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SCC-AFTER

Adjuvant Radiotherapy in Patients with High-risk Primary Cutaneous Squamous Cell Carcinoma AFTER surgery (SCC-AFTER): An Open Label, Multicentre, Two-arm Phase III Randomised trial.

PROTOCOL

V1.1, 18TH MARCH 2024

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

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General Information This protocol describes the SCC-After clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

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TRIAL COORDINATION

The SCC-AFTER trial is being coordinated by the Centre for Trials Research (CTR) Cardiff University, a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the SCC-AFTER Trial Management Group (TMG) on behalf of the NCRI Skin Cancer Clinical Studies Group (CSG).

For **all queries,** please contact the SCC-AFTER team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a Co-Investigators

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Randomisations:

Randomisation

Sites should provide a delegation log to the CTR SCC-After team during trial set up and update the log as required.

Site staff delegated to patient enrolment and/or data entry duties will be granted access to the trial database for enrolment and data entry.

A link to the randomisation system will be sent upon site activation along with a database User guide. See section 9.5 for more details.

If you have trouble accessing the system, or if it is unavailable, please email SCCAfter@cardiff.ac.uk to request enrolment of a patient.

Clinical queries:

Clinical Queries

SCCAfter@cardiff.ac.uk

All clinical queries will be directed to the most appropriate clinical person.

Serious Adverse Events (SAE):

SAE Reporting

Where the adverse event meets one of the serious categories, an SAE form should be completed by the responsible clinician and submitted to the CTR Safety Team via email within 24 hours of becoming aware of the event (See section 15 for more details).

Serious Adverse Event (SAE) email address:

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Glossary of abbreviations

ABPI	Association of the British Pharmaceutical Industry	**MHRA**	Medicine and Healthcare products Regulatory Agency
AE	Adverse Event	**MLTCs**	Multiple Long-term Conditions
AR	Adverse Reaction	**ModRUM**	Modular Resource-use Measure
ART	Adjuvant Radiotherapy	**NCA**	National Competent Authority
BAD	British Association of Dermatologists	**NCT**	National Clinical Trial
BWH	Brigham Women's Hospital	**NHS**	National Health Service
C&C	Capability and Capacity	**NICE**	National Institute for Clinical Excellence
CF	Consent Form	**NICE**	National Institute for Health and Care Excellence
CI	Chief Investigator	**OS**	Overall Survival
CRF	Case Report Form	**PAG**	Patient Advisory Group
cSCC	Cutaneous squamous cell carcinoma	**PFS**	Progression free survival
CT	Computerised Tomography	**PI**	Principal Investigator
CTA	Clinical Trial Authorisation	**PIS**	Participant Information Sheet
CTCAE	NCI Common Terminology Criteria for Adverse Events	**PPE-15**	Picker Patient Experience 15
CTR	Centre for Trials Research	**PPI**	Patient Public Involvement
CU	Cardiff University	**PRO**	Patient Reported Outcomes
DSUR	Development Safety Update Report	**PV**	Pharmacovigilance
EADO	European Association of Dermato- Oncology	**QA**	Quality Assurance
ECG	Electrocardiogram	**QALY**	Quality-adjusted Life Years
ECOG	Eastern Cooperative Oncology Group	**QoL**	Quality of Life
eCRF	Electronic Clinical Report Form	**QRI**	QuinteT Recruitment Intervention
EHR	Electronic Health Records	**R&D**	Research and Development
EOI	Expression of Interest	**RCR**	Royal College of Radiologists
EORTC	European Organisation for Research and Treatment of Cancer	**RCT**	Randomised Controlled Trial
EudraCT	European Clinical Trials Database	**REC**	Research Ethics Committee
FFPE	Formalin Fixed Paraffin Embedded	**RMDT**	Regional Multi-Disciplinary Team
GCP	Good Clinical Practice	**RPGD**	Radiotherapy Planning Guidance Document
GDPR	General Data Protection Regulations	**RTTQA**	Radiotherapy Trials Quality Assurance
GMP	Good Manufacturing Practice	**SAE**	Serious Adverse Event
GP	General Practitioner	**SAP**	Statistical Analysis Plan
HCRW	Health Care Research Wales	**SAR**	Serious Adverse Reaction
HE	Health Economics	**SCC-AFTER**	Adjuvant radiotherapy in patients with high-risk primary cutaneous Squamous Cell Carcinoma AFTER surgery
HRA	Health Research Authority	**SCI**	Skin Cancer Index

HTA	Health Technology Assessment	**SEAR**	Screened, Eligible, Approached, Randomised
HR	High Risk	**SmPC**	Summary Product Characteristics
HRA	Health Research Authority	**SoC**	Standard of Care
IB	Investigator Brochure	**SOP**	Standard Operating Procedure
IC	Informed Consent	**SSMDT**	Specialist Skin Multi-Disciplinary Team
ICF	Informed Consent Form	**SUSAR**	Suspected Unexpected Serious Adverse Reactions
ICH	International Conference on Harmonization	**SWAP**	Study Within a Project
IDMC	Independent Data Monitoring Committee	**TMF**	Trial Master File
IQR	Interquartile Range	**TMG**	Trial Management Group
IRAS	Integrated Research Application System	**TSC**	Trial Steering Committee
ISF	Investigator Site File	**UICC**	Union of International Cancer Control
ISR	Investigator Safety Report	**UK**	United Kingdom
ISRCTN	International Standard Randomised Controlled Trial Number	**UKDCTN**	UK Dermatology Clinical Trials Network
ITT	Intention-to-treat	**USM**	Urgent Safety Measure
LRR	Loco-Regional Recurrence	**USA**	United States of America
MA	Marketing Authorisation	**UV**	Ultraviolet
MDT	Multidisciplinary Team		
MedDRA	Medical Dictionary for Regulatory Activities		

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version

Synopsis

Study Title	Adjuvant radiotherapy in patients with high-risk primary cutaneous Squamous Cell Carcinoma AFTER surgery (SCC-AFTER): an open label, multicentre, two-arm phase III randomised trial.
Short title	Adjuvant radiotherapy in patients with high-risk primary cutaneous **S**quamous **C**ell **C**arcinoma **AFTER** surgery.
Acronym	SCC-AFTER
Clinical phase	Phase III
Funder and ref.	NIHR Health Technology Assessment (HTA) Programme. NIHR151760
Trial design	An open label, multicentre, two-arm, phase III, pragmatic group sequential randomised control trial to evaluate superiority, cost-effectiveness, and effects on quality of life (QoL) of adjuvant radiotherapy (ART) in completely resected high-risk (BWH T2b/3) primary cutaneous squamous cell carcinoma (cSCC). Patients will be randomised to either the ART followed by close clinical follow up (ART arm) or close clinical follow up only (comparator arm and current standard care). Patients will be assessed following UK guidance at baseline, mid-ART (ART arm only), 4 monthly for 2 years, then 6-monthly for year 3 (1-3). During the follow-up period, QoL and Health Economics (HE) will be assessed twice for year 1, annually in years 2 and 3. Progression and survival data will be collected throughout the trial. An internal pilot targeting recruitment of 100 patients within the first 12 months will determine feasibility. Two interim analyses after 77 and 115 events (600-760 randomised) trigger early stopping if the log-rank statistic is larger than +/- 3.36 and +/- 2.68 respectively. Stopping for efficacy means fewer participants and shorter follow-up. Otherwise, the trial will be analysed when at least 194 events have been reported. A Quintet Recruitment Intervention and INCLUSION Study Within a Project (SWAP) are included to optimise recruitment and inclusion of people with multiple long-term conditions, safeguard informed consent, address clinician equipoise, and identify organisational barriers.
Trial participants	Adult patients with histologically clear margins, high-risk (BWH T2b/3), primary cSCC are eligible. “Histologically clear margin” is defined in cSCC as where peripheral and deep tumour histological margins have been excised by ≥1 mm to fulfil criteria recommended by the Royal College of Pathologists and the British Association of Dermatology (BAD) guidelines for management of primary cSCC (1). It will be noted in screening if this is a barrier to recruitment for patients with cSCC lesions to the scalp.

	The participant population includes those who are older, immunocompromised, have chronic conditions, and those with cognitive impairments.
Planned sample size	840
Planned number of sites	25
Inclusion criteria	Patients are eligible to be included in the study only if all the following inclusion criteria and none of the exclusion criteria apply: 1) High-risk primary cSCC (T2b/T3 by BWH staging criteria) excised with adequate peripheral and deep surgical margins (according to BAD guidelines) with histologically clear margins (≥1mm by RCPath criteria). ^ 2) Time since excision surgery < 3 months (or < 4 months if necessary but < 3 months is preferred). 3) Eastern Co-operative Oncology Group (ECOG) performance status of ≤3 at enrolment. 4) 18 years and older at time of consent. 5) Fit for ART and able to attend radiotherapy outpatient appointments. 6) Life expectancy > 6 months. 7) Informed Consent obtained* which must be prior to any mandatory study-specific procedures, sampling, and analyses. ^Guidance criteria: Surgical margins: Peripheral: ≥6 mm or 10 mm, Deep: to next uninvolved anatomic surgical plane (galea on scalp). If a histological margin is close or involved, re-excision is allowed (as per BAD guidelines). * Patients should be provided with additional support and adjustments where needed (e.g., layering of information, involvement of a family member/friend as a support person, provide witnessed informed consent if unable to confirm informed consent in writing).
Exclusion criteria	1) Any current clinicopathological evidence of loco-regional recurrence of the index tumour. 2) Previous (within 3 years) or current non-index primary cSCC in skin drained by the same lymph node basin**. 3) cSCC on anatomical sites which interfere with suitability for ART (such as vermilion lip, eyelids, breast, anogenital area). 4) Patients with evidence of regional or distant disease at time of primary cSCC diagnosis. 5) Previous radiotherapy to the same area. 6) Patients with reproductive potential who are not willing to use contraception for the duration from trial consent until the last dose of radiotherapy if they are randomised to the ART arm.

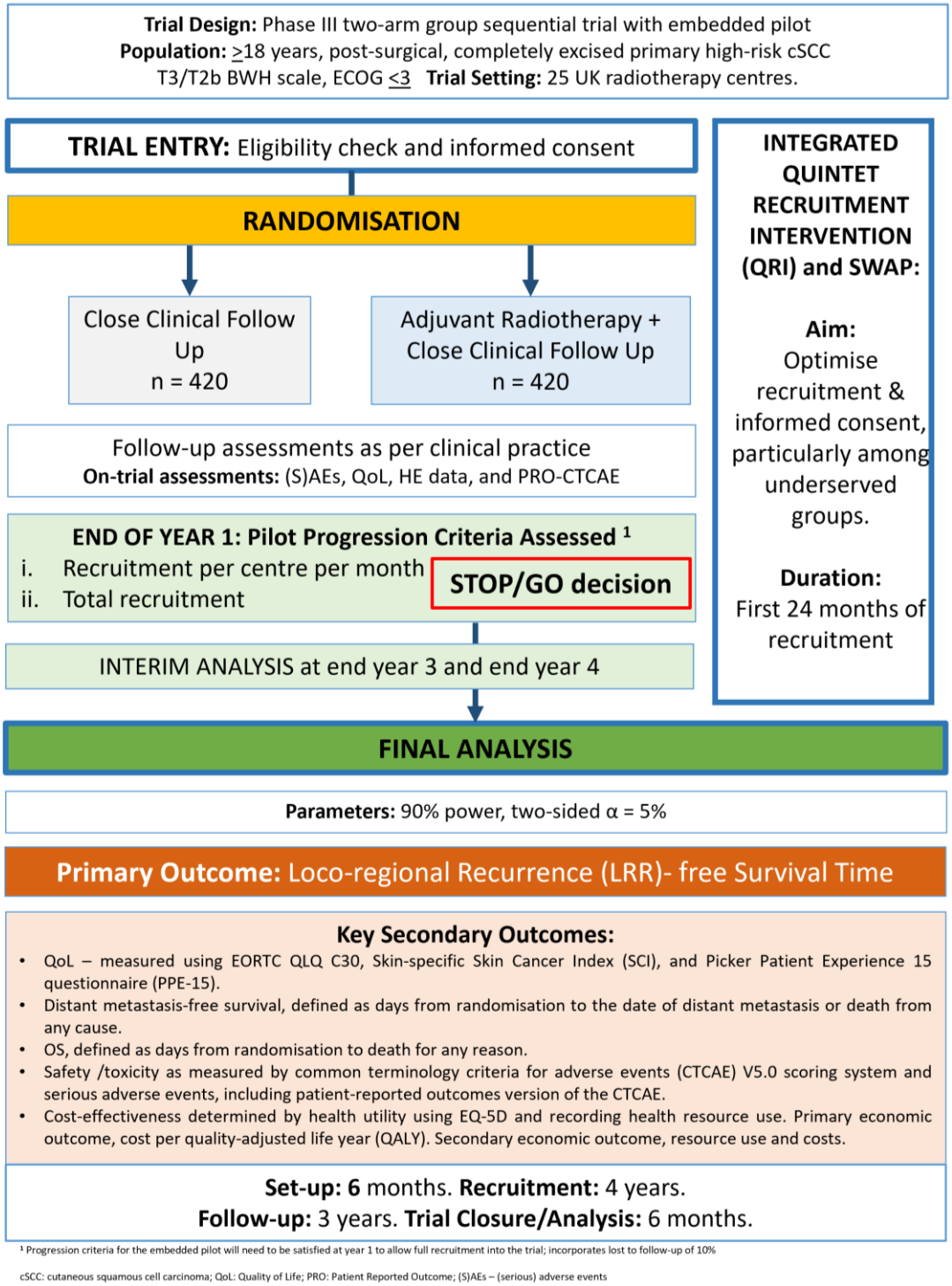
	7) Unable to lie still unattended for the duration of ART (estimated to be around 5 minutes). 8) Participation in another interventional clinical study that may affect the recurrence of cSCC (primary end point). 9) History of another malignancy where metastasis could cause diagnostic uncertainty or patients receiving active systemic anti-cancer treatment (excluding hormonal treatment for prostate or breast cancer) or radiotherapy***. ***Please discuss all patients with multiple cSCC draining to the same nodal basin as the index cSCC with the SCC-After trial team including those within the last 3 years.* ****Please discuss patients with malignancy of concern with the SCC-After trial team.*
Treatment duration	ART will commence within 12 weeks following surgery and only if the wound has sufficiently healed to receive radiotherapy (RT). Three different duration RT regimens are permitted in this trial; the clinician can choose which is appropriate for each patient depending on tumour and patient factors. Participants randomised to the ART arm will receive either: • 45Gy/10 treatments/2 weeks • 55Gy/20 treatments/4 weeks • 60Gy/30 treatments/6 weeks
Follow-up duration	Following ART participants will receive close clinical follow up for 3 years. Participants in the comparator arm will receive close clinical follow up for 3 years from date of randomisation.
Planned trial period	8 years (4 years recruitment and 3 years follow up)
Primary objective	To evaluate the efficacy of ART plus close clinical follow up compared to close clinical follow up alone (standard care) in reducing loco-regional recurrence (LRR) following complete excision of high-risk (BWH T2b/3) primary CSCC. • "Local recurrence" is defined as cSCC in or below the skin that does not have the clinical appearance of primary cSCC and is within or adjacent to the index primary site, or between the primary site and the regional lymph nodes. Diagnosis of local recurrence will be confirmed by the SSMDT/RMDT. • "Regional recurrence" is defined as cSCC which has spread to lymph node/s within the basin deemed to be draining the site of the index primary cSCC. In head and neck cSCC, these may be contralateral. Diagnosis of regional recurrence will be confirmed by the SSMDT (Regional MDT in Scotland, RMDT; MDT in Wales)

