



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

VERSION 3.0 9TH DECEMBER 2025

Sponsor:	Cardiff University, 30-36 Newport Road, Cardiff. CF24 0DE
Sponsor ref:	SPON1924-22
Funder:	NIHR Health Technology Assessment (HTA) Programme
Funder ref:	NIHR151760
REC ref:	24/EE/0049
IRAS number:	331136
ISRCTN	54806122
Q-Pulse Document Template Number:	TPL/003/001 v5.0

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.

Trial Sponsor:			
Name	Position:	Signature	Date
Cardiff University			
Sponsor Representative:			
Natalie Richards	Research Integrity & Governance Officer	See email dated 06/01/2026	
Director:			
Name	Signature	Date	
Angela Casbard	See email dated 18/12/2025	18/12/2025	
Joint Chief Investigators:			
Name	Signature	Date	
Prof Agata Rembielak	See email dated 19/12/2025	19/12/2025	
Prof Catherine Harwood	See email dated 18/12/2025	18/12/2025	

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.

Contact details – Chief Investigators & Co-Investigators

JOINT CHIEF INVESTIGATORS:

Professor Agata Rembielak

Consultant Clinical Oncologist
The Christie NHS Foundation Trust
Wilmslow Road
Manchester
M20 4BX
E-mail: agata.rembielak@nhs.net

Professor Catherine Harwood

Professor of Dermatology
The Royal London Hospital
Barts Health NHS Trust
London
E1 1BB
E-mail: catherine.harwood1@nhs.net

CO-INVESTIGATORS:

Professor Hywel Williams

Professor of Dermato-Epidemiology & Co-
Director at Centre of Evidence-Based
Dermatology
University of Nottingham
Email: hywel.williams@nottingham.ac.uk

Professor Charlotte Proby

Professor of Dermatology
University of Dundee
E-mail: c.proby@dundee.ac.uk

Dr Rubeta Matin

Consultant Dermatologist
Oxford University Hospitals NHS Foundation
Trust
Email: rubeta.matin@ouh.nhs.uk

Dr Kate Fife

Consultant Clinical Oncologist
Cambridge University, Hospitals NHS Foundation,
Trust
E-mail: kate.fife@nhs.net

Dr Jeremy Marsden

Honorary Consultant
NHS University Hospitals Birmingham NHS Trust
E-mail: jerry.marsden@btinternet.com

Dr Rachel Abbott

Dermatology Consultant
Cardiff and Vale University Health Board
E-mail: rachel.abbott@wales.nhs.uk

Professor Carrie Newlands

Consultant Maxillofacial Surgeon
Royal Surrey County Hospital NHS Foundation
Trust
E-mail: c.newlands@surrey.ac.uk

Dr Romaana Mir

Consultant Clinical Oncologist
East and North Hertfordshire NHS Trust
E-mail: romaana.mir@nhs.net

Dr Julia Wade

Senior Lecturer in Qualitative Health Science
University of Bristol
E-mail: julia.wade@bristol.ac.uk

Dr Victoria Shepherd

Principal Research Fellow
Cardiff University
Email: shepherdvl1@cardiff.ac.uk

Professor Dyfrig Hughes

Professor of Pharmacoeconomics
Bangor University
Email: d.a.hughes@bangor.ac.uk

Dr Lisette Nixon

Senior Research Fellow
Cardiff University
Email: nixonls@cardiff.ac.uk

Angela Casbard

Senior Research Fellow
Cardiff University
Email: casbardac@cardiff.ac.uk

Research Partner

Mrs Patricia Fairbrother
Trustee: Independent Cancer Patients' Voice
c/o CTR SCC- AFTER team

Mrs Aenone Harper Machin

Consultant Plastic Surgeon
Whiston Hospital
Email: Aenone.harper@sthk.nhs.uk

Mr Jonathan Pollock

Consultant Plastic Surgeon
Nottingham University Hospital
Email: Jonathan.Pollock@nuh.nhs.uk

