIST with the overall response rate (ORR) and clinical benefit (CB) calculated by summation of response parameters (e.g. CR, PR, SD and PD). Treatment of emergent adverse experiences will be summarized based on the severity grade using the Common Terminology Criteria for Adverse Events (CTCAE v4.03). Changes in haematology, serum biochemistry and other laboratory values will be summarized using descriptive methods. Differences will be calculated relative to the values collected at baseline / enrolment in the study. Progression-free survival and disease-free survival will be monitored by clinical assessment and CT/PET/MRI radiology will be performed for assessment of systemic disease at baseline and at 6, 12 and 24 months after commencing treatment. All subjects will be followed for overall survival until the close of the study. Changes in patient-rated outcomes (reported quality of life parameters) before treatment, at 12 months and at the time of best response, will be assessed using the Functional Assessment of Cancer Therapy – Melanoma (FACT-M), a health-related quality of life (HRQoL) instrument validated for patients with cutaneous melanoma. An estimated difference in the health-related costs will be performed after the conclusion of study by comparing the typical expenses incurred by a patient in each treatment arm compared to the existing treatment representing the standard of care (ILI) using a projected economic bootstrapping model.

Adverse Events and Safety Profile

Safety will be assessed by documenting toxicity using CTCAE v4.03 and recording other serious adverse events. An acceptable safety profile will be defined as 80% of patients receiving the treatment without any grade IV toxicity. An interim safety assessment will be performed using adverse event data available four weeks following the 5th patient completing imiquimod and DPCP treatments.

Quality Assurance

Comprehensive data management and quality assurance will be conducted in accordance with ANZCTR standards with strict operating procedures and policies. Operations meeting will be held to review trial progress, supported by at least annual trial management committee meetings. Patient data will be collected using standardized paper proformae (case report forms) and entered onto a secure database. With respect to the primary and secondary endpoints, the first 5 participants will be reviewed by a specialist expert dedicated reviewer thereafter 1 in every 5 patients (20%) will undergo select review. ANZMTG has strict data management protocols. All trial data will be cleaned and entered by the clinical trials data coordinator.

Substudies

Biological

In addition to examining clinical questions, this study supports a biological research programme. The trial includes the collection of blood, serum, plasma and tumour specimens which are stored within a Melanoma and Soft Tissue Bank (HREC-10-QPAH-153). Tumour specimens include material from pre-treatment biopsies with repeated biopsies performed at 4 weeks and 9 months after treatment commencement. In addition to formalin-fixed or paraffin-embedded material, fresh tissue will be provided for sequencing, RNA/protein analysis and BRAF mutation testing.

The primary objective of the translational research programme is to create an extensive tissue bank with parallel clinical information to facilitate novel investigations, hypothesis-generation and validation of existing concepts. Broad research questions include*: 'Are there genetic determinants of immunotherapeutic response in melanoma?', 'what are the biological differences between patients capable of producing robust treatment responses versus those with progressive disease?', 'are there specific biomarkers that can be used to predict disease progression or treatment response?'* and *'does preliminary treatment with topical immunotherapies lead to sustained patho-biological effects or translate into significant treatment or survival differences when commenced on systemic immunotherapies?'*

Health-related Quality of Life and Health Economic Evaluation

This trial also utilises assessments of patient-rated outcomes and changes in response to treatment. In this study, HRQoL will be assessed using the 51 item FACT-M. This is a multi-dimensional, melanoma-specific, validated instrument that was developed to measure HRQoL in patients with cutaneous melanoma. The FACT-M incorporates four general subscales within the core questionnaire and a disease/treatment melanoma-specific subscale. Derived using the five components together, an aggregate QoL score is produced where a higher value reflects improved overall well-being. [16]

To date, there is limited information available from formal evaluations of HRQoL in patients with in-transit metastases and this study will generate interesting data to compare with other melanoma cohorts [14, 17-20] Currently, the relative differences between topical therapies and other loco-regional treatments remains unknown. We hypothesise that DPCP and imiquimod therapy will improve loco-regional disease control compared to patients' baseline although this may be associated with higher levels of treatment-related morbidity. Consequently, it is important to measure HRQoL to determine the effects of these agents on patient-rated outcomes and differentiate against other available therapies.

An economic assessment will be performed on the conclusion of this study incorporating HRQoL data and treatment-related costs. The relative effect of treatment on HRQoL, disease progression, overall survival, resource consumption and estimated costs will serve as the primary inputs. While not powered to provide a comparative assessment, reference will be made to the historical standard or care represented by ILI as similar institutional treatment results and costs are available. It is hypothesized that imiquimod and DPCP are relatively cheap, convenient and clinically effective alternatives for patients with this disease-subtype.

DISCUSSION

Existing evidence supports the use of these agents for the topical treatment of cutaneous melanoma metastases. However, there is limited high-quality efficacy and safety data with well no established treatment regimen. Given both agents are relatively cheap, easy to administer and require only intermittent clinician review these properties make topical therapies attractive alternatives to more invasive and commonly used options. Counter-intuitively, there is a notable absence of studies measuring quality of life or health-related costs in this patient group.

Key priorities of this pilot study are to:

- Establish a standardized treatment regimen allowing for titration to therapeutic effect.
- Further assess the clinical efficacy and safety-profile of each investigational agent within this complex patient cohort.
- Improve the accuracy of power calculations.
- Determine how many patients can be effectively recruited for treatment.
- Evaluate the financial and logistical feasibility of implementing these therapies.

The additional data and revised procedures will assist further trial design and co-ordination within a full-scale multi-centre Phase II study. If these treatments prove effective it is expected that this will lead to improved patient-rated outcomes through a reduction in local disease, fewer serious treatment-related complications and more convenient application. It will also facilitate streamlined review and may lead to decreased healthcare-associated expenditure. Providing multi-disciplinary care within a high-quality environment will also inform on other important aspects of this complex patient sub-group's disease.

The TIDAL Melanoma Study is an investigator-initiated study that incorporates novel immunotherapeutics to inform on the technical aspects of treatment as well as the safety profile of the investigational agents, patient-rated outcomes and health economics. It aims to address a significant question with respect to the management of this challenging disease and will provide further evidence on clinical practice and treatment standards for advancement loco-regional melanoma.

ETHICS AND DISSEMINATION

The study has ethics approval (HREC/15/QPAH/632) from the Human Research Ethics Committee at the participating centre. and is being conducted in accordance with appropriate human research standards. The results of the study will be submitted for formal publication within a peer-reviewed journal.

TRIAL REGISTRATION – Australian New Zealand Clinical Trials Registry: ACTRN 12615001088538

Prospectively registered: 16 October 2015.

AUTHOR CONTRIBUTIONS

T. READ (Principal Investigator) – Manuscript writing, trial design, trial co-ordination and patient care.

J. THOMAS – Trial co-ordination and data management.

M. WAGELS – Manuscript editing, trial design and patient care.

S. WEBBER – Trial co-ordination, data collection and patient care.

H. SCHAIDER – Trial design and manuscript editing.

H. P. SOYER – Trial design and co-ordination.

B. M. SMITHERS – Manuscript editing, trial design and co-ordination and patient care.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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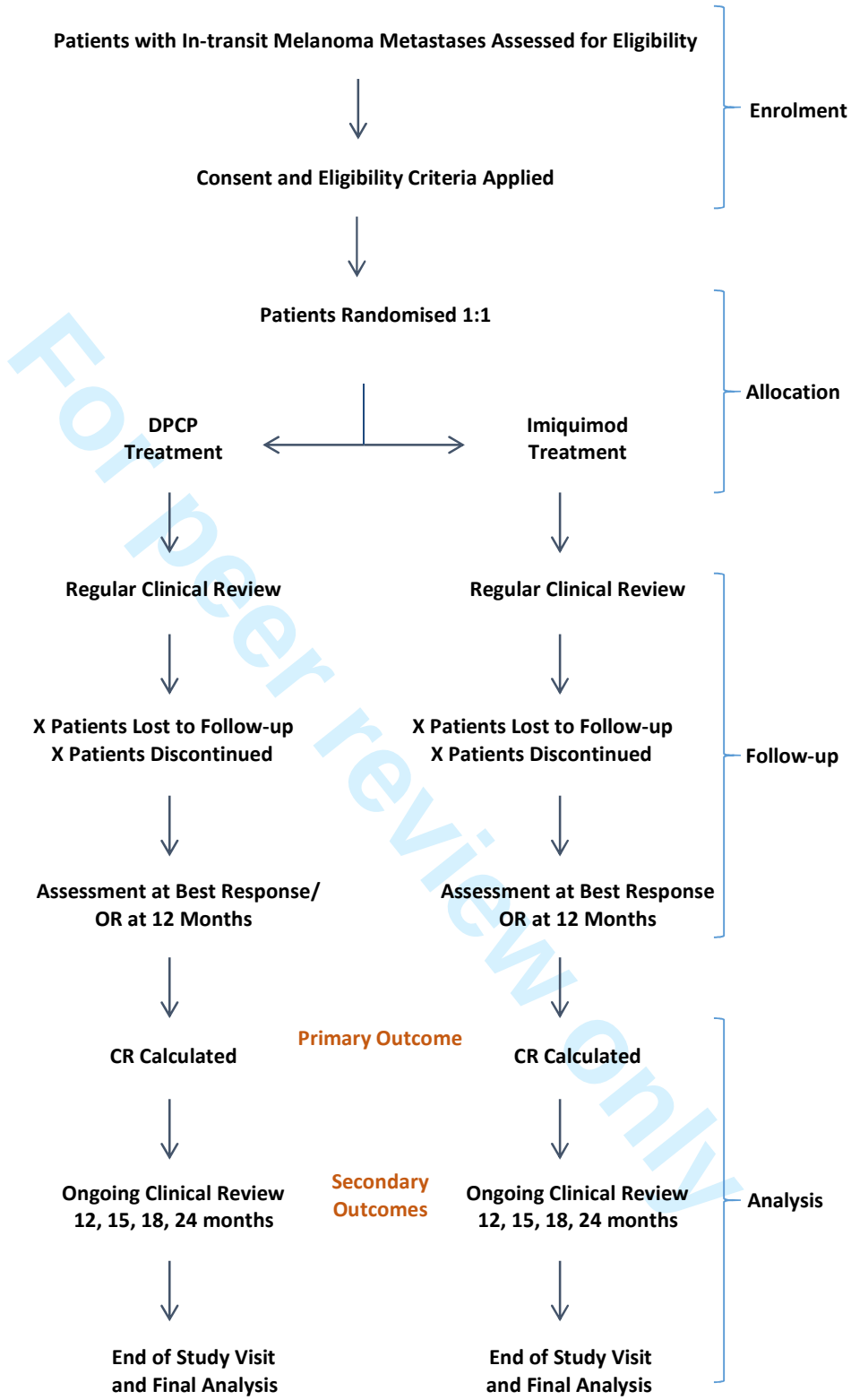