Secondary objectives	• To determine the impact on QoL of ART in completely resected high risk (BWH T2b/3) primary cSCC compared to standard clinical follow up. • To evaluate distant metastasis-free survival in both groups. • To evaluate overall survival (OS) in both groups. • To determine the safety of ART in terms of the proportion of patients experiencing toxicity compared with close clinical follow up. • To evaluate the cost-effectiveness of ART.
Tertiary/Exploratory objectives	Optimise recruitment and informed consent (Quintet Recruitment Intervention, QRI) particularly among patients historically underserved in trials research (Study within a project, SWAP)
Primary outcomes	Loco-regional recurrence (LRR)-free survival time: Time to LRR is defined as the time from randomisation to date of clinical detection of what is subsequently confirmed to be local, regional, or loco-regional recurrent disease.
Secondary outcomes	• QoL – measured using EORTC QLQ C30, skin-specific Skin Cancer Index (SCI), Picker Patient Experience 15 questionnaire (PPE-15), and EQ-5D (4, 5). • Distant metastasis-free survival, defined as days from randomisation to the date of distant metastasis or death from any cause. • OS, defined as days from randomisation to death for any reason. • Safety /toxicity as measured by common terminology criteria for adverse events (CTCAE) V5.0 scoring system and serious adverse events, including patient-reported outcomes version of the CTCAE. • Cost-effectiveness determined by health utility using EQ-5D and recording health resource use. Primary economic outcome, cost per quality-adjusted life year (QALY). Secondary economic outcome, resource use and costs (6).
Tertiary/Exploratory outcomes	Eligibility and recruitment challenges minimised for relevant under-served groups (such as older, frailer participants and those with multiple long-term conditions).
Interventional Procedure	This is a superiority trial of ART over no radiotherapy; the regimens themselves are not being compared. The regimens have been chosen to be approximately equivalent in terms of effectiveness of killing cancer cells balanced against the risk of long-term damage to normal tissues. The schedules are assumed to be equally effective in terms of preventing recurrence. Participants randomised to the ART arm will receive one of three regimens, depending on field diameter size, followed by 3-years of standard clinical follow up:

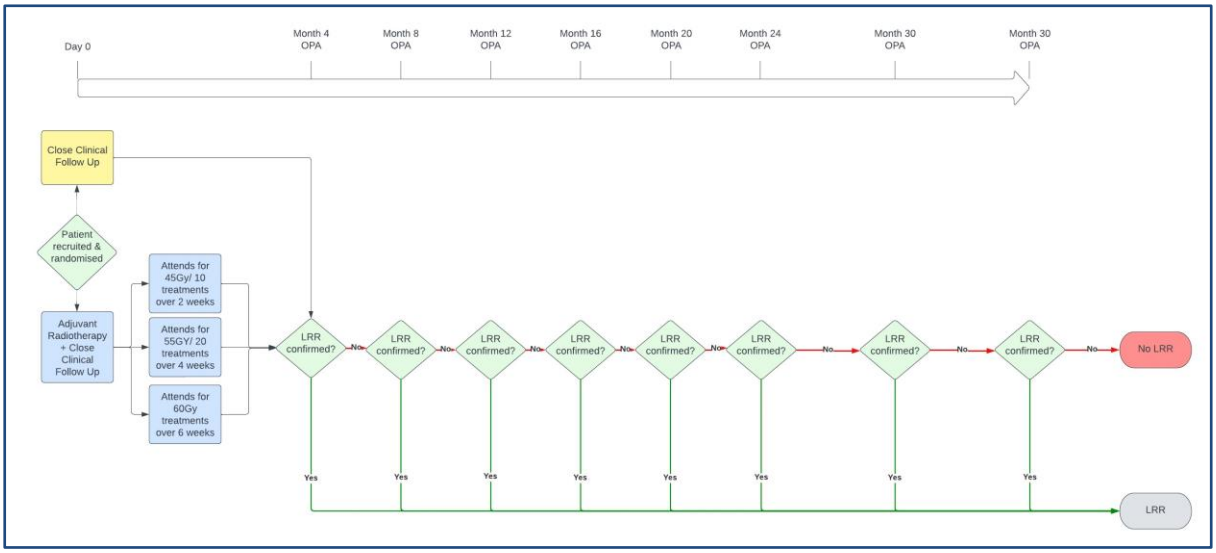
	• Total field diameter 8cm or less: 45Gy in 10 treatments over 2 weeks, or 55Gy in 20 treatments over 4 weeks, or 60Gy in 30 treatments over 6 weeks. • Total field diameter greater than 8cm: 55Gy in 20 treatments over 4 weeks, or 60Gy in 30 treatments over 6 weeks. The radiotherapy treatment is delivered once a day (Monday-Friday) as an outpatient procedure and will typically take between 5 and 20 minutes.

3 Trial summary & schema

3.1 Schema



3.2 Participant flow diagram



Day 0 = date of randomization. LRR: Loco-regional recurrence; OPA: Outpatient appointment

3.3 Trial Lay Summary

Cutaneous (skin) squamous cell carcinoma (cSCC) is a common skin cancer. Although cSCC is usually cured by surgery, it can return either in the skin where it started and/or in nearby lymph glands. This is called loco-regional recurrence. This skin cancer return happens in about 1 in 3 people with 'high-risk' cSCCs - those where the cancer cells look very active under the microscope. Recurrence can lead to serious problems such as pain, bleeding, infections, disfigurement, loss of physical function, discharge and odour, emotional distress. Recurrence causes approximately three quarters of cSCC deaths.

Return of the cancer after surgery is often due to skin cancer cells being unknowingly left behind or cancer cells breaking away into the surrounding skin. Extra treatment such as radiotherapy to the area where the cancer was removed might destroy any remaining cancer cells. However, we are not sure if radiotherapy definitely helps to prevent return of high-risk cSCCs and radiotherapy treatment after surgery takes several weeks, causes short-term skin inflammation (skin can become hot, irritated, red, and swollen) and possible long-term side effects such as skin discolouration on the areas targeted with the radiotherapy.
Finding out whether radiotherapy can reduce the risk of the cancer coming back after surgery is important as cSCC that returns is more difficult to treat with radiotherapy and can cause severe symptoms and death. Many hospitals are treating high-risk cSCC with radiotherapy after surgery without proof that it reduces the chances of cancer returning.

To answer whether radiotherapy is helpful and better than not using radiotherapy for reducing the chance of high-risk cSCC returning after surgery, we have developed a clinical trial where following surgery, participants with a high-risk cSCC would be allocated to either:

1) A course of radiotherapy and standard close clinical follow up;
2) Standard close clinical follow up alone.

Whether one person gets radiotherapy or not will be determined by chance - neither they nor their doctors will be able to choose. We will monitor all patients closely to check for cancer recurrence, treatment side effects and effects on their quality of life. We will compare costs of radiotherapy with cost of other treatments such as immunotherapy. If our study shows radiotherapy is effective in preventing the skin cancer from returning of cSCC, we will be able to recommend its use as a routine NHS treatment. If it is not effective or has too many side effects, we should stop using it.

Patients, carers, and clinical teams who look after people with cSCC have been consulted during development of the trial. All agreed that cSCC recurrence is very important and that knowing whether or not radiotherapy helps to prevent the skin cancer returning is an important question. When we were designing the clinical trial, we carried out a focus group and semi-structured interviews with 13 patients and 3 carers with experience of cSCC. They supported the study design and felt that reduction in loco-regional recurrence was an extremely important physical and emotional issue. They also made suggestions about how to improve recruitment and keep patients in the study. People with experience of cSCC will contribute to how the trial is run. Independent Cancer Patients' Voice (patients in research) charity supports this study. Skin cancer teams in 25 UK centres also agreed with the trial design and have committed to participating. We will share updates and results from the trial with our patients, patient support organisations and healthcare professionals to enable the best choice of treatment for patients with high-risk cSCC in the future.

4 Background

Cutaneous squamous cell carcinoma (cSCC) is a very common skin cancer driven by increasing ultraviolet (UV) exposure, immunosuppression, and an ageing population (7-11). Treatment, usually surgery, cures 95% (12). However, about 5% will recur locally at the primary skin site or within the adjacent draining lymph nodes, a situation termed loco-regional recurrence (LRR). Distant spread is much less frequent (<1%) and LRR accounts for 75% of cSCC-specific deaths and 93% of poor outcomes occur within 3 years of diagnosis of the primary tumour (13, 14). Treatment of loco-regional recurrence with surgery and/or radiotherapy is frequently not curative and further recurrence is both common and extremely difficult to treat. Mortality is highest in the most deprived quintile of the UK population (14). LRR causes substantial morbidity and impaired quality of life (QoL) - pain, bleeding,

ulceration, infection, odour, disfigurement, functional impairment, and psychosocial distress (9). Treatment of LRR often has further substantial morbidity as well as limited efficacy (15).

LRR usually occurs with so-called 'high-risk' primary cSCC. These are defined as tumour stage T2/T3 by Union of International Cancer Control (UICC) 8th Edition or T2b/T3 by Brigham and Womens' Hospital (BWH) classification (16), which has the best validated prognostic data. In the UK, about 10% of cSCC, or 4500-5000 tumours p.a., are BWH T2b/T3 (8); rates of LRR are 30% (T2b) and 50% (T3) (17, 18). Cemiplimab has been licensed since 2019 for salvage treatment of advanced LRR: overall responses approach 50%, but complete responses are only 13% (19, 20). Furthermore, the greatest burden of cSCC is seen in organ transplant recipients who have twice the risk of LRR and are twice as likely to die from LRR: cemiplimab is relatively contraindicated in transplant recipients because it may provoke allograft rejection. Prevention of LRR is therefore a priority, with recent European and world rankings suggest especially poor UK outcomes (10). In Australia and the US, high-risk cSCC is routinely treated with postoperative adjuvant radiotherapy (ART) with claimed improved outcomes in retrospective observational case series, case-control studies and uncontrolled prospective studies (21-24), but not all (25). Our feasibility surveys found widespread but variable use of ART in UK practice: simulated case-based discussions (CBD) with 25 specialist skin cancer multidisciplinary teams (SSMDTs) found clinical equipoise for ART use in high-risk cSCC (26, 27), as confirmed in a recent systematic review (25).

Establishing whether ART is clinically and cost-effective will be of immediate benefit to patients and will inform clinical guidelines and healthcare policy. National and international guidelines (British Association of Dermatologists [BAD], European Association of Dermato- Oncology [EADO] and US National Comprehensive Cancer Network) have all identified ART as an important evidence gap in cSCC care (1-3). The aims of SCC-AFTER are informed by extensive consultation with key stakeholder groups including British Association of Dermatologists (BAD), Royal College of Radiologists (RCR), British Association of Plastic, Reconstructive and Aesthetic Surgery, British Society of Dermatological Surgeons, National Facial and Oral Research Centre, British Association of Oral and Maxillofacial Surgeons, UK Dermatology Clinical Trials Network (UKDCTN), NCRI Skin Cancer Clinical Studies Group and NCRI CTRad group.