SPONSOR

Sponsor Representative

Title and name: **Natalie Richards**

Position: **Research Integrity & Governance Officer**

Institution: **Cardiff University**

E-mail : resgov@cardiff.ac.uk

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

Main Trial Email: SCCAfter@cardiff.ac.uk

Study Lead:	Dr Lisette Nixon
Trial Manager:	Ann White
Trial Administrator	Layton Driscoll
Senior Trial Manager	Dr Margherita Carucci
Data Manager:	Mahuampi Perez-Alijas
Senior Data Manager:	Ceri Frayne
Senior Trial Statistician:	Angela Casbard
Trial Statistician	Dr Catharine Porter
Director:	Angela Casbard
Pharmacovigilance and Safety Specialist Team	Email: ctr-safety@cardiff.ac.uk

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 activate within the study database if the patient is eligible and has consented. 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 randomisation of a patient.

Clinical and non-clinical queries:

Please contact the trial team: 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:

CTR-Safety@cardiff.ac.uk

Table of Contents

1	Amendment History	11
3	Trial summary & schema	19
3.1	Schema	19
3.2	Participant flow diagram.....	20
3.3	Trial Lay Summary	21
4	Background.....	22
4.1	Rationale for current trial/Justification of Treatment Options	24
	Research question	24
	Rationale for conducting this study	24
5	Trial objectives and outcome measures	25
5.1	Primary objective	25
	Null hypothesis	25
	Alternative hypothesis	25
5.2	Secondary objectives	25
5.3	Primary outcomes measure	25
5.4	Secondary outcomes measures	26
5.5	Tertiary objectives and outcomes	26
6	Trial design and setting	27
6.1	Risk assessment	28
7	Site and Investigator selection.....	28
8	Participant selection.....	29
8.1	Inclusion criteria	29
8.2	Exclusion criteria	30
9	Recruitment, screening, and registration	30
9.1	Participant identification	30
9.2	Screening logs	31
9.3	Recruitment rates	32
9.4	Informed consent.....	32
9.5	Randomisation.....	33
10	Withdrawal & lost to follow-up	34
10.1	Withdrawal.....	34
10.2	Lost to follow up	36
11	Trial Intervention	36
11.1	Radiotherapy Treatment	36
11.3	Radiotherapy quality assurance	37
11.7	Participant positioning and planning CT scan acquisition	38
11.9	Management of unscheduled gaps in RT treatment.....	38
12	Health Economics	38
13	Sample Management	39
14	Trial procedures.....	39
14.2	Pre-treatment assessments(additional to screening assessments for patients randomised to the radiotherapy arm).....	40
14.2	Assessments during radiotherapy	40
14.3	Post-treatment assessments (4, 8, 16, 12, 24, and 36 months following randomisation)	40
15	Pharmacovigilance	46
15.1	Definitions	46
15.2	Trial Specific SAE Reporting requirements	47
15.3	Causality	48