FIGURE 1 – TIDAL Melanoma Study Flowchart

TABLE 2 – DPCP STUDY SCHEDULE

Study Assessment	Screening and Randomisation		Treatment																		
Time Point	W-2	DOFT	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	6M	9M	12M	15M	18M	21M	24M	Termination
Informed Consent	X																					
Inclusion / Exclusion	X																					X
Medical History	X																					X
FACT-M Assessment	X					X								X	X		X		X		X	X
Pregnancy Test	X	X																				
Routine Blood Tests	X					X				X				X	X	X	X	X	X	X	X	X
Research Blood Tests	X					X				X				X	X	X	X	X	X	X	X	X
Physical Examination	X	X				X				X				X	X	X	X	X	X	X	X	X
CT HNCAP or CT-PET	X														X		X				X	X*
Measurement of ITM lesions		X				X				X				X	X	X	X	X	X	X	X	X
Photography of ITM lesions		X				X				X				X	X	X	X	X	X	X	X	X
RCM and Dermoscopy		X				X										X						
Biopsy of ITM lesions		X				X										X						
Randomisation	X																					
Application of 2% DPCP Sensitising Solution	X																					
Prescription for DPCP		X				X				X				X	X	X	X	X	X	X	X	
Application of DPCP Treatment Solution		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Titration of DPCP						X				X				X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

TABLE 3 – IMIQUIMOD STUDY SCHEDULE

Study Assessment	Screening and Randomisation	Treatment																			
Time Point	W-2	DOFT	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	6M	9M	12M	15M	18M	21M	24M	Termination
Informed Consent	X																					
Inclusion / Exclusion	X																					X
Medical History	X																					X
FACT-M Assessment	X					X								X	X		X		X		X	X
Pregnancy Test	X																					
Routine Blood Tests	X					X				X				X	X	X	X	X	X	X	X	X
Research Blood Tests	X					X				X				X	X	X	X	X	X	X	X	X
Physical Examination	X	X				X				X				X	X	X	X	X	X	X	X	X
CT HNCAP or CT-PET	X														X		X				X	X*
Measurement of ITM lesions		X				X				X				X	X	X	X	X	X	X	X	X
Photography of ITM lesions		X				X				X				X	X	X	X	X	X	X	X	X
RCM and Dermoscopy		X				X										X						
Biopsy of ITM lesions		X				X										X						
Randomisation	X																					
Prescription for ImiQ 5%		X													X							
Application of ImiQ 5% Treatment Solution		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BMJ Open

Protocol for the TIDAL Melanoma Study: Topical Imiquimod or Diphenylcyclopropenone for the Management of Cutaneous In-transit Melanoma Metastases – A Phase II Single Centre Randomised Pilot Study.

Journal:	*BMJ Open*
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Date Submitted by the Author:	05-Jun-2017
Complete List of Authors:	Read, Tavis; Queensland Melanoma Project, Princess Alexandra Hospital; The University of Queensland, Discipline of Surgery, The School of Medicine Webber, Scott; Dermatology Research Centre, The University of Queensland Diamantina Institute; Princess Alexandra Hospital, Department of Dermatology Thomas, Janine; Queensland Melanoma Project, Princess Alexandra Hospital Wagels, Michael; Queensland Melanoma Project, Princess Alexandra Hospital; The University of Queensland, Discipline of Surgery, The School of Medicine Schaider, Helmut; Dermatology Research Centre, The University of Queensland Diamantina Institute; Princess Alexandra Hospital, Department of Dermatology Soyer, H. Peter; Dermatology Research Centre, The University of Queensland Diamantina Institute; Princess Alexandra Hospital, Department of Dermatology Smithers, B. Mark; Queensland Melanoma Project, Princess Alexandra Hospital; The University of Queensland, Discipline of Surgery, The School of Medicine
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Research methods, Dermatology, Surgery
Keywords:	In-transit, Melanoma, Metastases, Topical, Immunotherapy, Clinical trials < THERAPEUTICS

BMJ Open – Study Protocol

TITLE: Protocol for the *TIDAL Melanoma Study*: *Topical Imiquimod or Diphenylcyclopropenone for the Management of Cutaneous In-transit Melanoma Metastases – A Phase II Single Centre Randomised Pilot Study.*

STUDY ACRONYM: *Topical Imiquimod or Diphenylcyclopropenone for Advanced Loco-regional (TIDAL) Melanoma Study*

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In-transit, melanoma, metastases, topical, immunotherapy, clinical trial

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CONFLICT OF INTEREST AND FUNDING

No conflicts of interest to declare. Dr Read was the recipient of a Queensland Government Junior Research Fellowship throughout the study period and publication process. This is an investigator-initiated, non-sponsored study.

ETHICS AND DISSEMINATION

The submitted study has institutional ethics approval (HREC/15/QPAH/632) and is being conducted in accordance with appropriate human research standards using the TIDAL-M-01 Protocol Version 3.4 (last amended 6 February 2017).

ABSTRACT

INTRODUCTION – In-transit melanoma metastases present a complex therapeutic challenge. Complete surgical excision of localized disease is considered the gold standard, however surgery is not always acceptable and alternatives are required. Early treatment results reported using imiquimod and diphenylcyclopropenone (DPCP) suggest that topical immunotherapies can be used to successfully treat select patients with melanoma metastases. A Phase II, randomized, single centre, pilot study was designed to assess the clinical efficacy and safety of DPCP and imiquimod for the treatment of superficial, cutaneous in-transit melanoma metastases.

METHODS AND ANALYSIS - This in an open-label, non-superiority, pilot study with no treatment cross-over. Eligible patients will be randomized in a 1:1 ratio to receive topical therapy for 12 months with a minimum follow-up period of 12 months. The target sample size is 30 patients, with 15 allocated to each treatment arm. The primary endpoint is the complete response rate of treated lesions using RECIST criteria. The trial incorporates health-related quality of life measures and biological tissue collection for further experimental sub-studies. In addition, the study will facilitate a health economic comparison with the existing standard of care, isolated limb infusion.

ETHICS AND DISSEMINATION – Approval was obtained from the Human Research Ethics Committee at the participating centre. and recruitment has commenced. The results of this study will be submitted for formal publication within a peer-reviewed journal.

TRIAL REGISTRATION – Prospectively registered on 16 October 2015 with the Australian New Zealand Clinical Trials Registry: ACTRN 12615001088538. This study conforms to the World Health Organisation Trial Registration Data Set.

Limitations and Strengths of This Study

- This trial is a proof of concept, pilot study with a small sample size and non-blinded design. While expediting the availability of high quality data useful for conducting a larger study, these factors will also reduce the generalisability of clinical findings to the in-transit melanoma patient population.
- This is a complex patient group and the inclusion of patients who have failed or are unsuitable for other treatments may introduce a selection bias for those with more aggressive disease-types.
- The broader DPCP dosing range compared with imiquimod may also create a treatment bias, with more individualized regimens 'tailored' to patients within the DPCP arm.
- The prospective design, randomized allocation of participants and strict clinical trial environment will improve the quality of data collected and evidence available for these therapies.
- The provision for titrating the dose and frequency of the investigational agents will help establish an evidence-based treatment regimen. The use of standardised clinical outcome measures will produce more accurate and precise efficacy data than is currently available; this will enhance the accuracy of power calculations required for a comparative study.
- In addition to technical information, the pilot study design will assist with evaluating the financial and logistical feasibility of establishing a full-scale study.
- The secondary outcomes including adverse events, patient-rated outcomes and health-related costs will facilitate further health and economic evaluations associated with these novel therapies.