A systematic review conducted by the British Association of Dermatologists cSCC Guidelines Development Group concluded that evidence for ART in completely excised high-risk cSCC was 'Weak' and identified this as a key research area (1). For this review, PubMed, MEDLINE, Embase and Cochrane databases were searched from 01/01/2007 to 30/01/2020 (see link to search strategy bjd19621-sup-0001-SupInfo.docx) and our updated review to April 2022 includes additional retrospective studies (21-24), but confirms the lack of any RCT data for ART. A recent systematic review of 33 observational studies (3867 cSCCs) found differences favouring ART for excised HR-cSCC, especially where PNI is present, but these differences were not statistically significant, and the authors concluded that "RCTs are needed to define the benefit of adjuvant radiotherapy in this setting" (25).

A very recently published, large (n=508 cSCCs) 2-centre retrospective comparison of ART for BWH T2b/T3 showed reductions in both non-nodal and nodal local recurrence of 58% and 51% respectively (24). Most treated tumours (64%) underwent ART to tumour bed alone. Half (52%) of the highest risk tumours (recurrent, 6 cm diameter, or BWH T3) underwent ART to tumour bed and nodal basin. These latest data support the potential benefit of ART, but this was a retrospective cohort study from academic tertiary referral centres and the authors stress the need to validate their findings in adequately powered prospective clinical trials.

Annual UK incidence of cSCC exceeds 52,000 per annum and has been increasing by 6% per year since 2013 (7, 8). Increasing numbers of long-term surviving organ transplant recipients (>57,400 UK adult transplant recipients in 2021) compounds this problem due to both multiplicity of cSCC and increased LRR in immunosuppressed patients (4, 5, 11, 28, 29), with significant resource implications and costs for the NHS. Long term survival of patients with HIV AIDS and with haematological malignancies such as chronic lymphocytic leukaemia (CLL), together with increasing numbers of patients on long term iatrogenic immunosuppression for immune-mediated inflammatory diseases further expands the numbers of immunosuppressed, as does the aging population, increasing our need to have a clear answer to this research question. With the high human and NHS cost of LRR, prevention is a priority. The proposed RCT is needed to establish benefit (or not) of ART for completely excised high-risk primary cSCC. If ART is effective in reducing LRR from cSCC, it should be incorporated into NHS treatment pathways, if ineffective it should be discontinued avoiding adverse effects, inconvenience, and cost.

Our study is designed to be both representative of the population affected by high-risk cSCC, and inclusive of those with multiple long-term conditions (MLTCs) (28) and socio-economically disadvantaged groups.

4.1 Rationale for current trial/Justification of Treatment Options

Research question

Following complete excision of high-risk primary cutaneous squamous cell carcinoma (HR cSCC) is adjuvant radiotherapy (ART) plus close clinical follow up superior in reducing loco-regional recurrence compared with close clinical follow up (standard care) alone?

Rationale for conducting this study

ART is identified by UK clinicians and by all international guidelines as a key area of clinical uncertainty in the management of high-risk cSCC (26, 27). Finding out whether ART is clinically and cost-effective in patients with these more aggressive tumours is an urgent priority. Despite the lack of evidence, a current commercial RCT of adjuvant immunotherapy in high-risk cSCC (NCT03969004) mandates ART in both arms prior to randomisation. Systemic immunotherapy is likely to incur much greater toxicity

and substantially higher NHS costs than ART and critically cannot be used in organ allograft recipients who carry the greatest burden of LRR. The cost of cemiplimab is £4.6K per treatment session, approved for up to 35 sessions, whereas a course of ART is approx. £5K in total. Consequently, there is an urgent need to define the role of ART as it may significantly reduce the need for immunotherapy.

A recently published 2-centre USA-based retrospective comparison of ART following clear margin resection of BWH T2b/T3 cSCC (n=508) estimated that patients receiving radiotherapy had half the risk of recurrence at 5 years (24). In contrast, a systematic review that included 3867 cSCC was unable to show a statistically significant benefit (27). A search of international clinical trials registry platform (https://trialsearch.who.int/Default.aspx) repeated on 10/05/2022 has not identified any clinical trials assessing ART for primary cSCC.

5 Trial objectives/endpoints and outcome measures

5.1 Primary objective

To evaluate the efficacy of ART plus close clinical follow up compared to close clinical follow up (standard care) alone in reducing loco-regional recurrence (LRR) following complete excision of high-risk (BWH T2b/3) primary cSCC.

Null hypothesis

There will be no difference in the LRR between the ART plus close clinical follow up arm and the close clinical follow up only arm.

Alternative hypothesis

ART plus close clinical follow up arm will demonstrate at least a 35% decrease in LRR compared to the close clinical follow up alone (standard care) arm.

5.2 Secondary objectives

- To determine the impact on QoL of ART in completely resected high risk (BWH T2b/3) primary cSCC compared to standard clinical follow up.
- To evaluate distant metastasis-free survival in both groups.
- To evaluate overall survival (OS) in both groups.
- To determine the safety of ART in terms of the proportion of patients experiencing toxicity compared with close clinical follow up.
- To evaluate the cost-effectiveness of ART.

5.3 Primary outcomes measure(s)

Loco-regional recurrence (LRR)-free survival time: time to LRR is defined as the time from randomisation to date of clinical detection of what is subsequently confirmed to be local, regional, or loco-regional recurrent disease.

- *'Local recurrence'* is defined as cSCC in or below the skin that does not have the clinical appearance of primary cSCC and is within or adjacent to the index primary site, or between the primary site and the regional lymph nodes. Diagnosis of local recurrence will be confirmed by the SSMDT/RMDT.

- '*Regional recurrence*' is defined as cSCC which has spread to lymph node/s within the basin deemed to be draining the site of the index primary cSCC. In head and neck cSCC, these may be contralateral. Diagnosis of regional recurrence will be confirmed by the SSMDT (Regional MDT in Scotland, RMDT).

5.4 Secondary outcomes measure(s)

- QoL – measured using EORTC QLQ C30, skin-specific Skin Cancer Index (SCI), and Picker Patient Experience 15 questionnaire (PPE-15) (4, 5).
- Distant metastasis-free survival, defined as days from randomisation to the date of distant metastasis or death from any cause.
- OS, defined as days from randomisation to death for any reason.
- Safety /toxicity as measured by common terminology criteria for adverse events (CTCAE) V5.0 scoring system and serious adverse events, including patient-reported outcomes version of the CTCAE.
- Cost-effectiveness determined by health utility using EQ-5D-5L and recording health resource use. Primary economic outcome, cost per quality-adjusted life year (QALY). Secondary economic outcome, resource use and costs (6).

5.5 Separate exploratory/translational objectives and endpoints

The QuinteT Recruitment Intervention (QRI) will investigate recruitment barriers with the aim of optimising recruitment and informed consent. The INCLUSION SWAP will identify barriers to recruiting under-served groups in this population, including older, frailer participants and those with multiple long-term conditions, through exploratory interviews and analysis of recruitment processes.

Consent will be collected from patients to allow future research relating to clinical pathological factors.

6 Trial design and setting

SCC-AFTER is an open label, multicentre, two-arm, phase III, pragmatic group sequential randomised control trial (RCT) to evaluate superiority, cost effectiveness and effects on QoL of post-operative ART followed by close clinical follow up compared to post-operative close clinical follow up (standard care) in completely resected high-risk (BWH T2b/3) primary cSCC.

Patients will be recruited from UK specialist skin cancer centres and expected to have been evaluated by specialist skin cancer multidisciplinary teams (SSMDTs) in England, by Regional MDTs in Scotland and by MDTs in Wales

Patients eligible for the study must have had completely excised high-risk primary cSCC (T2b/T3 by BWH staging criteria).

An internal pilot targeting recruitment of 100 patients within the first 12 months will determine feasibility. Recruitment prediction is based on site interest and experience on speed of site opening. Two interim analyses after 77 and 115 events (600-760 randomised) would trigger early stopping if the log-rank statistic is larger than +/- 3.36 and +/- 2.68 respectively. Stopping for efficacy means fewer participants and shorter follow-up. Otherwise, the trial will be analysed when at least 194 events have been reported.

It includes a QuinteT Recruitment Intervention (30) and an INCLUSION Study within a Project (SWAP) (integrated during trial set up and the internal pilot, months 0-18, and the first 18 months of main phase recruitment, months 19-36) designed to optimise recruitment, particularly among patients historically underserved in trials research. These include people with multiple long-term conditions (MLTC) and other under-served groups, address clinician equipoise and identify organisational barriers.

Timelines for delivery

Recruitment time is 4 years; follow-up 3 years; final 6 months for analysis, publication, and closure. Patients will be assessed in line with standard clinical practice including baseline, mid-ART (ART arm only), every 4 months for 2 years and then 6-monthly in the final year. QoL and Health Economics will be assessed twice in year 1 and annually in years 2 and 3. Progression and survival data will be collected throughout the trial. The integrated QRI will run during set-up (0-6 months), the pilot (7-18 months) and the first 18 months of main phase recruitment (19-36 months)

Anticipated impact and dissemination

Establishing whether ART is clinically and cost-effective will be of immediate benefit to patients and will inform clinical guidelines and healthcare policy nationally and internationally. If ART is effective in reducing LRR from cSCC, it should be incorporated into NHS treatment pathways, or discontinued if ineffective. We will share updates and results from the trial with our patients, patient support

organisations, SSMDTs and other healthcare professionals to ensure the best choice of treatment for patients with high-risk cSCC.

6.1 Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment document includes:

- The known and potential risks and benefits to human subjects.
- How high the risk is compared to normal standard practice.
- How the risk will be minimised/managed.

This trial has been categorised as low risk, where the level of risk is no higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 25.1).

7 Site and Investigator selection

SCC-After aims to recruit 840 patients over 4 years from specialist skin cancer centres and it will be carried out at participating sites within the UK. All sites who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial.

Before any site can begin recruitment a Principal Investigator (PI) at each site must be identified. The following documents must be in place and copies sent to the SCC-After Trial email account (see contact details on page 4):

- Confirmation of Capacity and Capability (C&C) from R&D department following sharing of local information pack.
- Favourable opinion of host care organisation/PI from Main Ethics committee.
- A signed Trial Agreement.
- Current Curriculum Vitae (CV) and Good Clinical Practice (GCP) training certificate of the PI.
- Completed Site Delegation Log and Roles and Responsibilities document.
- Full contact details for all host care organisation personnel involved, indicating preferred contact.

- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper.
- A copy of the Withdrawal Consent Form on host care organisation headed paper.
- A copy of the most recent approved GP letter on host care organisation headed paper.
- RTTQA Approval.

Upon receipt of all the above documents, the CTR Trial Manager will send written confirmation to the PI detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site will have received a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

Site initiation will be either by attendance at a national SCC-After launch meeting or by teleconference/videoconference by attendance of key personnel. Site teams will be required to engage in pre-initiation training.

8 Participant selection

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager before randomisation.

8.1 Inclusion criteria

1) High-risk primary cSCC (T2b/T3 by BWH staging criteria) excised with adequate peripheral and deep surgical margins (according to BAD guidelines) with histologically clear margins (≥1mm by RCPath criteria). Time since excision surgery < 3 months (or < 4 months if necessary but < 3 months is preferred).
2) ECOG performance status of 3 or less at enrolment.
3) Aged 18 years or older at time of consent.
4) Fit for ART and able to attend radiotherapy outpatient appointments.
5) Life expectancy > 6 months.
6) Informed Consent obtained* which must be prior to any mandatory study-specific procedures, sampling, and analyses.

* Patients should be provided with additional support and adjustments where needed (e.g., layering of information, involvement of a family member/friend as a support person, provide witnessed informed consent if unable to confirm informed consent in writing).

Note: this will include those patients who are elderly, frail and have multiple long-term chronic conditions who are a group at particular risk for cSCC. It will also include immunocompromised patients who are excluded from most clinical trials but have high rates of cSCC.

Patients with reproductive potential and are heterosexually active during the duration of the trial consent, must not be pregnant at the time of consent and agree to use contraception until the last dose of radiotherapy if they are randomised to the RT arm. Effective forms of contraception are described in section 15.8.

8.2 Exclusion criteria

1) Any current clinicopathological evidence of loco-regional recurrence of the index tumour.
2) Previous (within 3 years) or current non-index primary cSCC in skin drained by the same lymph node basin**.
3) cSCC on anatomical sites which interfere with suitability for ART (such as vermilion lip, eyelids, breast, anogenital area).
4) Patients with evidence of regional or distant disease at time of primary cSCC diagnosis.
5) Previous radiotherapy to the same area.
6) Patients with reproductive potential who are not willing to use contraception for the duration from trial consent until the last dose of radiotherapy if they are randomised to the ART arm.
7) Unable to lie still unattended for the duration of ART (estimated to be around 5 minutes).
8) Participation in another interventional clinical study that may affect the recurrence of cSCC (primary end point).
9) History of another malignancy where metastasis could cause diagnostic uncertainty or patients receiving active systemic anti-cancer treatment (excluding hormonal treatment for prostate or breast cancer) or radiotherapy.***

**Please consider discussing all patients with multiple cSCC draining to the same nodal basin as the index cSCC with the SCC-After trial team including those within the last 3 years.