15.4	Expectedness	49
15.5	Reporting Procedures	49
15.5.1	Participating Site Responsibilities	49
15.5.2	The CTR responsibilities	50
15.6	SUSAR reporting	51
15.7	Safety Reports	51
15.8	Contraception and pregnancy	51
15.8.1	Contraception	51
15.8.2	Pregnancy reporting whilst participating in the trial	51
15.9	Urgent Safety Measures (USMs)	52
16	Statistical considerations	52
16.1	Randomisation	52
16.2	Sample size	53
16.3	Missing, unused & spurious data	53
16.4	Procedures for reporting deviation(s) from the original SAP	54
16.5	Termination of the trial	54
16.6	Inclusion in analysis	54
17	Analysis	54
17.1	Main analysis	54
	Estimand framework	54
17.2	Interim analysis	56
17.3	Quality of Life (QoL) and clinical frailty	57
17.4	Quintet Recruitment Intervention (QRI) and INCLUSION Study Within A Project (SWAP) 58	
17.4.1	Consent processes for the QuinteT Recruitment Intervention	59
17.4.2	QRI + INCLUSION Data Analysis	60
	Screening and enrolment logs	60
	Recordings of recruitment conversations and interviews with patients and healthcare professionals	61
17.5	Cost effectiveness analysis	62
18	Data Management	62
18.1	Data collection	63
18.2	Completion of CRFs	63
18.3	QuinteT recruitment intervention	63
	Interviews	64
	QRI documentation	65
19	Translational research or sub trial	65
20	Protocol/GCP non-compliance	65
21	End of Trial definition	65
22	Archiving	66
23	Regulatory Considerations	66
23.2	Ethical and governance approval	66
23.3	Data Protection	66
23.4	Indemnity	66
23.5	Trial sponsorship	67
23.6	Funding	68
24	Trial management	68
24.1	TMG (Trial Management Group)	68
24.2	TSC (Trial Steering Committee)	68

24.3	IDMC (Independent Data Monitoring Committee).....	68
25	Quality Control and Assurance	69
25.1	Monitoring	69
25.2	Audits & inspections	69
26	Public Involvement and Engagement	69
27	Publication policy	69
28	References	70
29	Appendices	73
	Appendix 1 ECOG	73
	Appendix 2 Clinical Frailty Scale.....	74
	Appendix 3 Patient Reported Toxicities	74
	Appendix 4 : Quality of Life Questionnaires.....	88

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	PNI	Perineural Invasion
CTR	Centre for Trials Research	PPE-15	Picker Patient Experience 15
CU	Cardiff University	PPI	Patient Public Involvement
DSUR	Development Safety Update Report	PRO	Patient Reported Outcomes
EADO	European Association of Dermato- Oncology	PV	Pharmacovigilance
ECG	Electrocardiogram	QA	Quality Assurance
ECOG	Eastern Cooperative Oncology Group	QALY	Quality-adjusted Life Years
eCRF	Electronic Clinical Report Form	QoL	Quality of Life
EHR	Electronic Health Records	QRI	QuinteT Recruitment Intervention
EOI	Expression of Interest	R&D	Research and Development
EORTC	European Organisation for Research and Treatment of Cancer	RCR	Royal College of Radiologists
EudraCT	European Clinical Trials Database	RCT	Randomised Controlled Trial
FFPE	Formalin Fixed Paraffin Embedded	REC	Research Ethics Committee
GCP	Good Clinical Practice	RMDT	Regional Multi-Disciplinary Team
GDPR	General Data Protection Regulations	RPGD	Radiotherapy Planning Guidance Document
GMP	Good Manufacturing Practice	RTTQA	Radiotherapy Trials Quality Assurance
GP	General Practitioner	SAE	Serious Adverse Event
HCRW	Health Care Research Wales	SAP	Statistical Analysis Plan
HE	Health Economics	SAR	Serious Adverse Reaction
HRA	Health Research Authority	SCC-AFTER	Adjuvant radiotherapy in patients with high-risk primary cutaneous Squamous Cell Carcinoma AFTER surgery