INTRODUCTION

There has been a sustained increase in the incidence of cutaneous melanoma worldwide, with an estimated lifetime risk now of up to 1 in 147 in the UK and 1 in 25 in other Commonwealth nations. [1 - 3] With early detection, the five-year survival rate for melanoma is excellent (> 90%) however, the prognosis remains poor in patients with recurrent, loco-regional disease. [4] In-transit melanoma is an advanced form of disease (≥Stage IIIB) associated with a poor prognosis and significantly lower quality of life outcomes secondary to disease-related functional impairment and treatment side-effects. [4 - 6] Patients have an unpredictable clinical course with variable treatment responses. [7, 8] Currently, the management of these patients is variable with no consensus on the optimal therapeutic approach.

Complete surgical excision is effective for localized disease however, often surgery is not appropriate. Loco-regional treatments may improve quality of life however do not improve melanoma-specific survival. Existing strategies aim to maximize loco-regional disease control, while reducing disease and treatment-related morbidity. Due to the need for less-invasive, targeted non-surgical modalities, immunological-based therapies have recently been investigated for the treatment of melanoma metastases. [9]

Topical immunotherapies may improve disease control without a significant increase in treatment-related adverse events. In selected patients DPCP and imiquimod have been reported to produce response rates of up to 84% and 100% respectively. [10, 11] Lesion morphology may also be an important predictor of treatment response, with higher response rates observed with superficial (epidermotropic) lesions versus nodular or bulky types. [12, 13] Therefore, it appears patients can be rationally selected for treatment based on disease phenotype, while respecting patients' co-morbidities and functional status. [14] The agents appear to be convenient to administer, relatively cheap and generally well-tolerated, although these findings have not be established within a formal trial setting.

Study Rationale

The use of both agents has, to date, been reported in small case series with retrospective study designs. A Phase II, randomized, proof of concept, pilot study was therefore designed to formally evaluate imiquimod and DPCP for the selective management of superficial, cutaneous in-transit melanoma metastases. The aim of this study is to determine if either treatment is a clinically efficacious and well-tolerated alternative to current therapies in patients who cannot undergo, refuse or have failed surgery. The trial will also formally measure patient-rated outcomes, facilitate a health economic evaluation and include biological tissue collection for further experimental sub-studies.

TIDAL Melanoma Study (PICO Format)

Research Question – Can topical imiquimod or DPCP be used to effectively treat patients with superficial, cutaneous in-transit melanoma metastases?

Population – Adults ≥ 18 years with stage III / IV melanoma and biopsy confirmed superficial, cutaneous in-transit metastases that have failed, decline or are unsuitable for surgery.

Intervention – Patients will be randomized 1:1 to receive either topical imiquimod or DPCP therapy.

Comparison – This is a non-superiority, proof of concept, pilot study. Reference will be made to the local standard of care represented by isolated limb infusion where appropriate.

Outcome – The primary endpoint is the number of patients experiencing a complete response of treated lesions within 12 months of starting treatment as determined clinically using RECIST. Secondary outcomes include: the proportion of patients experiencing a non-complete response at 12, 18 and 24 months (partial response, stable disease or progressive disease), progression and disease-free survival, time to loco-regional and overall disease progression, rate of treatment-related adverse events and patient-rated outcomes.

Time – The primary outcome will be measured at the time of best response, with up to 12 months of treatment. Clinical assessments will be performed regularly during outpatient reviews with radiological surveillance at 12, 18 and 24 months and a planned minimum follow-up duration of 12 months from the time of best response. Patients will be excluded from the trial if they develop progressive loco-regional or systemic disease and will be treated in accordance with the standard of care available.

METHODS AND ANALYSIS

Trial Design

This is a Phase II randomized, proof of concept, pilot study to be performed at a single centre in Brisbane, Australia. It is designed as an open-label, dual arm, non-superiority trial without treatment cross-over. Eligible patients are to be randomised in a ratio of 1:1 to receive either imiquimod ('Treatment Arm A') or DPCP ('Treatment Arm B') therapy over a minimum duration of 12 months or until the time of complete response or disease progression. Treatment will be performed by the patient at home allowing for intermittent, scheduled clinical reviews within an outpatient setting. The minimum follow-up duration will be 12 months from the best response or disease progression and this will allow for close clinical and radiological surveillance (Figure 1).

Pilot Study Rationale

There is limited data describing the use of the investigational agents for this indication in the literature. Based on the existing rate of new patient assessment and treatment at our institution and the estimated accrual rate projected for the trial period, 30 subjects are planned for enrolment within the pilot study. Given this is a non-superiority, proof of concept, pilot study, formal power-calculations were not applied to determine allocation numbers. It is expected that the data collected using this target sample size will provide sufficient high quality data to confirm the efficacy rates reported in the literature and improve the accuracy of power calculations required for a full-scale comparative study. This will also help investigators establish a standardized treatment regimen that allows for dosing adjustment with titration to effect. In addition to technical information, the pilot study will assist with evaluating the financial and logistical feasibility (including patient compliance, data collection and costs) of establishing a full-scale study. The revised procedures are intended for use within a larger programme at multiple centres as a Phase II/III trial.

Allocation

Randomisation is provided by a web-based permuted block system and performed by the trial co-ordinator or principal investigator. The randomisation method uses permuted blocks of variable size between two to four participants and stratification factors are: 1. Age <65 OR ≥65 years at the time of diagnosis of in-transit metastases; AND 2. Time to develop in-transit metastases <12 months OR ≥12 months from the time of primary melanoma diagnosis. Patients are randomised in a 1:1 ratio and allocated to either treatment arm, thereby receiving one of two possible treatments.

Participants

Adults ≥ 18 years, with AJCC stage III or IV disease and biopsy-confirmed cutaneous in-transit melanoma metastases will be enrolled for treatment. Patients must be willing and able to comply with study requirements and provide valid consent. A minimum of five measurable lesions in anatomical locations suitable for topical treatment are required to enable initial and repeat lesion biopsies and the objective assessment of tumour response. Treated lesions will be between 2-15mm in diameter that can be accurately assessed by ruler/caliper. Macular, papular or small nodular morphology types will be included. Patients must be considered un-suitable for surgery by the treating clinician due to anatomical location or prohibitive disease factors, patient refusal or previous treatment failure. There will be a minimum duration of 12 weeks between completing other biological treatments (such as isolated limb infusion or PV-10 intralesional therapy). Women of child bearing potential must have a confirmed negative blood pregnancy test at study entry and use approved contraception throughout the study. Patients must have adequate renal, haematopoietic and hepatic function, with no clinically significant impairment or uncontrolled haematological, hepatic or renal disease.

Exclusion Criteria

- Considered eligible for concurrent treatment with systemic chemo- or immuno-therapies.
- Subjects who have received chemotherapy or other systemic cancer therapy within 12 weeks of the study.
- Subjects who have received other local therapy (e.g. surgery, cryotherapy, laser or radiofrequency ablation) to the treatment area within 4 weeks of study treatment.
- Life expectancy of less than 6 months or ECOG performance status ≥3.
- Medical or psychiatric condition that compromises the patient's ability to complete the treatment regimen or follow-up assessments as per protocol.
- Female subjects that are pregnant or lactating.
- Known history of immunodeficiency, including HIV positive subjects, uncontrolled central nervous system metastases, concomitant systemic corticosteroid or other immunosuppressive use or previous organ transplant.
- Known severe concurrent or inter-current illness including: cardiovascular, respiratory or immunological) illness, psychiatric disorders, or alcohol or chemical dependence that would, in the opinion of the investigator, compromise safety or compliance or interfere with interpretation of study results.
- Previous severe adverse or allergic reaction to either treatment agent.

Study Objectives

Primary Endpoint

The number of patients experiencing a complete response of treated lesions within 12 months of starting treatment as determined clinically using the Response Evaluation Criteria in Solid Tumors (RECIST). [15]

Secondary Endpoints

- Proportion of patients experiencing a non-complete response in target lesions (partial response, stable disease and progressive disease as per RECIST) at 12, 18 and 24 months after treatment commencement.
- Loco-regional progression-free and disease-free survival.
- Proportion of patients with overall disease progression including death following treatment.
- Patient-rated outcomes (health-related quality of life) before, at the time of best response and 12 months following treatment, assessed using the FACT-M subscale.
- Rate of treatment-related adverse events.
- Estimated health-related costs.

Recruitment

Potential subjects are initially assessed and screened through the Melanoma Outpatient Clinic at the Princess Alexandra Hospital, Brisbane, Australia. Consent, enrolment, treatment and follow-up occurs through a multi-disciplinary trials clinic with an emphasis on the outpatient treatment of patients with in-transit melanoma. This involves specialist care provided by dermatologists, surgeons, oncologists, trial nurses and other allied health professionals. Each eligible subject is enrolled in the study for up to 12 months of treatment with imiquimod or DPCP. The aim is for a minimum follow-up duration of 12 months (and up to 24 months) following the best response or progressive disease. The total recruitment window will be open for at least 24 months and the total study length is therefore estimated to be up to 36 months based on recruitment rates.

Investigational Agents

Imiquimod

Patients are treated using 5% topical imiquimod applied as a mixture within an aqueous cream. This concentration remains constant for the duration of treatment. A local inflammatory response is produced with application once daily, five days per week, with two rest days. The solution is applied with a 0.5cm margin surrounding lesions and left overnight for 8 hours duration. The treatment is continued so that a mild to moderate dermatitis is maintained with sequential treatments and this includes the provision to reduce the treatment frequency (Table 1).