***Please discuss patients with malignancy of concern with the SCC-After trial team

9 Recruitment, screening, and registration

9.1 Participant identification

Potential participants will be identified from surgical lists of excised cSCC, local MDT or regional MDTs by the recruiting site. Patients are eligible for the trial if all inclusion criteria are met (section 8.1) and none of the exclusion criteria apply (section 8.2). At the time of first discussion about the SCC-After

trial and prior to accepting or declining participation in the SCC-AFTER trial, patients demographic (non-identifiable) and health data will be recorded from medical records as part of the screening process. These data will be used to optimise the inclusivity of the SCC-AFTER recruitment and identify potential barriers to recruitment early. Patients may be invited to consent to audio-recording of these discussions in line with the consent processes outlined in section 17.3.1 below and using the specific QRI consent form, separate from the main trial consent form. The patient's informed consent to the SCC-AFTER main trial must be obtained before randomisation and before any trial-related procedures are undertaken.

Once informed consent to the main trial has been obtained:

- The patient must be randomised into the trial using the trial database. The CTR can be contacted as an alternative, SCCAfter@cardiff.ac.uk

The local PI or delegate must confirm the potential eligibility of a patient in the patient's medical notes (Initial and date source records) prior to randomisation. Any queries about whether a patient is potentially eligible to enter the trial should be discussed with the CTR trial team **before consent**. Any issues will be raised with the Chief Investigators or one of their delegates in their absence. It may be possible for participants to also be recruited into other clinical trials, but this should be discussed with the CTR before this is considered. Baseline non-identifiable demographic and health data recorded from medical records for all patients considered for the trial should be included in the SCC-AFTER screening log together with reasons for ineligibility, reasons why eligible patients have not been approached and reasons those declining the trial may give for not taking part.

9.2 Screening logs

A screening log of all patients with cSCC screened for participation in SCC-AFTER will be entered into a restricted access section of the main trial database to protect ethically approved sensitive data. The screening data allows differences in practice between sites to be detected and best practice shared between sites. In the case of the database being unavailable, any other fields of sensitive or unidentifiable data **must be redacted, by the site research team** prior to being sent to the CTR trial team.

These data will inform the QRI/SWAP objectives. The proportions of screened patients who are eligible, approached, agree to take part, and randomised will be quantified to identify points in the recruitment pathway at which patients are being 'lost' to recruitment. Reasons for 'loss' of patients at each stage (reasons not eligible, reasons not approached, reasons for declining participation and for each decliner, the management option chosen outside of the study) will be captured for all those who are not recruited. Screening logs will be analysed according to the SEAR (Screened, Eligible,

Approached, Randomised) framework (31) which has been adapted to capture data on diagnosis of cognitive impairment, multiple long term conditions and self-identified ethnicity.

9.3 Recruitment rates

A total of 840 participants will be recruited at over a period of 4 years.

9.4 Informed consent

The participant's informed consent must be obtained using the trial Consent Form, which follows the Participant Information Sheet. Information provision will be tailored to participants' communication needs to support their understanding, such as using large print format and layering of information (e.g., providing a summary information sheet prior to the Participant Information Sheet) where appropriate. The participant should be given sufficient time after the initial invitation to participate before being asked to provide informed consent. Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial. Consent may be taken by a medically qualified Investigator delegated the responsibility on the site delegation log by the local PI.

Please note, only when informed consent has been obtained from the participant and they have been randomised/enrolled into the trial can they be considered a trial participant.

If a potential participant is unable to provide a written signature on the Consent Form, verbal consent will be taken. In such cases, a member of the research team delegated to take consent, will read, and discuss the trial with the potential participant to ensure understanding of the trial. Another member of the research team will witness, sign, and date the Consent Form to confirm that consent has been given.

One copy of the completed consent form should be given to the participant, but the original copy should be kept in the investigator site file and a further copy should be kept with participant's hospital notes.

The right of the participant to refuse to participate in the trial without giving reasons must be respected. After the participant has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing their further treatment.

During the long-term follow-up period it is possible that participants with MLTCs such as dementia may experience a decline in their cognitive function. Where concerns about a participants' ability to provide ongoing consent to remain in the trial are raised, capacity will be assessed by an appropriately trained member of the research team (e.g., a research nurse) in accordance with the Mental Capacity Act 2005 (32). Where a participant is assessed as lacking capacity to consent to remain in the trial, a consultee (a family member or close friend) will be approached to provide advice about their continued participation (32). Where a participant has previously nominated a support person, they may be approached to act as a consultee or help identify someone to act in this role. Please note, it is not possible to prospectively retain consent if a participant loses capacity and the consultee must be provided with the consultee information sheet and declaration form to confirm consent for the participant to remain in the study. If a participant regains capacity during the study, they are required to be reconsented to remain in the study.

9.5 Randomisation

9.5.2 Randomisation

All patients will be randomised via the central SCC-AFTER database to the comparator or ART arm. Sites should complete the first part of the randomisation Electronic Case Report Form (eCRF), answering all the questions before submitting the randomisation. Once the randomisation is completed, the database will confirm whether the participant has been allocated to the close clinical follow up or ART and close clinical follow up arm.

A link to the randomisation system will be sent upon site activation along with a database user guide.

If the online system becomes unavailable for any reason, site staff should contact SCCAFTER@cardiff.ac.uk and a manual randomisation process will be initiated.

Participants will be randomised using minimisation with a random element. This will ensure balanced treatment allocation by a number of clinically important stratification factors (Stage of cancer, immunocompromised, time since surgery, age category, multiple long-term conditions). Randomisation will have an allocation ratio 1:1.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the trial.

If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

1. Withdrawal from Trial Treatment/Intervention (Radiotherapy) – but continue to attend follow up, complete questionnaires, and allow access to medical notes.
2. Withdrawal from completing study questionnaires – but continue to attend follow up and allow access to medical notes.
3. Withdraw from all aspects of the trial but consent to data being collected where available.
4. Withdraw from all aspects of the trial and all future data collection.
5. **Optional Trial elements**:
    1. QRI Sub-Study – withdraw consent to be contacted by QRI team but continue with all other aspects of the trial (unless recorded otherwise)
    2. Tissue Samples* – withdraw consent for collection of samples and associated data but continue with all other aspects of the trial (unless recorded otherwise)
6. Withdrawal of consent for use of already collected samples and data to be used in future research:
    1. Samples*: (if applicable)
        a. Tissue and associated data
        b. DNA from tissue and associated data
    2. Data:
        a. SCC-AFTER Trial data
        b. QRI Sub-Study Data and Interview recordings (if applicable)

* Further information in section 13, only applicable if patient consented to tissue collection.

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data/samples collected prior to participant withdrawal. The use of the data/samples collected prior to withdrawal of consent is based on informed consent before its withdrawal.

Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event. There is specific guidance on this contained in the Participant Information Sheet but briefly:

If a participant wishes to stop taking part in the trial completely, they will need to be seen one last time for an assessment and tests. If the participant is suffering a serious reaction to the trial treatment when they decide to stop, you will need to continue to collect information about them for as long as the reaction lasts.

A participant may withdraw or be withdrawn from trial treatment for the following reasons:

- Intolerance to trial intervention.
- Withdrawal of consent for treatment by the participant*.
- Any alteration in the participants condition which justifies the discontinuation of the intervention in the Investigator's opinion.
- Non-compliance.

*This may include a consultee or relative/next of kin/carer in the case of patients losing capacity.

In all instances participants who consent and subsequently withdraw should have a withdrawal form (see withdrawal form in trial pack) completed on their behalf or in conjunction with the participant by the researcher/clinician based on information provided by the participant. Any queries relating to potential withdrawal of a participant should be forwarded to the SCC-After trial team.

If the patient decides not to complete the Participant Withdrawal Form, any discussions held with the patient regarding their withdrawal, and aspect(s) of the trial they no longer wish to continue with should be recorded within the patient notes or other source records. The SCCAfter Withdrawal Form should then be completed using information provided by the participant. Any queries relating to potential withdrawal of a participant should be forwarded to SCCAFTER@cardiff.ac.uk.

10.2 Lost to follow up

How participants will be identified as lost to follow-up: A participant will be deemed lost to follow-up if they stop attending all scheduled trial visits without a loco-regional recurrence event being reported, in the absence of a withdrawal form indicating complete withdrawal from the trial.

Measures that we will take to try and get the missing info: If there is no evidence the patient has lost capacity. The site can continue to attempt to contact the patient or access their medical records while the trial is still open. Visits will be marked as not done on the trial database stating the reason as "patient did not attend".

Which outcome data will be collected from protocol non-adherers: Medical records of any skin examinations, CT scans or death data.

11 Trial Intervention

11.1 Radiotherapy Treatment

Radiotherapy should be delivered to the skin with electrons. Alternative radiotherapy techniques would be permitted but should be discussed with the SCC-After trials team. The radiotherapy dose

and fractionation are dependent on the size of the treatment field. The permitted radiotherapy dose and fractionation schedules are:

- Field diameter less than 8cm: 45Gy in 10 daily fractions over 2 weeks or 55Gy in 20 daily fractions over 4 weeks

- Field diameter 8cm or greater: 55Gy in 20 daily fractions over 4 weeks or 60Gy in 30 daily fractions over 6 weeks

Field diameter above is with reference to an 8cm circular radiotherapy field.

Fractionation (total dose, number of fractions, dose per fraction) Treatment once a day, Mon to Fri)	**EQD2 for tumour α/β-ratio 10Gy**	**EQD2 for normal tissues (e.g. bone) α/β-ratio 3Gy**
45Gy/10F/4.5Gy	54.38*	67.5**
55Gy/20F/2.75Gy	58.44	63.25
60Gy/30F/2Gy	60	60

*Shorter treatment time giving greater tumour radiobiological equivalence

**Smaller field size abrogating higher risk to normal tissue (bone)

EQD_2 calculator: https://www.mdcalc.com/calc/10111/radiation-biologically-effective-dose-bed-calculator

Detailed radiotherapy guidelines are provided in a separate document SCC-AFTER Radiotherapy Planning Guidance Document (RPGD). Investigators MUST follow the detailed instructions in the RPGD, which will be distributed by the CTR in conjunction with the National Radiotherapy Trials Quality Assurance (RTTQA) Group.

11.3 Radiotherapy quality assurance

The quality assurance programme for the trial will be co-ordinated by the National RTTQA Group. Participating centres will submit a pre-trial facility questionnaire prior to gaining RTTQA approval.

The details of the QA programme can be found at www.rttrialsqa.org.uk.

11.7 Participant positioning and planning CT scan acquisition

Use of a CT scan in planning is not required. In some instances, clinician decision or local standard of care may indicate it is required and this will be allowed and documented.

11.9 Management of unscheduled gaps in RT treatment

For the purpose of the trial treat as Royal College of Radiologists (RCR) category 1 patients so patients should be treated on bank holidays/weekends or 2 treatments on one day (33).

12 Health Economics

A cost-utility analysis of ART versus standard clinical follow up will be performed from the perspective of the NHS and Personal Social Services and adopting a lifetime horizon of analysis. A modelled extrapolation of trial data will estimate the incremental cost per quality-adjusted life years (QALYs) for ART vs. standard clinical follow up.

Resource use will be estimated from eCRF entries and using patient questionnaires administered alongside QoL assessments. A bespoke resource use measure will be developed from existing questionnaires catalogued in our Database of Instruments for Resource Use Measurement (34) and include items from the generic, modular resource-use measure (ModRUM) (35). Principal items of resource use will include hospital services and stays, and primary, community and social care services. Unit costs will be obtained from standard sources, including the NHS reference costs (36) for ART and hospital costs, and PPSRU's Unit Costs of Health and Social Care (37) for primary, community and social care, and the British National Formulary for medicines. Costs will be based on the most recent at the time of analysis.

Health outcome will be based on participants' responses to the EQ-5D-5L questionnaire, administered at baseline, end of ART or equivalent (approximately 7 weeks post-randomisation) for close clinical follow up arm, 4 months, 12 months, 24 months, and 23 months. Utilities will be calculated using NICE's preferred method at the time of analysis (currently the EEPRU 5L/3L cross-walk tariff) (38).

13 Sample Management

The Formalin Fixed Paraffin Embedded (FFPE) surgical block is collected as part of routine clinical practice and is collected for all patients on the cSCC pathway, regardless of participation in the SCC-AFTER trial. This surgical tissue block is stored at NHS sites in line with NHS retention guidelines. Patients will be asked for consent for the previously collected (before entry into SCC-AFTER) FFPE surgery block to be used for future research.

There is no funding for sample collection, and it is the intention to request this collection of surgical tissue blocks at a later date when funding has been secured. If funding is not secured the surgical tissue block will remain at the NHS sites in line with NHS retention guidelines and site SOPs.

14 Trial procedures

The schedule of assessments can be found in table 1. A breakdown of the QoL questionnaires and clinician and patient reported toxicity timepoints. All procedures to be carried out by clinical and/or research team at the participating site, according to the site delegation log.