HTA	Health Technology Assessment	SCI	Skin Cancer Index
HR	High Risk	SEAR	Screened, Eligible, Approached, Randomised
HRA	Health Research Authority	SmPC	Summary Product Characteristics
IB	Investigator Brochure	SoC	Standard of Care
IC	Informed Consent	SOP	Standard Operating Procedure
ICF	Informed Consent Form	SSMDT	Specialist Skin Multi-Disciplinary Team
ICH	International Conference on Harmonization	SUSAR	Suspected Unexpected Serious Adverse Reactions
IDMC	Independent Data Monitoring Committee	SWAP	Study Within a Project
IQR	Interquartile Range	TMF	Trial Master File
IRAS	Integrated Research Application System	TMG	Trial Management Group
ISF	Investigator Site File	TSC	Trial Steering Committee
ISR	Investigator Safety Report	TSF	Trial Site File
		UICC	Union of International Cancer Control
ISRCTN	International Standard Randomised Controlled Trial Number	UK	United Kingdom
ITT	Intention-to-treat	UKDCTN	UK Dermatology Clinical Trials Network
LRR	Loco-Regional Recurrence	USM	Urgent Safety Measure
MA	Marketing Authorisation	USA	United States of America
MDT	Multidisciplinary Team	UV	Ultraviolet
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	<ul style="list-style-type: none"> Summary of changes made since previous version
Number 5	2.0	28/04/2025	<ul style="list-style-type: none"> Trial team personnel and contact details Glossary of abbreviations Synopsis updated - inclusion criteria 1 guidance criteria, inclusion criteria 2, exclusion criteria 8 wording clarification, Treatment duration, Primary objective SMDT/MDT wording, and addition of clinical frailty to secondary objectives & outcomes. Trial schema updated Section 5.2 Secondary objectives amended to include clinical frailty Section 5.3 Primary outcome measure amended to include Northern Ireland Section 5.4 Secondary outcome measures amended to include clinical frailty Section 5.5 Tertiary objectives and outcomes added Section 6 Trial design and setting updated to include that the trial will recruit in Northern Ireland, define events for analysis, and update study timelines. Section 8.1 Inclusion criteria 1,2 & 3 wording clarification Exclusion criteria 8 wording clarification Baseline non-identifiable demographic and health data moved from section 9.1 to 9.2 Section 9.3 Recruitment time period updated to approximately 4 years Section 9.4 Informed consent legislation updated to include Northern Ireland and Scotland Section 9.5 Randomisation stratification factors corrected Section 10.2 Lost to follow up data collection methods updated Section 11 Radiotherapy Treatment

			<ul style="list-style-type: none"> • Section 14 Trial procedures updated to include that clinician reported toxicity may be completed by an appropriately qualified member of the medical team who is delegated to carry out these assessments. • Section 14.1 Screening (baseline) assessments, 14.3 Post treatment assessments and Tables 1 & 2 updated to include clinical frailty scale • Section 14.3 Post treatment Toxicity assessments corrected to 36 months • Section 15.4 Expectedness Table 5 Graft Failure definition updated • Section 16 updated with event definition and composite endpoint strategy • Section 17 Main Analysis Estimands framework added • Section 17.2 Interim analysis timeframes updated • Section 17.3 updated to include clinical frailty scale • Section 18.1 Data Collection updated to reference database user guide. • Section 18.2 Completion of CRFs updated with quality control of QoL questionnaires instructions. • Section 29 Appendices updated to include clinical frailty scale
Number 7	3	09/09/2025	<ul style="list-style-type: none"> • Inclusion Criteria no.1 wording updated in Synopsis and Section 8.1 • Section 14.1 Screening baseline assessment corrected to randomisation within 3-4 months of surgery • Section 14.2 Pre-treatment assessments updated to pregnancy testing as per local practice • Table 1 updated to add comparator arm assessment column • Section 3.1 Amended trial schema to show number of events required at each interim analysis rather than estimated years. Wording updated to after 77 and 115 events • Section 5.3 Updated to include death from loco-regional recurrence as a primary event • Section 9.5 Table of stratification factors added

		12/11/2025	<ul style="list-style-type: none"> • Section 16.2 Added details on alpha-spending at interim and final analysis. • Section 16.3 Updated to include details of SAP content. Added high-level information on dealing with missing data. • Section 16.5 Follow up data collection clarified • Section 17.1 Updated to include that details of estimand framework for secondary endpoints that will be included in the SAP and details of group sequential design. Added details on alpha-spending at interim and final analysis and methodology used for controlling the Type I error. • Section 17.3 Updated to include exploratory statistical significance tests • Section 21 Updated to provide clarity on end of trial definition and follow up.
--	--	------------	--

.