DPCP

Patients are sensitized to DPCP using a 2% solution applied to a clinically accessible contact point (e.g. medial arm). Two weeks following sensitisation the definitive treatment is commenced. Treatments concentrations range from 0.005% to 5% applied as a mixture within an aqueous cream. The optimal dose of DPCP is based on an individual's clinical response. A contact dermatitis is produced following application. The ideal maintenance dose is gradually reached by titrating the dose from 0.005% so that a mild to moderate dermatitis is achieved with consecutive treatments. The solution is applied to the treatment area with a 0.5cm margin surrounding lesions and left for 24-48 hours total duration.

Treatment Interruption / Temporary Suspension

At the discretion of clinicians, treatment can be temporarily withheld due to the development of significant treatment-related side-effects. This interruption period can continue for up to 4 weeks without the patient being excluded from the trial. In the event of a severe treatment reaction the dose and frequency can also be adjusted in accordance with the regimen.

Treatment Schedule

Eligible patients commence treatment within four weeks of signing informed consent. Both treatments are self-administered by patients or their carer with regular clinical reviews conducted in the outpatient setting.

1. Patients randomised to Treatment Arm A receive topical 5% imiquimod cream applied to target lesions up to 5 times weekly for the first 16 weeks and second daily thereafter. The total treatment area is recommended as <25 cm^2.

2. Patients randomised to Treatment Arm B receive topical DPCP cream. Patients successfully sensitised using the 2% solution commence the treatment two weeks after initial contact. This involves application of 0.005% DPCP once weekly for the first 8 weeks. Regular clinical review as per the treatment schedule enables titration of up to a 5% solution applied once or twice per week to achieve the desired therapeutic effect.

Table 1. Imiquimod and DPCP Treatment Regimens

Week	Imiquimod	DPCP
1 - 8	5% Imiquimod applied to lesions 5 days per week with 2 rest days.	0.005% DPCP applied once weekly
8 - 16	Imiquimod applied to lesions 5 days per week (as tolerated). If a sustained, moderate treatment reaction is noted then frequency modified to every second day (3 days per week).	DPCP concentration titrated to effect (up to 5% concentration) and applied once per week to lesions. DPCP can be used up to twice per week to achieve moderate treatment reaction.
16-52	Imiquimod applied on alternate days (3 days per week) to lesions as tolerated.	DPCP applied at maintenance dose as tolerated in order to achieve moderate erythematous reaction and clinical effect.

End of Trial Review and Continuing Treatment

Following the conclusion of the trial or with clinical progression patients will be offered ongoing treatment at the current standard of care. Patients will continue to be reviewed at regular clinical outpatient appointments. During the final visit, a comprehensive clinical assessment of tumour response, medical examination, radiological evaluation and serum biochemical work-up will be performed. If a patient experiences a complete response, further topical treatment on the trial is ceased within four weeks. There is no conclusive evidence concerning the effect of continuing the therapy after this point and various regimens have been reported. Arbitrarily continuing treatment may influence the validity of the disease-free and progression-free survival calculations within this study.

Statistical Analysis

All subjects who are enrolled and receive either therapy will be evaluated for the primary and secondary outcomes using an intention to treat analysis. Exploratory univariate and bivariate analyses will be conducted to assess for factors significantly associated with a complete response and a multivariate cox-regression model will be used to adjust for significant dependent variables. Progression-free, disease-free and overall-survival will be calculated using Kaplan Meier Survival Estimates. Treatment failures include: no clinical response after 3 months of treatment, loco-regional disease recurrence or progression of target lesions within the treatment field. Persistent disease will be evaluated clinically using dermoscopy then confirmed on histopathology.

Treatment Response

Based on existing evidence it is expected that most patients will develop a clinical response to both therapies within 1-3 months of commencing treatment and experience clinical regression within 6-12 months. If no clinical response is demonstrated using the treatment regimen within 3 months, topical therapy is discontinued and the patient is recorded as a treatment failure. Baseline documentation of target lesions is performed prior to treatment commencement. This is performed using standardized data collection forms and colour photography. Up to 20 measurable metastases are identified as target lesions and recorded at baseline. The change in the longest diameter for all target lesions is used to assess the objective tumor response following treatment using RECIST. Regular radiological and serum biochemical assessments are also integrated within the treatment and follow-up regimen.

Outcomes Assessments

Treatment response will be determined through clinical and photographic assessment for palpable or visual lesions at baseline and at the time of best response or up to 12 months following the commencement of treatment. Efficacy will be measured using RECIST with the overall response rate (ORR) and clinical benefit (CB) calculated by summation of response parameters. Treatment of emergent adverse experiences will be based on the severity grade using the Common Terminology Criteria for Adverse Events (CTCAE v4.03). Changes in haematology, serum biochemistry and other laboratory values will be summarized using descriptive methods. Differences will be calculated relative to the values collected at study enrolment. Progression-free and disease-free survival will be monitored by clinical assessment and CT/PET/MRI radiology will be performed for assessment of systemic disease at baseline and at 6, 12 and 24 months after commencing treatment. All subjects will be followed for overall survival until the close of the study. Changes in patient-rated outcomes before treatment, at 12 months and the time of best response, will be assessed using the Functional Assessment of Cancer Therapy – Melanoma (FACT-M), a health-related quality of life (HRQoL) instrument. An estimated difference in the health-related costs will be performed after the conclusion of study by comparing the typical expenses incurred by a patient in each treatment arm with ILI using existing institutional data and a projected economic bootstrapping model.

Adverse Events and Safety Profile

Safety will be assessed by documenting toxicity using CTCAE v4.03 and recording other serious adverse events. An acceptable safety profile is defined as 80% of patients receiving the treatment without any grade IV adverse events. An interim safety assessment will be performed within four weeks of the 5th patient completing imiquimod and DPCP treatment.

Quality Assurance

Comprehensive data management will be conducted in accordance with ANZCTR standards with strict operating procedures and policies. Operation meetings will be held to review trial progress, supported by at least annual trial management committee meetings. Patient data will be collected using standardized case report forms and entered onto a secure database. With respect to the primary and secondary endpoints, the first 5 participants will be reviewed by an expert dedicated reviewer and thereafter 1 in every 5 patients will undergo select review. Personal information will be collected, maintained and shared confidentially throughout and after the study's completion. The trial coordinator is responsible for data cleaning and entry.

Substudies

Biological

In addition to examining clinical questions, this study supports a biological research programme. The trial includes the collection of blood, saliva and tumour specimens which are stored within a Melanoma and Soft Tissue Bank (HREC-10-QPAH-153). Tumour specimens include material from pre-treatment biopsies with repeated biopsies performed at 4 weeks and 9 months after treatment commencement. In addition to formalin-fixed or paraffin-embedded material, fresh tissue will be provided for sequencing, RNA/protein analysis and BRAF mutation testing.

The primary objective of the translational research programme is to create an extensive tissue bank with parallel clinical information to facilitate novel investigations, hypothesis-generation and validation of existing concepts. Broad research questions include*: 'Are there genetic determinants of immunotherapeutic response in melanoma?', 'What are the biological differences between patients capable of producing robust treatment responses versus those with progressive disease?', 'Are there specific biomarkers that can be used to predict disease progression or treatment response?'* and *'Does preliminary treatment with topical immunotherapies lead to sustained biological effects or translate into subsequent treatment or significant survival differences when commenced on systemic immunotherapies?'*

Health-related Quality of Life and Health Economic Evaluation

This trial utilises assessments of patient-rated outcomes and changes in response to treatment. In this study, HRQoL will be assessed using the 51 item FACT-M. This is a multi-dimensional, melanoma-specific, validated instrument that was developed to measure HRQoL in patients with cutaneous melanoma. The FACT-M incorporates four general subscales within the core questionnaire and a melanoma-specific subscale. Derived using the five components together, an aggregate score is produced, where a higher value reflects improved overall well-being. [16]

To date, there is limited information available from formal evaluations of HRQoL in patients with in-transit metastases and this study will generate interesting data to compare with other melanoma cohorts [14, 17-20] Currently, the relative differences between topical therapies and other loco-regional treatments remains unknown. We expect that DPCP and imiquimod therapy will improve loco-regional disease control compared to patients' baseline although this may be associated with higher levels of treatment-related morbidity. Consequently, it is important to measure HRQoL to determine the effects of these agents on patient-rated outcomes and differentiate them from other available therapies.

An economic assessment will be performed on the conclusion of this study incorporating various data points. The relative effect of treatment on HRQoL, disease progression, overall survival, resource consumption and estimated treatment-related costs will serve as the primary inputs. While not powered to provide a statistically significant comparative assessment, reference will be made to the historical standard of care (ILI) as institutional treatment outcomes and cost data are available. It is hypothesized that imiquimod and DPCP are relatively cheap, convenient and clinically effective alternatives for patients with this disease-subtype.

DISCUSSION

Existing evidence supports the use of these agents for the topical treatment of cutaneous melanoma metastases. However, there is limited high-quality efficacy and safety data and no well-established treatment regimens. Both agents are relatively inexpensive, easy to administer and require only intermittent clinician review and these properties make topical therapies attractive alternatives to more invasive and commonly used options. Counter-intuitively, there is an absence of studies measuring quality of life or health-related costs in this patient group.