14.1 Screening (baseline) assessments

Randomisation should be within 2 months of surgery. A window up to 3 months post-surgery will be allowed. Where additional time has been needed to heal or for other reasons to be discussed with the SCC-AFTER trial team before the patient is consented.

Patients should undergo the following assessments at the time of trial entry and no more than 2 weeks after randomisation:

- Medical History.
- Physical Examination.
- Height/Weight.
- ECOG performance status.
- Toxicity Assessment.
- QoL Questionnaires (to be completed after trial consent). EQ-5D, EORTC QLQ30, health utilisation.

Toxicity should be assessed according to CTCAE 5.0.

14.2 Pre-treatment assessments; additional to screening assessment for patients randomised to the radiotherapy arm

Patients should undergo the following assessments at the time of trial entry and before treatment with radiotherapy. Radiotherapy should start within one month of randomisation.

- Physical Examination.
- Pregnancy test in people of childbearing potential who are randomised to the Radiotherapy treatment arm.
- Key concomitant medication check.

All baseline assessments and pre-treatment assessments must be completed prior to the start of any radiotherapy treatment.

14.2 Assessments during radiotherapy

Patient and clinician reported toxicity assessment at the end of each second week of treatment.

Note: This will be one assessment for those receiving 10 fractions, 2 assessments for those receiving 20 fractions and 3 assessments for those receiving 30 fractions

QoL questionnaires EQ-5D-5L, EORTC QLQ30, SCI, and health utilization at the end of radiotherapy treatment. Patients in the comparator arm will be asked to return QoL questionnaires at 7 weeks post randomisation +/- 3 weeks.

14.3 Post-treatment assessments (4, 8, 16, 12, 24, and 36 months following randomisation)

The patient is expected to be followed up as per standard of care at each of these time points and this would usually be at a skin clinic. Information regarding any changes to the surgery site or involved lymph nodes should be recorded.

Physical Examination

Toxicity Assessment (4, 8, 16, 24, 26 months)

QoL Questionnaires (4, 12, 24, 36 months) EQ-5D, EORTC QLQ30, SCI, PPE-15 (12 months only), and health utilisation (4, 12, 24, 36 months). See appendix 2 for table of QoL questionnaires and clinician and patient reported toxicity timepoints.

Visits should be completed at time point +/- 4 weeks. Visits may be carried out remotely if this is standard of care and the assessing clinician is able to appropriately assess the patient. In such instances patients may complete the questionnaire by phone or post back to the recruiting site. Remote/telephone support option is available if required.

In addition to the QRI and INCLUSION SWAP (see 17.3), qualitative interviews will be undertaken with up to 25 participants, purposively sampled to include those reporting good and poor outcomes from each trial arm, the ‘oldest old’ and people living with MLTCs to investigate people’s experiences of receiving ART and close clinical follow up and nuances of participant outcomes (39). These interviews will take place at 6-8 months years post randomisation.

Table 1. Schedule of enrolment, interventions, and assessments

SCC-AFTER **Schedule of Assessments**	**Screening**	**Baseline**	**Treatment Phase** **(Patients randomized to RT arm only)**				**Post treatment** **OR** **Follow Up**	**Follow up every 4 months**						**Follow up every 6 months**	
			Before start of treatment (Pre-RT)	**Week 10#, week 1&2** **End of week 2 check**	**Week 10#, week 3&4** **End of week 4 check**	**Week 10#, week 5&6** **End of week 6 check**	**ART am= completion of ART** **Comparator arm= 7 weeks (+/- 4 weeks) from randomization**	**4**	**8**	**12**	**16**	**20**	**24**	**30**	**36**
Medical History	x														
Physical examination (skin surgical site, regional lymph nodes with full skin examination if appropriate)	x		x				x		x	x	x	x	x	x	x
Height /Weight		x													
Performance status (ECOG)	x														
MDT review	x														
Key Concomitant medication check			x												
Record current medication		x	x				x	x		x			x		x
QRI	x	x													
ART planning[$]			x												

ART treatment[$]				x	x*	x**									
Informed consent		x													
Toxicity assessment / AEs		x		x	x	x	x	x	x		x		x		x
Randomisation		x													
Pregnancy test (if applicable)		*	x												
QoL and HE Questionnaires[&]		x		*	*	*	x	x		x			x		x

[$]for participants randomised to receive ART

*for participants receiving 4 weeks of ART treatment

** for participants receiving 6 weeks of ART treatment

[&] EQ-5D-5L, Skin-specific Cancer Index, and EORTC QLQ-C30 , Picker Patient Experience 15 questionnaire. Please see additional table 2 for breakdown of questionnaires per hospital visit. Health Resource Utilisation should be completed in conjunction with the patient and a research nurse.

Table 2: Questionnaire administration per visit

						Time From Randomisation Date								
	Baseline	End of 2 weeks ART (for ART arm only)	End of 4 weeks ART (for ART arm only)	End of 6 weeks ART (for ART arm only)	Completion of ART (for ART arm only)	7 weeks (+/- 4 weeks) (for Non ART arm only)	4 Months	8 Months	12 Months	16 Months	20 Months	24 Months	30 Months	36 Months
EQ-5D	✓	✖	✖	✖	✓	✓	✓	✖	✓	✖	✖	✓	✖	✓
EORTC QLQ-C30	✓	✖	✖	✖	✓	✓	✓	✖	✓	✖	✖	✓	✖	✓
SCI	✓	✖	✖	✖	✓	✓	✓	✖	✓	✖	✖	✓	✖	✓
PPE-15	✖	✖	✖	✖	✖	✖	✖	✖	✓	✖	✖	✖	✖	✖
Patient Reported Toxicities	✓	✓	✓	✓	✖	✓	✓	✓	✖	✓	✖	✓	✖	✓
To be completed by Clinicians: **Clinician Reported Toxicities**	✓	✓	✓	✓	✖	✓	✓	✓	✖	✓	✖	✓	✖	✓
To be completed by research team (in conjunction with patient): **Health Utilisation/ Economics**	✓	✖	✖	✖	✓	✓	✓	✖	✓	✖	✖	✓	✖	✓

Concomitant Medications	✓	✖	✖	✖	✓	✓	✓	✖	✓	✖	✖	✓	✖	✓

15 Pharmacovigilance

Recording of serious adverse events (SAEs) must start from the time of randomisation and must be performed at least until 4 months after randomisation (or until 30 days following the last fraction of radiotherapy if later).

The Principal Investigator is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR PV and Safety Specialist unless the SAE is specified as not requiring immediate reporting (see section 15.2).

15.1 Definitions

Table 3. SAE definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to radiotherapy which is related to any dose administered to that participant.
Serious Adverse Event (SAE)	Any adverse event that - • Results in death. • Is life-threatening*. • Required hospitalisation or prolongation of existing hospitalisation**. • Results in persistent or significant disability or incapacity. • Consists of a congenital anomaly or birth defect. • Other medically important condition***. Please see section 15.2 for exceptions
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is **related** to Radiotherapy at any dose administered.

Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information table in Section 15.3.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event, or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

**** Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g., for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

***** Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

15.2 Trial Specific SAE Reporting requirements

In addition to the SAE reporting requirements defined in Table 4, for the purposes of this trial the following events will also be considered SAEs and must be captured on the SAE form and reported to the CTR with 24 hours of knowledge of the event:

- Skin graft failure.
- Infection requiring intravenous antibiotics (where infection started in area of surgery or radiotherapy), where CTCAE grade 3 or above.
- Bleeding considered related to the surgery or radiotherapy requiring hospitalisation.

For the purposes of this trial the following events will not require reporting as SAEs:

- Disease progression (unless more severe than expected in this population).
- Hospitalisation to facilitate radiotherapy delivery.

These should be completed in the participant's notes and entered on the relevant toxicities eCRF page within a maximum of 4 weeks from the assessment date.

Pre-existing conditions should only be reported if they met the definitions for an SAE and if the condition worsens to a CTCAE grade 3 or above.

15.3 Causality

Causal relationship will be assessed for trial treatments and procedures:

Procedures: Radiotherapy

The Principal Investigator (or another delegated medically qualified doctor from the trial team) and Chief Investigator (or another medically qualified doctor from the Trial Management Group) will assess each SAE to determine the causal relationship:

Table 4. SAE relationship

Relationship	**Description**	**Reasonable possibility that the SAE may have been caused by the radiotherapy?**
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g., the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g., because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

15.4 Expectedness

The Chief Investigator (or another delegated appropriately qualified individual) will assess each SAR to perform the assessment of expectedness.

The expectedness assessment should be made with reference to the list of expected adverse events in Table 4. Expectedness decisions must be based purely on whether the event is listed. Other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease. SARs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. Fatal and life-threatening SARs should not be considered expected.

The table below lists the expected adverse events with radiotherapy.

Table 5. Expectedness assessment

Intervention	List to be used for expectedness assessment
Radiotherapy	Graft failure. Bleeding considered related to the surgery or radiotherapy requiring hospital admission. Infection requiring i.v. antibiotics (where infection started in area of surgery or radiotherapy).

15.5 Reporting Procedures

15.5.1 Participating Site Responsibilities

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via secure email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, month, and year of birth and initials. The participant's name (or any other personal identifiers) should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, CTR/pharmaceutical companies may request additional information relating to any

SAEs/SARs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

CTR-Safety@Cardiff.ac.uk

Serious adverse events should be reported from time of randomisation, throughout the treatment period up to 4 months from randomisation. Serious adverse events relating to graft failure should be reported up to 12 months after randomisation. Serious adverse reactions (such as long-term side effects of trial treatment under investigation) should continue to be reported until the end of follow up as defined in the protocol.

Serious Adverse events (SAE) in oncology trials should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

An SAE form should contain at least the minimum information:

- Full participant trial number.
- An Adverse Event / Adverse Reaction.
- Trial intervention.
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log).

If any of these details are missing, the site will be contacted, and the information must be provided by the site to the CTR within 24 hours.

All other AEs should be reported on the CRF following the CRF procedure described in Section 18.2.

15.5.2 The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form.

The CTR should continue reporting SAEs until 4 months after randomisation. Graft failure should be reported as and SAE up to 12 months after randomisation.

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs are reported to the Research Ethics Committee.

15.6 SUSAR reporting

Cardiff University is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting SUSARs and other SARs to the relevant ethics committees) as follows:

SUSARs which are both fatal or life-threatening and not fatal or life-threatening must be reported to the REC within 15 calendar days of receipt at the CTR.

If the report is incomplete then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report, for all fatal and non-fatal, life-threatening, and non-life threatening.

Any additional, relevant information must be reported within a further 15 days.

15.7 Safety Reports

A list of all SAEs (expected and unexpected) will be reported annually to the trial sponsor.

15.8 Contraception and pregnancy

15.8.1 Contraception

The majority of patients will fall outside of being of childbearing potential or are the partner of such a person. For participants who are of childbearing potential, they should follow local standard of care regarding contraception as long as this a highly effective form of contraception. Note, Radiotherapy has a demonstrated human teratogenicity/fetotoxicity.

15.8.2 Pregnancy reporting whilst participating in the trial

Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g., termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant or the female partner of a male participant, this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion etc. Without follow-up of the pregnancy, it would not be possible for the CTR to know if a congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the radiotherapy. Information on a pregnancy in a trial participant will be captured on the CTR Pregnancy Report Form supplied to sites by the CTR.

Sites should report pregnancy occurring within SAE reporting periods stipulated in this trial protocol. Congenital anomalies or birth defects are considered an SAE and so these events must also be

reported to the CTR on a trial-specific SAE form. The CTR will report this within as a SUSAR 15 days to the Ethics Committee.

15.9 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator or Principal Investigator may carry out in order to protect the subjects of a trial against any immediate hazard to their health or safety. Any urgent safety measure relating to this trial must be notified to the Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

16 Statistical considerations

The design is two-arm group-sequential phase III trial, with a time to event outcome of locoregional recurrence-free survival and two formal interim analysis after 77 and 115 events and a final analysis. A group sequential design was selected due to the large effect size that we hope to detect and provides the potential to make cost savings by stopping the trial early in the event of a large enough effect size at either of the two interims. LRR free survival was considered the most important endpoint because LRR causes mortality, significant morbidity and reduces quality of life. The trial also includes a SWAP to address recruitment issues in this underserved population.

16.1 Randomisation

Participants recruited should be randomized to each group with a fixed ratio of 1:1 using a centralized internet randomization. Randomisation will be by minimisation with a random element. Randomisation stratification factors will be; age category, stage of cancer, immunocompromised, time since surgery and perineural invasion. The trial is open-label since participants in the intervention arm will receive radiotherapy.

16.2 Sample size

Assuming a conservative LRR of 20% for T2b and 50% for T3 cSCC (16, 17), and UK data confirm 92% of recurrence is within 3 years (14). Our extensive SSMDT and PPI work support a 35% reduction as a meaningful clinical effect in LRR as justification for use of ART (26, 27). This plausibility of this effect size is also supported by a recently published observational study (24). For the primary outcome to improve LRR-free survival from the current rate of 80% to 87% at 3 years (reduction in LRR events of 35%) translates into a hazard ratio of 0.624. In absolute terms, for a LRR of 20 out of 100 recurrences, 35% reduction translates to 7 fewer recurrences.