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 Squamous Cell Carcinoma AFTER surgery
Acronym	SCC-AFTER
Clinical phase	Phase III
Funder and ref.	NIHR Health Technology Assessment (HTA) Programme (NIHR151760)
Trial design	<p>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).</p> <p>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). Participants will be assessed following UK guidance at baseline, mid-ART (ART arm only), 4 monthly for 2 years, then 6-monthly for year 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.</p> <p>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.</p> <p>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.</p>
Trial participants	<p>Adult patients with histologically clear margins, high-risk (BWH T2b/3), primary cSCC are eligible.</p> <p>“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 . It will be noted in screening if this is a barrier to recruitment for patients with cSCC lesions to the scalp.</p>



	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	<p>Patients are eligible to be included in the study only if all the following inclusion criteria and none of the exclusion criteria apply:</p> <ol style="list-style-type: none"> 1) High-risk primary cSCC (T2b/T3 by BWH staging criteria) excised with histologically clear peripheral and deep margins (≥ 1mm by RCPATH criteria*). Surgical excision margins should be consistent with BAD guidelines (peripheral and deep) and will be recorded. 2) Time since excision surgery < 3 months (< 4 months acceptable only if necessary). 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. <p>* For SCC on the scalp, a deep histological margin of 0.8mm - < 1mm is eligible if confirmed to have resected either galea or galea and periosteum or galea, periosteum and bone and the galea is not infiltrated by tumour and the SSMDT assesses that surgical treatment is complete</p> <p>** 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).</p>
Exclusion criteria	<ol style="list-style-type: none"> 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.

	<p>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.</p> <p>7) Unable to lie still unattended for the duration of ART (estimated to be around 5 minutes).</p> <p>8) Participation in another interventional clinical study that may affect the recurrence of cSCC.</p> <p>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****.</p> <p><i>***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.</i></p> <p><i>****Please discuss patients with malignancy of concern with the SCC-AFTER trial team.</i></p>
<p>Treatment duration</p>	<p>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</p> <ul style="list-style-type: none"> • 45Gy/10 treatments/2 weeks • 55Gy/20 treatments/4 weeks • 60Gy/30 treatments/6 weeks <p>The clinician can choose which is appropriate for each patient depending on tumour and patient factors.</p>
<p>Follow-up duration</p>	<p>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. After these periods of close clinical follow up, any further recurrence and vital status data will be collected from routine visits until the end of the trial.</p>
<p>Planned trial period</p>	<p>8 years (4 years recruitment and 3 years follow up)</p>
<p>Primary objective</p>	<p>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.</p> <p>- “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</p>