Key priorities of this pilot study are to:

- Further assess the clinical efficacy and safety-profile of each investigational agent.
- Improve the accuracy of power calculations.
- Establish a treatment regimen allowing for titration to therapeutic effect.
- Determine how many patients can be effectively recruited for treatment.
- Evaluate the financial and logistical feasibility of implementing these therapies.

The additional data and revised procedures will assist further trial design and co-ordination within a full-scale multi-centre Phase II/III study. If these treatments prove effective it is expected this will lead to improved patient-rated outcomes through a reduction in local disease, fewer serious treatment-related complications and more convenient application. It will also streamline review and may lead to decreased healthcare-associated expenditure. Providing multi-disciplinary care within a high-quality environment will apprise of other important aspects of this complex disease.

The TIDAL Melanoma Study is an investigator-initiated study that incorporates novel immunotherapeutics to inform on the technical aspects of treatment as well as the efficacy and safety profiles of the investigational agents, patient-rated outcomes and health economics. It aims to address a significant question with respect to the management of this challenging disease and will provide further evidence on clinical practice and treatment standards for advanced loco-regional melanoma.

ETHICS AND DISSEMINATION

The study has ethics approval (HREC/15/QPAH/632) from the Human Research Ethics Committee at the participating centre. and is being conducted in accordance with appropriate human research standards. The results of the study will be submitted for formal publication within a peer-reviewed journal.

TRIAL REGISTRATION – Australian New Zealand Clinical Trials Registry: ACTRN 12615001088538

Prospectively registered: 16 October 2015.

AUTHOR CONTRIBUTIONS

T. READ (Principal Investigator) – Manuscript writing, trial design, trial co-ordination and patient care.

S. WEBBER – Trial co-ordination, data collection and patient care.

J. THOMAS (Trial Co-ordinator) – Trial co-ordination and data management.

M. WAGELS – Manuscript editing, trial design and patient care.

H. SCHAIDER – Trial design and manuscript editing.

H. P. SOYER – Trial design and co-ordination.

B. M. SMITHERS – Manuscript editing, trial design and co-ordination and patient care.

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The TIDAL Melanoma Study is an investigator initiated trial with logistical support provided by the Queensland Melanoma Project. Dr Tavis Read was the recipient of a Junior Research Fellowship awarded by the Queensland Government and Clinical Research Fellowship awarded by the PA Research Foundation both which supported the establishment of this study.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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FIGURE LEGEND

FIGURE 1 – TIDAL Melanoma Study Flowchar

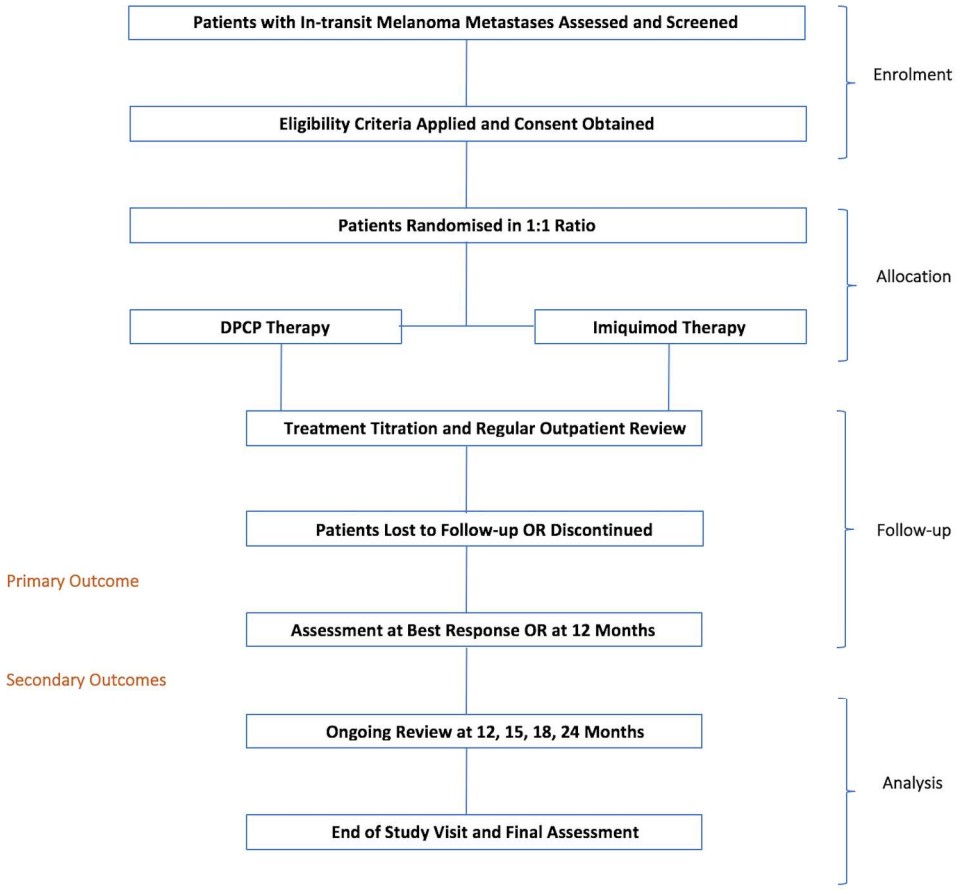

FIGURE 1 – TIDAL Melanoma Study Flowchart.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3,5
Objectives	7	Specific objectives or hypotheses	3,5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3,4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	1

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	2
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	9
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	5
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	7

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Protocol for the TIDAL Melanoma Study: Topical Imiquimod or Diphenylcyclopropenone for the Management of Cutaneous In-transit Melanoma Metastases – A Phase II Single Centre Randomised Pilot Study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016816.R2
Article Type:	Protocol
Date Submitted by the Author:	05-Jul-2017
Complete List of Authors:	Read, Tavis; Queensland Melanoma Project, Princess Alexandra Hospital; The University of Queensland, Discipline of Surgery, The School of Medicine Webber, Scott; Dermatology Research Centre, The University of Queensland Diamantina Institute; Princess Alexandra Hospital, Department of Dermatology Thomas, Janine; Queensland Melanoma Project, Princess Alexandra Hospital Wagels, Michael; Queensland Melanoma Project, Princess Alexandra Hospital; The University of Queensland, Discipline of Surgery, The School of Medicine Schaider, Helmut; Dermatology Research Centre, The University of Queensland Diamantina Institute; Princess Alexandra Hospital, Department of Dermatology Soyer, H. Peter; Dermatology Research Centre, The University of Queensland Diamantina Institute; Princess Alexandra Hospital, Department of Dermatology Smithers, B. Mark; Queensland Melanoma Project, Princess Alexandra Hospital; The University of Queensland, Discipline of Surgery, The School of Medicine
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Research methods, Surgery, Dermatology, Immunology (including allergy)
Keywords:	In-transit, Melanoma, Metastases, Topical, Immunotherapy, Clinical trials < THERAPEUTICS

BMJ Open – Study Protocol

TITLE: Protocol for the *TIDAL Melanoma Study*: *Topical Imiquimod or Diphenylcyclopropenone for the Management of Cutaneous In-transit Melanoma Metastases – A Phase II Single Centre Randomised Pilot Study.*

STUDY ACRONYM: *Topical Imiquimod or Diphenylcyclopropenone for Advanced Loco-regional (TIDAL) Melanoma Study*

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KEY WORDS

In-transit, melanoma, metastases, topical, immunotherapy, clinical trial

WORD COUNT

- 247 (abstract)
- 3,197 (body exc. references)
- 1 table. 1 figure.

CONFLICT OF INTEREST

None to declare.

FUNDING SOURCES

Dr Read was the recipient of a Junior Research Fellowship funded by the Queensland Government. This is an investigator-initiated, non-sponsored study.

ETHICS AND DISSEMINATION

This study has institutional ethics approval (HREC/15/QPAH/632) and is being conducted in accordance with appropriate human research standards using the TIDAL-M-01 Protocol Version 3.4 (last amended 6 February 2017).

ABSTRACT

INTRODUCTION – Patients with in-transit melanoma metastases present a therapeutic challenge. Complete surgical excision of localised disease is considered the gold standard, however surgery is not always acceptable and alternatives are required. Early treatment results reported using imiquimod and diphenylcyclopropenone (DPCP) suggest that topical immunotherapies can be used to successfully treat select patients with melanoma metastases. A Phase II, randomised, single centre, pilot study was designed to assess the clinical efficacy and safety of DPCP and imiquimod for the treatment of superficial, cutaneous in-transit melanoma metastases.

METHODS AND ANALYSIS - This is an open-label, non-superiority, pilot study with no treatment cross-over. Eligible patients are randomised in a 1:1 ratio to receive topical therapy for 12 months with a minimum follow-up period of 12 months. The target sample size is 30 patients, with 15 allocated to each treatment arm. The primary endpoint is the number of patients experiencing a complete response of treated lesions as determined clinically using RECIST. This trial incorporates health-related quality of life measures and biological tissue collection for further experimental sub-studies. The study will also facilitate a health economic analysis.

ETHICS AND DISSEMINATION – Approval was obtained from the Human Research Ethics Committee at the participating centre. and recruitment has commenced. The results of this study will be submitted for formal publication within a peer-reviewed journal.