The sample size was calculated based on the time-to event outcome of LRR free survival, using the artmenu package in Stata 17. With the expected 3-year LRR-free survival of 0.8 in the standard clinical

follow up arm, and a HR of 0.624, with 1:1 allocation ratio and applying a two-sided type I error rate of 5% and 90% power, 194 events are required for analysis of the primary outcome. Recruiting 752 patients over 4 years with these assumptions predicts that this number of events will be observed after approximately 3 years follow-up. Allowing for 10% dropouts (loss to follow up, withdrawals, deaths from other causes – all censored observations), and rounding up slightly, the total sample size required is 840 patients.

We will use competing risks regression to account for death from other causes or distant metastasis events prior to local recurrence. Because most of these events will be due to death from other causes rather than distant metastases, we do not expect this to be more than the 10% we have allowed for attrition. However, if competing events are seen to be higher than expected during trial monitoring, we will discuss with the funders about the possibility of recruiting more patients to achieve the target number of LRR events.

16.3 Missing, unused & spurious data

Detail provided in the Statistical Analysis Plan (SAP).

16.4 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

16.5 Termination of the trial

Two interim analyses after 77 and 115 events (600-760 randomized) would trigger early stopping if the log-rank statistic is larger than +/- 3.36 and +/- 2.68 respectively. Stopping for efficacy means fewer participants and shorter follow-up. Otherwise, the trial will be analyzed when at least 194 events have been reported.

16.6 Inclusion in analysis

All randomised participants will be included in the Intention-to-treat (ITT) analysis of the primary endpoint. Full details will be provided in the SAP. In general, a treatment policy approach to estimands will be used to deal with intercurrent events such as adverse events and discontinuation of treatment. Patients that withdraw completely or are lost to follow-up will be censored at the date last known to be recurrence free and patients that die due to other causes will be censored at the time of death. Full details on the estimand framework and handling of missing data will be provided in the SAP.

17 Analysis

17.1 Main analysis

The trial will be analysed when at least 194 events have been reported.

Patients that withdraw completely or are lost to follow-up will be censored at the date last known to be recurrence free and patients that die due to other causes will be censored at the time of death.

A full statistical analysis plan will be finalised prior to the first formal analysis of this group sequential trial. The primary analysis is the stratified logrank test. The design will include two formal interim analyses after 77 and 115 events (appx. 600 and 760 randomised), allowing the trial to stop early if, at each formal interim analysis the log-rank test statistic is larger than +/- 3.36 and +/- 2.68 respectively. Stopping for efficacy at either interim analysis would mean fewer participants need to be recruited and follow-up can be reduced for the remaining patients. If the test statistic is not large enough at the interim analyses, the trial will continue to the full target, and will be analysed when at least 194 events have been reported. The log-rank test will be significant if the final test statistic is greater +/- 1.98 (45). The total alpha spent in all 3 analyses adds up to 5%. We will actively monitor recruitment (LRR event rates, dropout rates) to project when the necessary number of events might occur. This will allow timely recruitment adjustments if needed. Recruitment projections are based on 100 patients in year 1, 200 in year 2, 240 in year 3 and 300 in year 4. Alternative study lengths and recruitment periods were considered; this was found to be the most realistic in ensuring recruitment to the required sample size in the shortest overall duration.

If proportional hazards assumptions are not violated, then a Cox regression model will be used to estimate the hazard ratio for the primary outcome and for secondary outcomes of distant metastasis-free survival and overall survival, adjusted for prognostic factors. If the proportional hazards model is strongly violated, then restricted mean survival analysis methodology will be used for multivariable analysis.

17.2 Interim analysis

Internal Pilot or feasibility studies progression criteria. Proposed length of internal pilot phase: 18 months (12 months from opening to recruitment).

An internal pilot targeting recruitment of 100 patients within the first 12 months will determine feasibility. Recruitment prediction is based on site interest and experience on speed of site opening.

In our MDT survey, >90% of MDTs discussed 5 or more HR-cSCC patients per month and 25% discussed >15, which is in line with the published incidence of HR-cSCC (7). The average predicted recruitment from the 25 centres was 2-3 patients per month. We will use a traffic light system to determine feasibility and have developed a recruitment prediction based on the recently obtained expressions

of interest (EOIs) and experience on speed of centre opening. This takes a very conservative approach having taken a quarter of the expected recruitment received in the EOIs from centres, with additional reduction of outliers. The population served by the MDT was taken into consideration for further adjustment. The figures shown in the table 5 below would be at the timepoint 12 month from opening the first site.

Table 6. Traffic light feasibility

	Red	Amber	Green
Number of centres open	<8	Between 8 and 15	>15
Latest monthly recruitment	<10	Between 10 and 16	>16
Total number of patients recruited	<50	Between 50 and 100	>100

Two interim analyses after 77 and 115 events (600-760 randomised) trigger early stopping if the log-rank statistic is larger than +/- 3.36 and +/- 2.68 respectively. Stopping for efficacy means fewer participants and shorter follow-up.

17.3 Quality of Life (QoL)

QoL improvement will be assessed primarily using the global health status derived from the EORTC QLQ-C30 questionnaire at 4 months from baseline (change from baseline in global health status score) between the two arms. This will be calculated as per scoring instructions in the EORTC QLQ-C30 manual. For analyses, descriptive statistics will be produced, using medians and interquartile ranges (IQRs) instead of means and standard deviations in cases of heavily skewed data. The standardized Skin Cancer Index questionnaire will be analysed, and missing data handled in accordance with their respective guidelines. Proportion of patients experiencing a change from baseline for each measure as well as mean group changes will be calculated. Associations between the reporting of skin toxicity due to radiotherapy between clinicians and patients (using CTCAE, v5.0) at the same timepoints will be explored. In addition, sub-group analyses based on age, gender, treatment arm, will be undertaken. Statistical significance tests will be carried out if clinically significant differences are observed. Independent samples t-tests will be used to compare means, and the nonparametric equivalent will be used to compare medians in the case of skewed data. Proportions will be compared using the chi-square test. Associations will be explored using multivariate regression analyses if sample size allows.

17.4 Quintet Recruitment Intervention (QRI) and INCLUSION Study Within A Project (SWAP)

To address recruitment and inclusion challenges, we have integrated a Quintet Recruitment Intervention (QRI) (40), a mixed methods intervention developed to optimise recruitment and informed consent. A complementary 'Study Within A Project' (SWAP) (41) will be conducted alongside, to optimise inclusion of particular participant groups facing additional recruitment and retention challenges and develop methodological tools to promote inclusion more broadly during trial recruitment. This integrated study is referred to as QRI+INCLUSION.

The QRI comprises two iterative and overlapping phases (30). Phase 1 involves mixed methods data collection of screening data and qualitative data involving patients and professionals to gain a detailed understanding of the recruitment process. Phase 2 involves feedback of findings to the Chief Investigator and Trial Management Group, to agree tailored interventions to improve recruitment and informed consent. The SWAP will overlay an inclusivity lens on all QRI activity.

Phase 1

- Pre-trial workshops: QRI: Professionals' views will be explored in 2-3 workshops involving clinical co-applicants and recruiters at collaborating sites to facilitate exploration of patient screening/identification pathways, eligibility criteria and equipoise. This work is covered by a separate Research Ethics Committee (REC) approval (University of Bristol, Faculty of Health Sciences Research Ethics Committee).
- Mapping of screening, eligibility, and recruitment pathways, which will help to identify where patients are lost from the recruitment pathway, including those from under-served groups e.g., non-English speaking, capacity to consent, or where geographical or deprivation factors may have affected recruitment.
- Patients will be invited to consent to the recording of all conversations during which participation in the trial is discussed.
- Professional and patient interviews, with purposive sampling to investigate reasons for losses to recruitment and explore experiences of under-served groups and potential barriers to inclusion.
- A QuinteT researcher will observe all TMG and TSC meetings during which the study protocol and patient facing paperwork is developed and finalised, with a focus on discussion and final presentation of equipoise and eligibility criteria.

Phase 2

Findings from phase 1 will be presented to the CIs and TMG. If recruitment difficulties are evident across the trial or at particular sites, the CI/TMG and QuinteT team will agree actions to improve recruitment and information provision. The specific actions implemented will be grounded in the

findings from analysis of the data above, with format dependent on the nature of the recruitment barriers identified and may include feedback to individual recruiters, study wide feedback or amendments to recruitment pathways.

17.4.1 Consent processes for the QuinteT Recruitment Intervention

a) Health care professional consent

Recruiting staff and TMG member consent will be obtained through a 'master' consent form that covers all aspects of the QRI. The consent form will set out individual clauses, with the option to select 'Yes' or 'No' for each research activity accordingly. Site team coordinators or the QuinteT researcher will obtain written consent from all relevant site staff. This will be a one-off process to cover consent for all future recordings of appointments, interviews, and observations of TMG/investigator meetings throughout the study.

b) Patient consent

***Audio recording/observing recruitment appointments*:**

Patients will be sent a copy of the PIS in advance or given the PIS in an initial face to face discussion. Patients will be provided with sufficient time to read the information, ask any questions, and consider participation in the QRI/Information study, which involves consenting to the audio recording of discussions about the study and/or a qualitative interview with the QRI researcher.

A flexible one or two-step consent process will be offered for capturing consent to audio-recording initial discussions about potential participation in the SCC-AFTER study.

1) One step: where patients have had the PIS sent in advance, site team members will invite a decision on participation in the QRI/information study and collect consent using approved consent processes to audio record the recruitment discussion and take part in a qualitative interview respectively.
2) Two step: where patients have not previously seen the SCC PIS, site team members will invite spoken consent to audio record the conversation about the study at the very start of the recruitment consultation. At the end of this conversation, patients will be asked to confirm whether they wish to follow up spoken consent with approved consent processes. Patients will be able to provide consent using approved processes at the end of this consultation or at a later date. Future discussions about potential SCC-AFTER participation will be audio-recorded subject to receiving this consent; if patients choose not to provide consent, the recording made from their initial discussion will be deleted, and no further recordings made.

All approved consent processes for the QRI/Information study will mirror those described for the main trial (see section 9.4) with the aim of optimising inclusion in the QRI + INCLUSION study.

Interviews

Patients will receive information about the interview processes in the PIS and will be able to provide consent using approved consent processes to take part in an interview at the same time as giving consent to audio recording of the recruitment consultation as described above. The QRI consent form will give the option to decline the QRI+INCLUSION study, consent to only the audio recording of recruitment consultations or only the interview, or consent to both.

17.4.2 QRI + INCLUSION Data Analysis

Screening and enrolment logs

The QuinteT researcher will analyse data using the Screened, Eligible, Approached, randomised (SEAR) (31) framework to observe differences between sites in recruitment patterns as new sites open. Simple descriptive analyses will identify points in the recruitment pathway at which patients are lost to recruitment to the cohort or trials and the reasons why. Detailed screening, eligibility, approach, and recruitment pathways will be compiled for sites, noting the point at which patients receive information about the study, which members of the clinical team they meet, and the timing and frequency of appointments. Recruitment pathways will be compared with details specified in the trial protocol and pathways from other sites to identify practices that are potentially more/less efficient. Numbers of screened, eligible, approached, and recruited patients will be compared across sites and considered in relation to estimates specified in the grant application/study protocol. Additional analysis of screening logs will focus on key non-identifiable demographic and health data recorded from medical records relevant to under-served groups. These data will drive the purposive sampling of and be triangulated with the qualitative data findings (see below) to identify barriers and potential solutions to recruitment.

Recordings of recruitment conversations and interviews with patients and healthcare professionals

Audio recordings of recruitment conversations will be sought from a purposefully sampled range of recruiting sites (showing higher and lower recruitment and including those agreeing to and declining to participate) to ensure maximum variation and recordings will be analysed by the QuinteT researchers.

The audio recordings will be used to explore information provision, management of patient treatment preferences, and randomisation decisions to identify recruitment difficulties and improve information provision. Audio-recorded recruitment consultations will be subjected to targeted transcription with relevant sections first identified then transcribed and identifying data removed before fuller analysis. Analysis will employ content, thematic, and novel analytical approaches, as described in the QuinteT recruitment intervention protocol (30).

Those declining participation within the trial and consenting to the QRI will be invited to take part in an interview to investigate their experiences of being given information about the trial and their understanding of trial information. Participants will be purposively sampled to include potential participants across a range of trial sites, with those who decline the study or those who accept participation then immediately decline the allocated intervention being prioritised for interview.

Healthcare professionals involved in recruiting patients to the study or working within the trial site teams to support recruitment may also be invited to take part in an interview to investigate their experiences of trial recruitment processes.

The screening, eligibility, approach and recruitment challenges relating to under-served groups identified in the previous QRI Phase 1 activities will inform the sampling of patients to explore their experiences of being approached about participation and of healthcare professionals to explore their views on factors impacting on inclusion of these groups.

All interview data will be analysed thematically using constant comparative approaches derived from Grounded Theory methodology (42) and triangulated with findings from analyses of SEAR data and analyses of audio recorded recruitment discussions where available.

Findings from the investigation of recruitment to SCC-AFTER will be fed back to the CI and TMG, where appropriate, to determine actions to optimise recruitment to the trial. Actions may include feedback to individuals or in groups as appropriate and will include template patient pathways, individualised or generic ‘tips’ sheets for recruiters and delivery of recruiter training.

The INCLUSION SWAP will triangulate the findings from the screening and recruitment logs, interviews and recruitment conversations using an inclusivity lens to enable conclusions to be drawn about the barriers to the recruitment of groups such as people with MLTC and/or other exclusionary factors. This will be included in the ‘tips’ sheets and other guidance and feedback as appropriate.

17.5 Cost effectiveness analysis

A full Health Economic Analysis Plan will be specified prior to data lock (43). Patient-level cost and utilities will be analysed using regression models to estimate mean costs associated with clinically meaningful health states (e.g., LRR and progression-free survival, progressive disease, toxicity, disease-specific and all-cause death). These states will be the basis of a Markov model to extrapolate

costs and consequences over time. The regression analyses will account for the distributions of costs and utilities and correct for any baseline imbalance in EQ-5D-5L utility scores (44). Parametric functions will be used to model LRR, progression-free and overall survival. Different functional forms will be tested for suitability based on goodness of fit criteria and informed by external data from published sources (45).

A stochastic sensitivity analysis will be carried out to estimate the incremental cost-effectiveness ratio, and to assess the probability of cost-effectiveness for given threshold values of willingness to pay. This will consider simultaneous uncertainty in parameter inputs and provide evidence suitable to decision makers on the cost-effectiveness of ART. Additional sensitivity and scenario analyses, will be undertaken to account insofar as possible, different sources of uncertainty. A stratified cost-effectiveness analysis will be conducted for valid sub-groups that will be specified *a priori*.

18 Data Management

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents."* There is only one set of source data at any time for any data element, as defined in site source data agreement.

Source data include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. Sites will retain all original source of data from these investigations for future reference. On all trial-specific documents, other than the signed consent form, the participant will be referred to by the trial participant ID, not by name.

18.1 Data collection

Patient randomisation and data collection will take place via electronic online databases. Further information can be found in the SCC-After site manual.

18.2 Completion of CRFs

Electronic CRFs

Data recording for this trial will be via web-based systems. These are secure encrypted systems which comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018 standards. After a site has supplied the CTR trial team with a completed delegation log and completed all other processes required to open for recruitment, each user at the site will be emailed a link to

activate their account and a username by which they can access these systems in combination with a password set by the user.

A link to the randomisation system will be sent upon site activation along with a database user guide.

The data entry system can be accessed via: https://redcap.ctr.cardiff.ac.uk/redcap/

Sites will be provided with a guide on using these systems.

Data is expected to be entered by sites within four weeks after the scheduled visit/assessment. If a participant misses a visit/assessment but relevant data is available, for example from a hospital visit unrelated to the trial, this data should be provided. Data queries will be flagged on RedCAP by the CTR trial team; unresolved queries and overdue forms will be flagged via email to the site on a regular basis.

Quality of Life Questionnaires

A paper CRF will be used to collect the patient reported outcomes via the QoL questionnaires (EORTC QLQ-C30, SCI, PPE-15, EQ-5D) and patient reported toxicities. Completed paper questionnaires containing the participant's trial ID, month and year of birth, initials and date of completion are to be entered onto REDCap by a delegated site staff listed on the delegation log and, the original kept in the participant file at site. A copy is to be returned to the CTR using the Freepost labels contained within the Investigator Site File (ISF) and 'Confidential' marked on the envelope upon request for Quality Control purposes.

Participating sites will be provided with training and instructions on how to complete and return the CRFs. The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner.

18.3 QuinteT recruitment intervention

Recordings of recruitment conversations

Recruitment conversations will be recorded by a research team member using a method of secure data capture and storage in line with University of Bristol procedures (as outlined on the University of Bristol website). Audio-recordings will be transferred by secure data transfer by the approved qualitative research team members onto a secure drive at the University of Bristol for long-term storage and analysis. Audio-recordings will be labelled with the SCC-AFTER participant identification number; identifiable patient details will not be used.

Audio-recordings will be subject to targeted transcription and edited to protect the anonymity of respondent. Transcription will be undertaken by an approved transcription service/transcriber that has signed the necessary confidentiality agreements with the University of Bristol. Data will be

managed using NVivo software and stored on encrypted drives at the University of Bristol, in line with the university's data storage policies and in line with GDPR legislation.

At the end of the study, audio-recordings will be kept for at least 15 years before they will be destroyed. Transcripts will be stored for at least 15 years in secure research data storage designated 'controlled access', so can only be accessed by approved individuals who are interested in conducting their own analyses of the data. These individuals will have to submit an application to do this, which will be assessed by an independent committee. However, all data will have identifiable information removed before they are made available, and there will be no way to identify any individuals mentioned in interviews/appointments.

Interviews

Approved qualitative research team members from University of Bristol will access participants' contact details via the trial database or have these securely passed them by the research team for the purposes of contacting patients who have consented to interviews as part of the QRI. Team members will be provided with an individual user account for the database with restricted, password-controlled access.

Interviews with patients and staff will be recorded directly by the qualitative researcher using processes for secure data capture and storage in line with University of Bristol procedures (as outlined on the University of Bristol website). Recordings will be held on a secure drive with restricted access at the University of Bristol for long-term storage and analysis. Recordings will be labelled with the SCC-AFTER participant identification number by the Bristol team; identifiable patient details will not be used. At the end of the trial, recordings will be held for a minimum of 15 years after which they will be destroyed.

Participants will not be identifiable in reports produced to describe the QRI findings at the end of the study.

QRI documentation

Paper or electronic documentation which is generated through the process of performing the QRI will be stored securely at the University of Bristol with access restricted only to approved personnel.

19 Translational research or sub trial

There is no current funding for a translational sample collection, although a number of areas around tumour characteristics and response to treatment would provide valuable information relating to treatment of the disease.

Consent will be collected to use the surgical sample (or biopsy) collected as routine standard of care by NHS sites, for future translational use and this collection will be made when funding is secured.

20 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

21 End of Trial definition

The treatment phase will be followed by a follow-up period which will continue for a minimum of 3 years from time of randomisation. Progression/death data for all patients will continue to be collected until the last patient has completed 3 years.

The end of the trial is defined as the date of final data capture to meet the trial endpoints. In this case end of trial is defined as the final follow-up collection, which will be at least 3 years after final patient is randomised.

Sponsor must notify the REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

22 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 15 years. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor.

Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

23 Regulatory Considerations

23.2 Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally “recognised” by the United Kingdom Ethics Committee Authority for review and approval.

This trial protocol will be submitted through HCRW which assesses governance and legal compliance for the NHS in Wales. Additional governance review and approval will be obtained through HRA as this is required to open sites in England. The HRA approval process replaces the need for local checks of legal compliance and related matters by participating sites in England—this means sites do not give site specific governance approval.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. Confirmation of C&C of the host care organisation must be obtained before recruitment of participants within that host care organisation.

23.3 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2018. The data custodian for this trial is the division director of the CTR.

23.4 Indemnity

- Non-negligent harm: This trial is an academic, investigator-led and designed trial, coordinated by the CTR. The Chief Investigator, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.
- Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a participant being treated within the hospital, whether or not the participant is participating in this trial. Cardiff University does not accept liability for any breach in the other hospital's duty of care, or any negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site management organisations.

23.5 Trial sponsorship

Cardiff University will act as Sponsor for trial. Delegated responsibilities will be assigned to the sites taking part in this trial.

The trial is being sponsored by Cardiff University with responsibilities delegated to the CTR. The CTR shall be responsible for ensuring that the trial is performed in accordance with the following:

- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996).
- UK Policy Framework for Health and Social Care Research.
- The General Data Protection Regulation 2016.
- The Human Tissue Act 2004.
- Other regulatory requirements as appropriate.

The trial will be conducted in compliance with the protocol and Good Clinical Practice as required by the regulations.

23.6 Funding

This study is funded by NIHR Health Technology Assessment (HTA) Programme. Funder reference NIHR151760.

24 Trial management

24.1 TMG (Trial Management Group)

The Trial Management Group (TMG) will be responsible for the day-to-day running of the trial and will meet once every three months. The TMG members will include the Chief Investigators, Co-investigators, CTR representatives, specialist advisors and consumer representatives. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

24.2 TSC (Trial Steering Committee)

The Trial Steering Committee (TSC) will be a committee of independent members providing overall supervision of the trial. The role of the TSC is to act on behalf of the sponsor, to provide overall supervision for the trial, to ensure that it is conducted in accordance with GCP, and to provide advice through its independent chairperson. The TSC will review the recommendations of IDMC and will decide on continuing or stopping the trial, or modifying the protocol as required. It will meet at least annually when it will consider each report of the IDMC, as well as results of other trials and new information which has arisen and recommend appropriate action. TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

24.3 IDMC (Independent Data Monitoring Committee)

The data will be reviewed by an Independent Date Monitoring Committee (IDMC), consisting of at least two Clinicians (not entering patients into the trial) and an independent Statistician. The IDMC will be asked to recommend whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients. A decision to discontinue recruitment, in all patients or in selected subgroups, will be made only if the result is likely to convince a broad range of Clinicians including PIs in the trial and the general clinical community. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDMC will make confidential recommendations to the Trial Steering Committee (TSC).

25 Quality Control and Assurance

25.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the SCC-AFTER trial. Low+ monitoring levels and triggered on site monitoring (with the option of being remote) will be employed and are fully documented in the trial monitoring plan.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Where electronic health records (EHR) are being used, trial teams and monitors should check EHR process early in trial and periodically thereafter.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local R&D.

25.2 Audits & inspections

The trial does not involve an Investigational Medicinal Product (IMP) or a device and therefore does not require Clinical Trial Authorisation (CTA) from the MHRA. The trial will be submitted through the Research Governance process of the host care organisation for review and approval. The research governance approval of the host care organisation must be obtained before the start of the trial within that host care organisation.

The trial may be participant to inspection and audit by Cardiff University under their remit as Sponsor.

The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC/ IRB review, and regulatory inspection(s), providing direct access to source data / documents.

26 Public Involvement and Engagement

Patients and carers with lived experience of non-melanoma skin cancers will have provided input into the design of the study and all patient-facing materials. A patient advisory group (PAG) has been formed to provide a voice for the often underrepresented experiences of non-melanoma skin cancer patients and carers. The PAG will consult on all patient-facing documentation and input throughout the running the trial.

27 Publication policy

All publications and presentations relating to the trial will be authorised by the Trial Management Group. The CTR publication policy will hold details of publications and dissemination policies.

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29 Appendices

Appendix 1: Quality of Life Questionnaires.

EQ-5D

Date Completed:

D	D	M	M	Y	Y	Y	Y

Under each heading, please tick the ONE box that best describes your health **TODAY**

Mobility

1. I have no problems in walking about ☐
2. I have slight problems in walking about ☐
3. I have moderate problems in walking about ☐
4. I have severe problems in walking about ☐
5. I am unable to walk about ☐

Self-Care

1. I have no problems washing or dressing myself ☐

☐

2. I have slight problems washing or dressing myself
3. I have moderate problems washing or dressing myself ☐
4. I have severe problems washing or dressing myself ☐
5. I am unable to wash or dress myself ☐

Usual Activities - *(e.g. work, study, housework, family or leisure activities)*

1. I have no problems doing my usual activities ☐
2. I have slight problems doing my usual activities ☐
3. I have moderate problems doing my usual activities ☐
4. I have severe problems doing my usual activities ☐
5. I am unable to do my usual activities ☐

Pain/Discomfort

1. I have no pain or discomfort ☐
2. I have slight pain or discomfort ☐
3. I have moderate pain or discomfort ☐
4. I have severe pain or discomfort ☐
5. I have extreme pain or discomfort ☐

Anxiety/Depression

1. I am not anxious or depressed ☐

☐

2. I am slightly anxious or depressed
3. I am moderately anxious or depressed ☐
4. I am severely anxious or depressed ☐
5. I am extremely anxious or depressed ☐

Health Thermometer Date Completed:

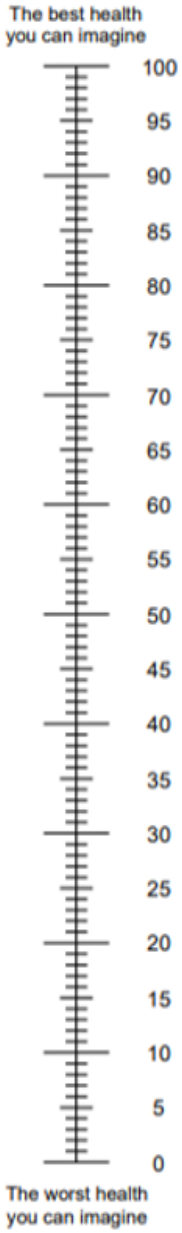
D	D	M	M	Y	Y	Y	Y

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.

- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



EORTC QLQ-C30 (v3)

Date Completed:

D	D	M	M	Y	Y	Y	Y

We are interested in some things about you and your health. Please answer all the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhoea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you	Very Poor						Excellent
29. How would you rate your overall health during the past week?	1	2	3	4	5	6	7
30. How would you rate your overall quality of life during the past week?	1	2					

D	D	M	M	Y	Y	Y	Y

This questionnaire is interested in your feelings about your skin cancer. For each question please circle the number from 1-5 that best applies.