TRIAL REGISTRATION – Prospectively registered on 16 October 2015 with the Australian New Zealand Clinical Trials Registry: ACTRN 12615001088538. This study conforms to the World Health Organisation Trial Registration Data Set.

Limitations and Strengths of This Study

- This trial is a proof of concept, pilot study with a small sample size and non-blinded design. While expediting the availability of high quality data useful for conducting a larger study, these factors will also reduce the generalisability of clinical findings to the in-transit melanoma patient population.
- This is a complex patient group and the inclusion of patients who have failed or are unsuitable for other treatments may introduce a selection bias for those with more aggressive disease-types.
- The broader DPCP dosing range compared with imiquimod may also create a treatment bias, with more individualised regimens 'tailored' to patients within the DPCP arm.
- The prospective design, randomised allocation of participants and strict clinical trial environment will improve the quality of data collected and evidence available for these therapies.
- The provision for titrating the dose and frequency of the investigational agents will help establish an evidence-based treatment regimen. The use of standardised clinical outcome measures will produce more accurate and precise efficacy data than is currently available. This will enhance the reliability of power calculations required for a comparative superiority study.
- In addition to technical information, the pilot study design will assist with evaluating the financial and logistical feasibility of establishing a full-scale study.
- The secondary outcomes including adverse events, patient-rated outcomes and health-related costs will facilitate further health and economic evaluations associated with these novel therapies.

INTRODUCTION

There has been a sustained increase in the incidence of cutaneous melanoma worldwide, with an estimated lifetime risk now of up to 1 in 147 in the UK and 1 in 25 in other Commonwealth nations. [1 - 3] With early detection the five-year survival rate for melanoma is excellent (> 90%), however the prognosis remains poor in patients with recurrent, loco-regional disease. [4] In-transit melanoma is an advanced form of disease (≥Stage IIIB) associated with a poor prognosis and significantly lower quality of life outcomes secondary to disease-related functional impairment and treatment side-effects. [4 - 6] Patients have an unpredictable clinical course and variable treatment responses. [7, 8] Currently, the management of these patients is variable with no consensus on the optimal therapeutic approach.

Complete surgical excision is effective for localised disease, however surgery is often inappropriate. Loco-regional treatments may improve quality of life but do not improve melanoma-specific survival. Existing strategies aim to maximise loco-regional disease control while reducing disease and treatment-related morbidity. Due to the need for less-invasive, non-surgical modalities, immunological-based therapies have been investigated for the treatment of melanoma metastases. [9]

Topical immunotherapies may improve disease control without a significant increase in treatment-related adverse events. In selected patients DPCP and imiquimod have been reported to produce response rates of up to 84% and 100% respectively. [10, 11] Lesion morphology may also be an important predictor of treatment response, with higher response rates observed with superficial (epidermotropic) lesions versus nodular or bulky types. [12, 13] Therefore it appears patients can be rationally selected for treatment based on disease phenotype, while respecting their co-morbidities and functional status. [14] The agents appear to be convenient to administer, relatively cheap and generally well-tolerated, although these findings have not been established within a formal trial setting.

Study Rationale

The use of both agents has, to date, been reported in small case series with retrospective study designs. A Phase II, randomised, proof of concept, pilot study was therefore designed to formally evaluate imiquimod and DPCP for the selective management of superficial, cutaneous in-transit melanoma metastases. The aim of this study is to determine if either treatment is a clinically efficacious and well-tolerated alternative to current therapies in patients who cannot undergo, refuse or have failed surgery. The trial will also formally measure patient-rated outcomes, facilitate a health economic evaluation and include biological tissue collection for further experimental sub-studies.

TIDAL Melanoma Study (PICO Format)

Research Question – Can topical imiquimod or DPCP be used to effectively treat patients with superficial, cutaneous in-transit melanoma metastases?

Population – Adults ≥ 18 years with stage III / IV melanoma and biopsy confirmed superficial, cutaneous in-transit metastases that have failed, decline or are unsuitable for surgery.

Intervention – Patients will be randomised 1:1 to receive either topical imiquimod or DPCP therapy.

Comparison – This is a non-superiority, proof of concept, pilot study. It is not powered to detect a significant difference in the primary outcome between the investigational agents. Reference will be made to the standard of care represented by isolated limb infusion (ILI) where appropriate.

Outcome – The primary endpoint is the number of patients experiencing a complete response of treated lesions within 12 months of starting treatment as determined clinically using RECIST. Secondary outcomes include: the proportion of patients experiencing a non-complete response at 12, 18 and 24 months (partial response, stable disease or progressive disease), progression and disease-free survival, time to loco-regional and overall disease progression, rate of treatment-related adverse events and patient-rated outcomes.

Time – The primary outcome will be measured at the time of best response, with up to 12 months of treatment. Clinical assessments will be performed regularly during outpatient reviews with radiological surveillance at 12, 18 and 24 months. The planned minimum follow-up duration is 12 months from the time of best response. Patients will be excluded from the trial if they develop progressive loco-regional or systemic disease and will be treated in accordance with the standard of care available.

METHODS AND ANALYSIS

Trial Design

This is a Phase II, randomised, proof of concept, pilot study to be performed at a single centre in Brisbane, Australia. It is designed as an open-label, dual arm, non-superiority trial without treatment cross-over. Eligible patients are randomised in a ratio of 1:1 to receive either imiquimod ('Treatment Arm A') or DPCP ('Treatment Arm B') therapy over a minimum duration of 12 months or until the time of complete response or disease progression. Treatment will be performed by the patient at home allowing for intermittent scheduled clinical reviews within an outpatient setting. The planned minimum follow-up duration is 12 months from the best response or disease progression, this will allow for close clinical and radiological surveillance (Figure 1).

Pilot Study Rationale

There is limited data describing the use of the investigational agents for this indication in the literature. Based on the existing rate of new patients treated at our institution plus the estimated accrual rate projected for the trial period, 30 subjects are planned for enrolment within the pilot study. Given this is a non-superiority, proof of concept, pilot study, formal power-calculations were not applied to determine allocation numbers. It is expected that this target sample size will provide sufficient high quality data to confirm the efficacy rates reported in the literature and improve the accuracy of power calculations required for a full-scale superiority study. This will also help investigators establish a standardised treatment regimen that allows for dosing adjustment with titration to effect. In addition to technical information, the pilot study will assist with evaluating the financial and logistical feasibility (including patient compliance, data collection and costs) of establishing a full-scale study. The revised procedures are intended for use within a larger programme at multiple centres as a Phase II/III trial.

Allocation

Randomisation is provided by a web-based permuted block system and performed by the trial coordinator or principal investigator. The method uses permuted blocks of variable size between two to four participants and stratification factors are: 1. Age <65 OR ≥65 years at the time of diagnosis of in-transit metastases; AND 2. Time to develop in-transit metastases <12 months OR ≥12 months from the time of primary melanoma diagnosis. Patients are randomised in a 1:1 ratio and allocated to either treatment arm, thereby receiving one of two possible treatments.

Participants

Adults ≥ 18 years, with AJCC stage III or IV disease and biopsy-confirmed cutaneous in-transit melanoma metastases will be enrolled for treatment. Patients must be willing and able to comply with study requirements and provide valid consent. A minimum of five measurable lesions in anatomical locations suitable for topical treatment are required to enable initial and repeat lesion biopsies and the objective assessment of tumour response. Treated lesions will be between 2-15mm in diameter that can be accurately assessed by ruler/caliper. Macular, papular or small nodular morphology types will be included. Patients must be considered unsuitable for surgery by the treating clinician due to the anatomical location, prohibitive disease factors, patient refusal or previous treatment failure. A minimum duration of 12 weeks is required between completing other biological treatments (such as ILI or PV-10 intralesional therapy). Women of child bearing potential must have a confirmed negative blood pregnancy test at study entry and use approved contraception throughout the study. Patients must have adequate renal, haematopoietic and hepatic function, with no clinically significant impairment.

Exclusion Criteria

- Considered eligible for concurrent treatment with systemic chemo- or immuno-therapies.
- Subjects who have received chemotherapy or other systemic cancer therapy within 12 weeks of the study.
- Subjects who have received other local therapy (e.g. surgery, cryotherapy, laser or radiofrequency ablation) to the treatment area within 4 weeks of study treatment.
- Life expectancy of less than 6 months or ECOG performance status ≥3.
- Medical or psychiatric condition that compromises the patient's ability to complete the treatment regimen or follow-up assessments as per protocol.
- Female subjects that are pregnant or lactating.
- Known history of immunodeficiency, including HIV positive subjects, uncontrolled central nervous system metastases, concomitant systemic corticosteroid or other immunosuppressive use or previous organ transplant.
- Known severe concurrent or inter-current illness including: cardiovascular, respiratory, or immunological illness, psychiatric disorders, or substance dependence that would, in the opinion of the Investigator, compromise safety or compliance or interfere with interpretation of study results.
- Previous severe adverse or allergic reaction to either treatment agent.

Study Objectives

Primary Endpoint

The number of patients experiencing a complete response of treated lesions within 12 months of starting treatment as determined clinically using the Response Evaluation Criteria in Solid Tumors (RECIST). [15]

Secondary Endpoints

- Proportion of patients experiencing a non-complete response in target lesions (partial response, stable disease and progressive disease as per RECIST) at 12, 18, and 24 months after treatment commencement.
- Loco-regional progression-free and disease-free survival.
- Proportion of patients with overall disease progression including death following treatment.
- Patient-rated outcomes (health-related quality of life) before, at the time of best response, and 12 months from the conclusion of treatment.
- Rate of treatment-related adverse events.
- Estimated health-related costs.