During the past month, how much have you...	Very Much	Quite a Bit	Moder-ately	A Little Bit	Not at All
1. Worried that your skin cancer will spread to another part of your body?	1	2	3	4	5
2. Felt anxious about your skin cancer?	1	2	3	4	5
3. Worried that family members may also develop skin cancer?	1	2	3	4	5
4. Worried about the cause of skin cancer?	1	2	3	4	5
5. Felt frustrated about your skin cancer?	1	2	3	4	5
6. Worried that your tumour may become a more serious type of skin cancer?	1	2	3	4	5
7. Worried about new skin cancers occurring in the future?	1	2	3	4	5
8. Felt uncomfortable when meeting new people?	1	2	3	4	5
9. Felt concerned that your skin cancer may worry friends or family?	1	2	3	4	5
10. Worried about the length of time before you can go out in the public?	1	2	3	4	5
11. Felt bothered by people's questions related to your skin cancer?	1	2	3	4	5
12. Felt embarrassed by your skin cancer?	1	2	3	4	5
13. Worried about how large the scar will be?	1	2	3	4	5
14. Thought about how skin cancer affects your attractiveness?	1	2	3	4	5
15. Thought about how noticeable the scar will be to others?	1	2	3	4	5

PPE-15

Date Completed:

D	D	M	M	Y	Y	Y	Y

When completing this questionnaire please answer about any instances occurring since the surgery for your skin cancer.

1. When you had important questions to ask a doctor, did you get answers that you could understand?
   - 1 Yes, always ☐
   - 2 Yes, sometimes ☐
   - 3 No ☐

2. When you had important questions to ask a doctor, did you get answers that you could understand?
   - 1. Yes, always ☐
   - 2. Yes, sometimes ☐
   - 3. No ☐
   - 4. I had no need to ask ☐

3. When you had important questions to ask a nurse, did you get answers that you could understand?
   - 1 Yes, always ☐
   - 2 Yes, sometimes ☐
   - 3 No ☐
   - 4 I had no need to ask ☐

4. Sometimes in a hospital, one doctor or nurse will say one thing and another will say something quite different. Did this happen to you?
   - 1 Yes, often ☐
   - ☐

2 Yes, sometimes

3 No ☐

5. If you had any anxieties or fears about your condition or treatment, did a doctor discuss them with you?

1 Yes, completely ☐

2 Yes, to some extent ☐

3 No ☐

4 I didn't have any anxieties or fears ☐

6. Did doctors talk in front of you as if you weren't there?

1 Yes, completely ☐

2 Yes, sometimes ☐

3 No ☐

7. Did you want to be more involved in decisions made about your care and treatment?

1 Yes, definitely ☐

2 Yes, to some extent ☐

3 No ☐

8. Overall, did you feel you were treated with respect and dignity while you were in hospital?

1 Yes, always ☐

2 Yes, sometimes ☐

☐

3 No

9. If you had any anxieties or fears about your condition or treatment, did a nurse discuss them with you?

1 Yes, completely ☐
2 Yes, to some extent ☐
3 No ☐
4 I didn't have any anxieties or fears ☐

10. Did you find someone on the hospital staff to talk to about your concerns?

1 Yes, definitely ☐
2 Yes, to some extent ☐
3 No ☐
4 I had no concerns ☐

11. Were you ever in pain?

1 Yes ☐
2 No ☐

If Yes… Do you think the hospital staff did everything they could to help control your pain?

1 Yes, definitely ☐
2 Yes, to some extent ☐
☐

3 No

12. If your family or someone else close to you wanted to talk to a doctor, did they have enough opportunity to do so?

1	Yes, definitely	☐
2	Yes, to some extent	☐
3	No	☐
4	No family or friends were involved	☐
5	My family didn't want or need information	☐
6	I didn't want my family or friends to talk to a doctor	☐

13. Did the doctors or nurses give your family or someone close to you all the information they needed to help you recover?

1	Yes, definitely	☐
2	Yes, to some extent	☐
3	No	☐
4	No family or friends were involved	☐
5	My family or friends didn't want or need information	☐

For the following questions that ask about medicines/medications, please take this to mean any treatments (including but not limited to radiotherapy and surgery) that you may have received for your skin cancer:

14. Did a member of staff explain the purpose of the medicines you were to take at home in a way you could understand?

1	Yes, completely	☐
2	Yes, to some extent	☐
3	No	☐
4	I didn't need an explanation	☐
5	I had no medicines - go to question 15	☐

15. Did a member of staff tell you about medication side effects to watch for when you went home?

1	Yes, completely	☐
2	Yes, to some extent	☐
3	No	☐
4	I didn't need an explanation	☐

16. Did someone tell you about danger signals regarding your illness or treatment to watch for after you went home?

1	Yes, completely	☐
2	Yes, to some extent	☐
3	No	☐

Patient Reported Toxicities

Date Completed:

D	D	M	M	Y	Y	Y	Y

1. Did your squamous cell skin cancer affect your head or neck region (this includes your scalp, face, ears or neck)?

a. Yes – please complete **both sections** of this questionnaire (all 20 questions) ☐

b. No – please skip to **section 2** of this questionnaire and only answer questions 14-20 ☐

Section 1 – Please only complete this section if your squamous cell skin cancer affected your head or neck region. For each question, please tick the option you feel best describes the degree to which you experienced the symptom described. If you did not experience the symptom, please tick the None/Never option.

1. PRO-CTCAE® Symptom Term: Dry mouth

In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?

1. None ☐
2. Mild ☐
3. Moderate ☐
4. Severe ☐
5. Very Severe ☐

2. PRO-CTCAE® Symptom Term: Difficulty swallowing

In the last 7 days, what was the SEVERITY of your DIFFICULTY SWALLOWING at its WORST?

1. None ☐
2. Mild ☐

☐

3. Moderate
4. Severe ☐
5. Very Severe ☐

3. PRO-CTCAE® Symptom Term: Taste changes

In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?

1. None ☐
2. Mild ☐
3. Moderate ☐
4. Severe ☐
5. Very Severe ☐

4. PRO-CTCAE® Symptom Term: Rash

In the last 7 days, did you have any RASH?

1. Yes ☐
2. No ☐

5. PRO-CTCAE® Symptom Term: Skin dryness

In the last 7 days, what was the SEVERITY of your DRY SKIN at its WORST?

1. None ☐
2. Mild ☐
3. Moderate ☐

4. Severe ☐
5. Very Severe ☐

6. PRO-CTCAE® Symptom Term: Hair loss

In the last 7 days, did you have any HAIR LOSS?

1. Not at all ☐
2. A little bit ☐
3. Somewhat ☐
4. Quite a bit ☐
5. Very much ☐

7. PRO-CTCAE® Symptom Term: Itching

In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?

1. None ☐
2. Mild ☐
3. Moderate ☐
4. Severe ☐
5. Very Severe ☐

8. PRO-CTCAE® Symptom Term: Hives

In the last 7 days, did you have any HIVES (ITCHY RED BUMPS ON THE SKIN)?

1. Yes ☐
2. No ☐

9. PRO-CTCAE® Symptom Term: Sensitivity to sunlight

In the last 7 days, did you have any INCREASED SKIN SENSITIVITY TO SUNLIGHT?

1. Yes ☐
2. No ☐

10. PRO-CTCAE® Symptom Term: Radiation skin reaction

In the last 7 days, what was the SEVERITY of your SKIN BURNS FROM RADIATION at their WORST?

1. None ☐
2. Mild ☐
3. Moderate ☐
4. Severe ☐
5. Very Severe ☐

11. PRO-CTCAE® Symptom Term: Skin darkening

In the last 7 days, did you have any UNUSUAL DARKENING OF THE SKIN?

1. Yes ☐
2. No ☐

12. PRO-CTCAE® Symptom Term: Watery eyes

a. In the last 7 days, what was the SEVERITY of your WATERY EYES (TEARING) at their WORST?

1. None ☐
2. Mild ☐

☐

3. Moderate
4. Severe ☐
5. Very Severe ☐

b. In the last 7 days, how much did WATERY EYES (TEARING) INTERFERE with your usual or daily activities?

1. Not at all ☐
2. A little bit ☐
3. Somewhat ☐
4. Quite a bit ☐
5. Very much ☐

13. PRO-CTCAE® Symptom Term: Nosebleed

a. In the last 7 days, how OFTEN did you have NOSEBLEEDS?

1. Never ☐
2. Rarely ☐
3. Occasionally ☐
4. Frequently ☐
5. Almost constantly ☐

b. In the last 7 days, what was the SEVERITY of your NOSEBLEEDS at their WORST?

1. None ☐
2. Mild ☐
3. Moderate ☐
4. Severe ☐

5. Very Severe ☐

Section 2 - Please answer the following questions (14-20) no matter which part of your body was affected by your skin cancer. For each question, please tick the option you feel best describes the degree to which you experienced the symptom described. If you did not experience the symptom, please tick the None/Never option.

14. PRO-CTCAE® Symptom Term: General pain

a. In the last 7 days, how OFTEN did you have PAIN?

1. Never ☐
2. Rarely ☐
3. Occasionally ☐
4. Frequently ☐
5. Almost constantly ☐

b. In the last 7 days, what was the SEVERITY of your PAIN at its WORST?

1. None ☐
2. Mild ☐
3. Moderate ☐
4. Severe ☐
5. Very Severe ☐

c. In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?

1. Not at all ☐
2. A little bit ☐
3. Somewhat ☐
4. Quite a bit ☐

5. Very much ☐

15. PRO-CTCAE® Symptom Term: Fatigue

a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?

1. None ☐
2. Mild ☐
3. Moderate ☐
4. Severe ☐
5. Very Severe ☐

b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?

1. Not at all ☐
2. A little bit ☐
3. Somewhat ☐
4. Quite a bit ☐
5. Very much ☐

16. PRO-CTCAE® Symptom Term: Anxious

a. In the last 7 days, how OFTEN did you feel ANXIETY?

1. Never ☐
2. Rarely ☐
3. Occasionally ☐
4. Frequently ☐

5. Almost constantly ☐

b. In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST?

1. None ☐
2. Mild ☐
3. Moderate ☐
4. Severe ☐
5. Very Severe ☐

c. In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities?

1. Not at all ☐
2. A little bit ☐
3. Somewhat ☐
4. Quite a bit ☐
5. Very much ☐

17. PRO-CTCAE® Symptom Term: Discouraged

a. In the last 7 days, how OFTEN did you FEEL THAT NOTHING COULD CHEER YOU UP?

1. Never ☐
2. Rarely ☐
3. Occasionally ☐
4. Frequently ☐

☐

5. Almost constantly

b. In the last 7 days, what was the SEVERITY of your FEELINGS THAT NOTHING COULD CHEER YOU UP at their WORST?

1. None ☐
2. Mild ☐
3. Moderate ☐
4. Severe ☐
5. Very Severe ☐

c. In the last 7 days, how much did FEELING THAT NOTHING COULD CHEER YOU UP INTERFERE with your usual or daily activities?

1. Not at all ☐
2. A little bit ☐
3. Somewhat ☐
4. Quite a bit ☐
5. Very much ☐

18. PRO-CTCAE® Symptom Term: Sad

a. In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS?

1. Never ☐
2. Rarely ☐
3. Occasionally ☐
4. Frequently ☐
5. Almost constantly ☐

b. In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST?

1. None ☐
2. Mild ☐
3. Moderate ☐
4. Severe ☐
5. Very Severe ☐

c. In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTERFERE with your usual or daily activities?

1. Not at all ☐
2. A little bit ☐
3. Somewhat ☐
4. Quite a bit ☐
5. Very much ☐

19. PRO-CTCAE® Symptom Term: Decreased libido

a. In the last 7 days, what was the SEVERITY of your DECREASED SEXUAL INTEREST at its WORST?

1. None ☐
2. Mild ☐
3. Moderate ☐
4. Severe ☐
5. Very severe ☐
6. Not sexually active ☐

☐

7. Prefer not to answer

20. OTHER SYMPTOMS

a. Do you have any other symptoms that you wish to report?

1. Yes ☐
2. No ☐

Please list any other symptoms:

1. Symptom:……..

In the last 7 days, what was the SEVERITY of this symptom at its WORST?

1. Mild ☐
2. Moderate ☐
3. Severe ☐
4. Very Severe ☐

2. Symptom:……..

In the last 7 days, what was the SEVERITY of this symptom at its WORST?

1. Mild ☐
2. Moderate ☐
3. Severe ☐
4. Very Severe ☐

3. Symptom:……..

In the last 7 days, what was the SEVERITY of this symptom at its WORST?

1. Mild ☐
2. Moderate ☐
3. Severe ☐
4. Very Severe ☐

4. Symptom:……

In the last 7 days, what was the SEVERITY of this symptom at its WORST?

1. Mild ☐
2. Moderate ☐
3. Severe ☐
4. Very Severe ☐

5. Symptom:……

In the last 7 days, what was the SEVERITY of this symptom at its WORST?

1. Mild ☐
2. Moderate ☐
3. Severe ☐
4. Very Severe ☐

Appendix 2: ECOG

Table 2: ECOG Criteria

Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Dead