Recruitment

Potential subjects are initially assessed and screened through the Melanoma Outpatient Clinic at the Princess Alexandra Hospital, Brisbane, Australia. Consent, enrolment, treatment, and follow-up occurs through a multi-disciplinary trials clinic with an emphasis on the outpatient treatment of patients with in-transit melanoma. This involves specialist care provided by dermatologists, surgeons, oncologists, trial nurses, and other allied health professionals. Each eligible subject is enrolled in the study for up to 12 months of treatment with imiquimod or DPCP. The aim is for a minimum follow-up duration of 12 months (and up to 24 months) following the best response or progressive disease. The total recruitment window will be open for at least 24 months and the total study length is therefore estimated to be up to 36 months based on recruitment rates.

Investigational Agents

Imiquimod

Patients are treated using 5% topical imiquimod applied as a mixture within an aqueous cream. This concentration remains constant for the duration of treatment. A local inflammatory response is produced with application once daily, five days per week, with two rest days. The solution is applied with a 0.5cm margin surrounding lesions and left overnight for 8 hours duration. The total treatment area is recommended as <25 cm^2. The treatment is continued so that a mild to moderate dermatitis is maintained with sequential treatments and this includes the provision to reduce the treatment frequency (Table 1).

DPCP

Patients are sensitised to DPCP using a 2% solution applied to a clinically accessible contact point (e.g. medial arm). Two weeks following sensitisation the definitive treatment is commenced. Treatment concentrations range from 0.005% to 5% applied as a mixture within an aqueous cream. The optimal dose of DPCP is based on an individual's clinical response. A contact dermatitis is produced following application. The ideal maintenance dose is gradually reached by titrating the dose from 0.005% so that a mild to moderate dermatitis is achieved with consecutive treatments. The solution is applied to the treatment area with a 0.5cm margin surrounding lesions and left for 24-48 hours total duration (Table 1).

Table 1. Imiquimod and DPCP Treatment Regimens

Week	Imiquimod	DPCP
1 - 8	5% Imiquimod applied to lesions 5 days per week with 2 rest days.	0.005% DPCP applied once weekly.
8 - 16	Imiquimod applied to lesions 5 days per week (as tolerated). If a sustained, moderate treatment reaction is noted then frequency modified to every second day (3 days per week).	DPCP concentration titrated to effect (up to 5% concentration) and applied once per week to lesions. DPCP can be used up to twice per week to achieve moderate treatment reaction.
16-52	Imiquimod applied on alternate days (3 days per week) to lesions as tolerated.	DPCP applied at maintenance dose as tolerated in order to achieve a moderate erythematous reaction.

Treatment Interruption / Temporary Suspension

At the discretion of clinicians, treatment can be temporarily withheld due to the development of significant treatment-related side-effects. This interruption period can continue for up to 4 weeks without the patient being excluded from the trial. In the event of a severe treatment reaction the dose and frequency can also be adjusted in accordance with the regimen.

Treatment Schedule

Eligible patients commence treatment within four weeks of signing informed consent. Both treatments are self-administered by patients or their carer with regular clinical reviews conducted in the outpatient setting (Supplementary Tables 1 and 2).

1. Patients randomised to Treatment Arm A receive topical 5% imiquimod cream. This is applied to target lesions up to 5 times weekly for the first 8 weeks with 2 rest days. From 8 to 16 weeks if a sustained, moderate treatment reaction is achieved the frequency is modified to every second day (3 days per week). Imiquimod is applied on alternate days from weeks 16 to 52.

2. Patients randomised to Treatment Arm B receive topical DPCP cream. Patients successfully sensitised using the 2% solution commence the treatment two weeks after initial contact. This involves application of 0.005% DPCP once weekly for the first 8 weeks. Regular clinical review as per the treatment schedule enables titration of up to a 5% solution applied once or twice per week to achieve the desired therapeutic effect.

End of Trial Review and Continuing Treatment

Following the conclusion of the trial, or with clinical progression, patients will be offered further treatment at the current standard of care. Patients will continue to be reviewed at regular clinical outpatient appointments. During the final visit, a comprehensive clinical assessment of tumour response, medical examination, radiological evaluation, and serum biochemical work-up will be performed. If a patient experiences a complete response, further topical treatment on the trial is ceased within four weeks. There is no conclusive evidence concerning the effect of continuing the therapy after this point and various regimens have been reported. Arbitrarily continuing treatment may influence the validity of the disease-free and progression-free survival calculations within this study.

Statistical Analysis

All subjects who are enrolled and receive either therapy will be evaluated for the primary and secondary outcomes using an intention-to-treat analysis. Exploratory univariate and bivariate analyses will be conducted to assess for factors significantly associated with a complete response and a multivariate Cox regression model will be used to adjust for significant dependent variables. Progression-free, disease-free and overall-survival will be calculated using Kaplan-Meier Survival Estimates. Treatment failures include: no clinical response after 3 months of treatment, loco-regional disease recurrence, or progression of target lesions within the treatment field. Persistent disease will be evaluated clinically using dermoscopy then confirmed on histopathology.

Treatment Response

Based on existing evidence it is expected that most patients will develop a clinical response to both therapies within 1-3 months of commencing treatment and experience clinical regression within 6-12 months. If no clinical response is demonstrated using the treatment regimen within 3 months, topical therapy is discontinued and the patient is recorded as a treatment failure. Baseline documentation of target lesions is performed prior to treatment commencement. This is performed using standardised data collection forms and colour photography. Up to 20 measurable metastases are identified as target lesions and recorded at baseline. The change in the longest diameter for all target lesions is used to assess the objective tumor response following treatment using RECIST. Regular radiological and serum biochemical assessments are also integrated within the treatment and follow-up regimen.

Outcomes Assessments

Treatment response will be determined through clinical and photographic assessment for palpable or visual lesions at baseline and at the time of best response or up to 12 months following the commencement of treatment. Efficacy will be measured using RECIST with the overall response rate (ORR) and clinical benefit (CB) calculated by summation of response parameters. Treatment of emergent adverse experiences will be based on the severity grade using the Common Terminology Criteria for Adverse Events (CTCAE v4.03). Changes in haematology, serum biochemistry and other laboratory values will be summarised using descriptive methods. Differences will be calculated relative to the values collected at study enrolment. Progression-free and disease-free survival will be monitored by clinical assessment and CT/PET/MRI radiology will be performed for assessment of systemic disease at baseline and at 6, 12 and 24 months after commencing treatment. All subjects will be followed for overall survival until the close of the study. Changes in patient-rated outcomes before treatment, at 12 months and the time of best response will be assessed using the Functional Assessment of Cancer Therapy – Melanoma (FACT-M), a health-related quality of life (HRQoL) instrument. An estimated difference in the health-related costs will be performed after the conclusion of study by reviewing the typical expenses incurred by a patient in each treatment arm and comparing these with ILI using a projected economic bootstrapping model.

Adverse Events and Safety Profile

Safety will be assessed by documenting toxicity using CTCAE v4.03 and recording other serious adverse events. An acceptable safety profile is defined as 80% of patients receiving the treatment without any grade IV adverse events. An interim safety assessment will be performed within four weeks of the 5th patient completing imiquimod and DPCP treatment.

Quality Assurance

Comprehensive data management will be conducted in accordance with ANZCTR standards with strict operating procedures and policies. Operation meetings will be held to review trial progress, supported by a minimum of annual trial management committee meetings. Patient data will be collected using standardised case report forms and entered onto a secure database. With respect to the primary and secondary endpoints, the first 5 participants will be reviewed by an expert dedicated reviewer and thereafter 1 in every 5 patients will undergo select review. Personal information will be collected, maintained and shared confidentially throughout and after the study's completion. The trial coordinator is responsible for data cleaning and entry.

Substudies

Biological

In addition to examining clinical questions, this study supports a biological research programme. The trial includes the collection of blood, saliva and tumour specimens which are stored within a Melanoma and Soft Tissue Bank (HREC-10-QPAH-153). Tumour specimens include material from pre-treatment biopsies with repeated biopsies performed at 4 weeks and 9 months after treatment commencement. In addition to formalin-fixed or paraffin-embedded material, fresh tissue will be provided for sequencing, RNA/protein analysis and BRAF mutation testing.

The primary objective of the translational research programme is to create an extensive tissue bank with parallel clinical information to facilitate novel investigations, hypothesis-generation and validation of existing concepts. Broad research questions include*: 'Are there genetic determinants of immunotherapeutic response in melanoma?', 'What are the biological differences between patients capable of producing robust treatment responses versus those with progressive disease?', 'Are there specific biomarkers that can be used to predict disease progression or treatment response?'* and *'Does preliminary treatment with topical immunotherapies lead to sustained biological effects or translate into subsequent treatment or significant survival differences when commenced on systemic immunotherapies?'*

Health-related Quality of Life and Health Economic Evaluation

This trial utilises assessments of patient-rated outcomes and changes in response to treatment. In this study HRQoL will be assessed using the 51 item FACT-M. This is a multi-dimensional, melanoma-specific, validated instrument that was developed to measure HRQoL in patients with cutaneous melanoma. The FACT-M incorporates four general subscales within the core questionnaire and a melanoma-specific subscale. Derived using the five components together, an aggregate score is produced where a higher value reflects improved overall well-being. [16]

To date, there is limited information available from formal evaluations of HRQoL in patients with in-transit melanoma metastases and this study will generate novel data to compare with other melanoma cohorts [14, 17-20] Currently, the relative

differences between topical therapies and other loco-regional treatments remains unknown. We expect that DPCP and imiquimod therapy will improve loco-regional disease control compared with patients' baseline although this may be associated with higher levels of treatment-related morbidity. Consequently, it is important to measure HRQoL to determine the effects of these agents on patient-rated outcomes and differentiate them from other available therapies.

An economic assessment will be performed on the conclusion of this study incorporating various data points. The relative effect of treatment on HRQoL, disease progression, overall survival, resource consumption and estimated treatment-related costs will serve as the primary inputs. Reference will be made to the standard of care (ILI) as long-term institutional treatment outcomes and healthcare cost data are currently available. It is hypothesised that imiquimod and DPCP are both relatively cheap, convenient, and clinically effective non-invasive therapies for patients with this disease-subtype.

DISCUSSION

Existing evidence supports the use of these agents for the topical treatment of cutaneous melanoma metastases. However, there is currently limited high-quality efficacy and safety data and no well-established treatment regimens. Both agents are relatively inexpensive, easy to administer and require only intermittent clinician review and these properties make topical therapies attractive alternatives to more invasive and commonly used options. Counter-intuitively, there is an absence of studies measuring quality of life or health-related costs in this patient group.

Key priorities of this pilot study are to:

- Further assess the clinical efficacy and safety-profile of each investigational agent.
- Improve the accuracy of power calculations.
- Establish a treatment regimen allowing for titration to therapeutic effect.
- Determine how many patients can be effectively recruited for treatment.
- Evaluate the financial and logistical feasibility of implementing these therapies.

The additional data and revised procedures will assist further trial design and co-ordination within a full-scale Phase II/III study. If these treatments prove effective it is expected this will lead to improved patient-rated outcomes through a reduction in local disease, fewer serious treatment-related complications, and more convenient application. It will also streamline review and may lead to decreased healthcare-associated expenditure. Providing multi-disciplinary care within a high-quality environment will apprise of other important aspects of this complex disease.

The TIDAL Melanoma Study is an investigator-initiated study that incorporates novel immunotherapeutics to inform on the technical aspects of treatment as well as the efficacy and safety profiles of the investigational agents, patient-rated outcomes, and health economics. It aims to address a significant question with respect to the management of this challenging disease and will provide further evidence on clinical practice and treatment standards for advanced loco-regional melanoma.

ETHICS AND DISSEMINATION

The study has ethics approval (HREC/15/QPAH/632) from the Human Research Ethics Committee at the participating centre and is being conducted in accordance with appropriate human research standards. The results of the study will be submitted for formal publication within a peer-reviewed journal.

TRIAL REGISTRATION – Australian New Zealand Clinical Trials Registry: ACTRN 12615001088538

Prospectively registered: 16 October 2015.

AUTHOR CONTRIBUTIONS

T. READ (Principal Investigator) – Manuscript writing, trial design, co-ordination, data collection and patient care.

S. WEBBER – Trial co-ordination, data collection and patient care.

J. THOMAS (Trial Co-ordinator) – Trial co-ordination and data management.

M. WAGELS – Manuscript and protocol editing, trial design and patient care.

H. SCHAIDER – Trial design and manuscript editing.

H. P. SOYER – Trial design and co-ordination.

B. M. SMITHERS – Manuscript editing, trial design, co-ordination and patient care.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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FIGURE LEGEND

FIGURE 1 – TIDAL Melanoma Study Flowchart

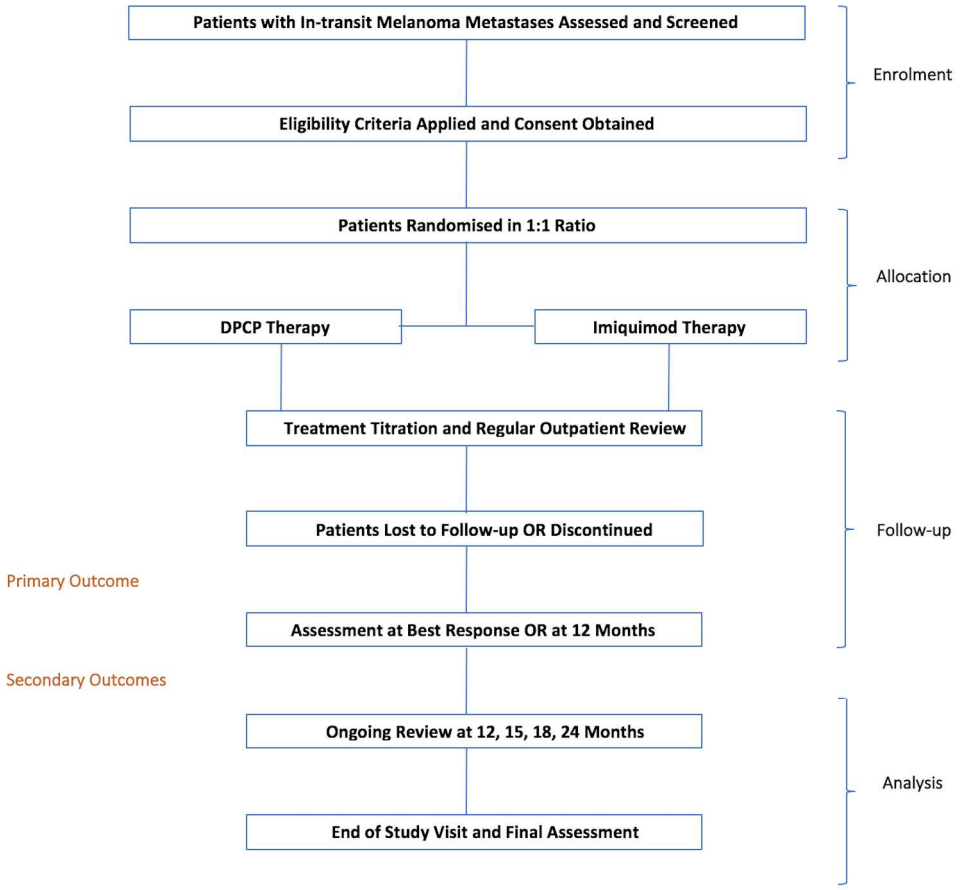

FIGURE 1. TIDAL Melanoma Study Flowchart.

Supplementary Table 1. DPCP Study Schedule

Study Assessment	Screening and Randomisation	Treatment Period																			
Time Point	W-2	DOFT	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	6M	9M	12M	15M	18M	21M	24M	Termination
Informed Consent	X																					
Inclusion / Exclusion	X																					X
Medical History	X																					X
FACT-M Assessment	X					X								X	X		X		X		X	X
Pregnancy Test	X	X																				
Routine Blood Tests	X					X				X				X	X	X	X	X	X	X	X	X
Research Blood Tests	X					X				X				X	X	X	X	X	X	X	X	X
Physical Examination	X	X				X				X				X	X	X	X	X	X	X	X	X
CT HNCAP or CT-PET	X														X		X				X	X*
Measurement of lesions		X				X				X				X	X	X	X	X	X	X	X	X
Photography of lesions		X				X				X				X	X	X	X	X	X	X	X	X
RCM and Dermoscopy		X				X										X						
Biopsy of lesions		X				X										X						
Randomisation	X																					
Application of 2% DPCP Sensitising Solution	X																					
Prescription for DPCP		X				X				X				X	X	X	X	X	X	X	X	
Application of DPCP Treatment Solution		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Titration of DPCP						X				X				X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

DOFT = Day of First Treatment

Supplementary Table 2. Imiquimod Study Schedule

Study Assessment	Screening and Randomisation	Treatment Period																			
Time Point	W-2	DOFT	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	6M	9M	12M	15M	18M	21M	24M	Termination
Informed Consent	X																					
Inclusion / Exclusion	X																					X
Medical History	X																					X
FACT-M Assessment	X					X								X	X		X		X		X	X
Pregnancy Test	X																					
Routine Blood Tests	X					X				X				X	X	X	X	X	X	X	X	X
Research Blood Tests	X					X				X				X	X	X	X	X	X	X	X	X
Physical Examination	X	X				X				X				X	X	X	X	X	X	X	X	X
CT HNCAP or CT-PET	X														X		X				X	X*
Measurement of lesions		X				X				X				X	X	X	X	X	X	X	X	X
Photography of lesions		X				X				X				X	X	X	X	X	X	X	X	X
RCM and Dermoscopy		X				X										X						
Biopsy of lesions		X				X										X						
Randomisation	X																					
Prescription for ImiQ 5%		X													X							
Application of ImiQ 5% Treatment Solution		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

DOFT = Day of First Treatment

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	3,5
Objectives	7	Specific objectives or hypotheses	3,5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	3,4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	4
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	4
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	4
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	4
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	7
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	7
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	7
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	1
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	1

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	2
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	9
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	5
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	7

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.