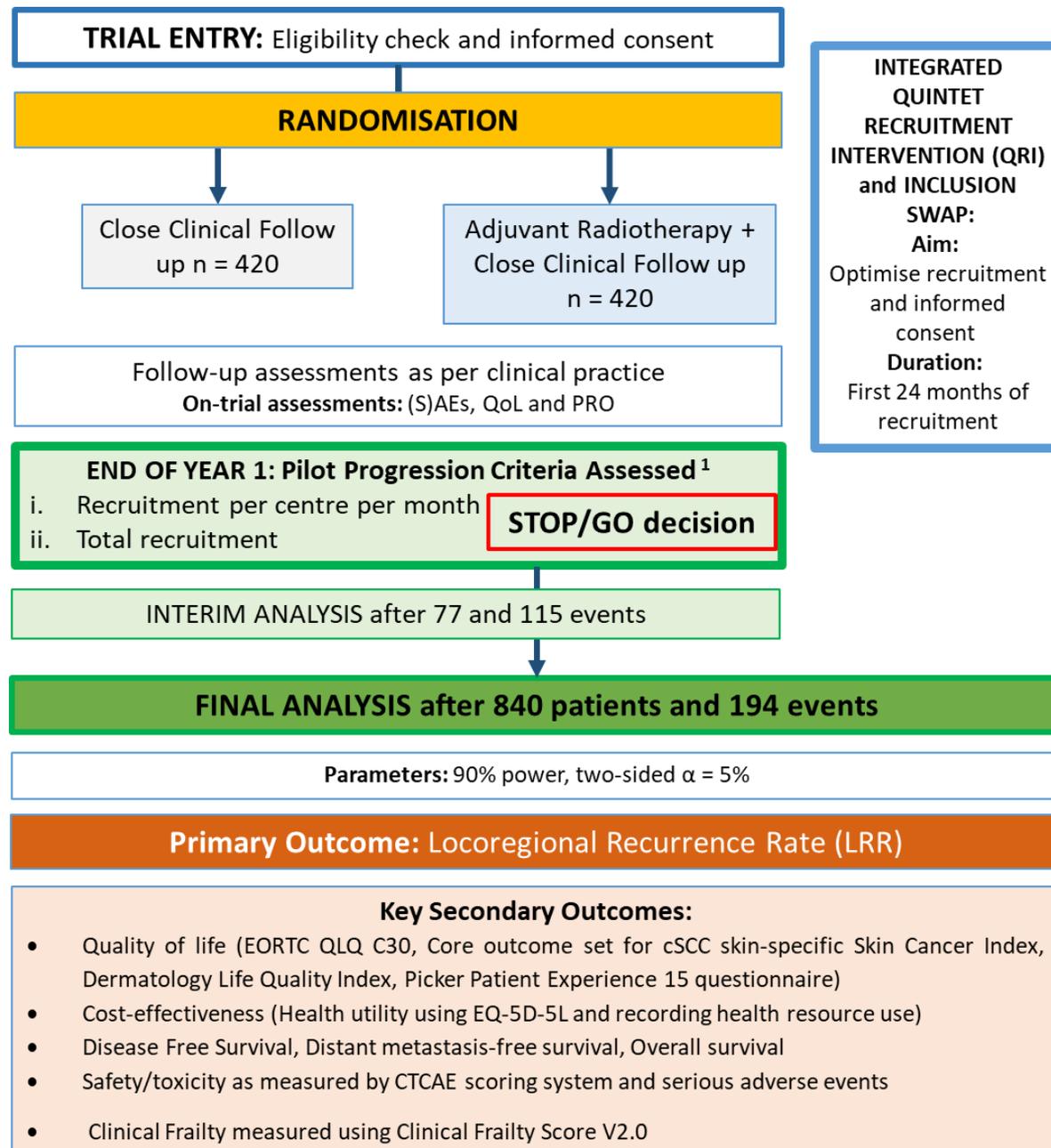
	<p>the regional lymph nodes. Diagnosis of local recurrence will be confirmed by the SSMDT (England)/RMDT (Scotland)/MDT (Wales).</p> <p>- “Regional recurrence” is defined as cSCC which has spread to lymph node/s within the basin deemed to be draining the site of the index primary cSCC. In head and neck cSCC, these may be contralateral. Diagnosis of regional recurrence will be confirmed by the SSMDT (England)/ RMDT (Scotland and Northern Ireland)/ MDT (Wales)</p>
Secondary objectives	<ul style="list-style-type: none"> • To determine the impact on QoL and clinical frailty 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 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	<ul style="list-style-type: none"> • QoL – measured using EORTC QLQ-C30, skin-specific Skin Cancer Index (SCI), Picker Patient Experience 15 questionnaire (PPE-15), and EQ-5D-5L (Appendix 4). • Clinical frailty – measured using Clinical frailty scale (CFS)V2.0 (Appendix 2). • 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 (Appendix 3). • 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.

Tertiary 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	<p>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:</p> <ul style="list-style-type: none"> • 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. <p>The radiotherapy treatment is delivered once a day (Monday-Friday) as an outpatient procedure and will typically take between 5 and 20 minutes.</p>



3 Trial summary

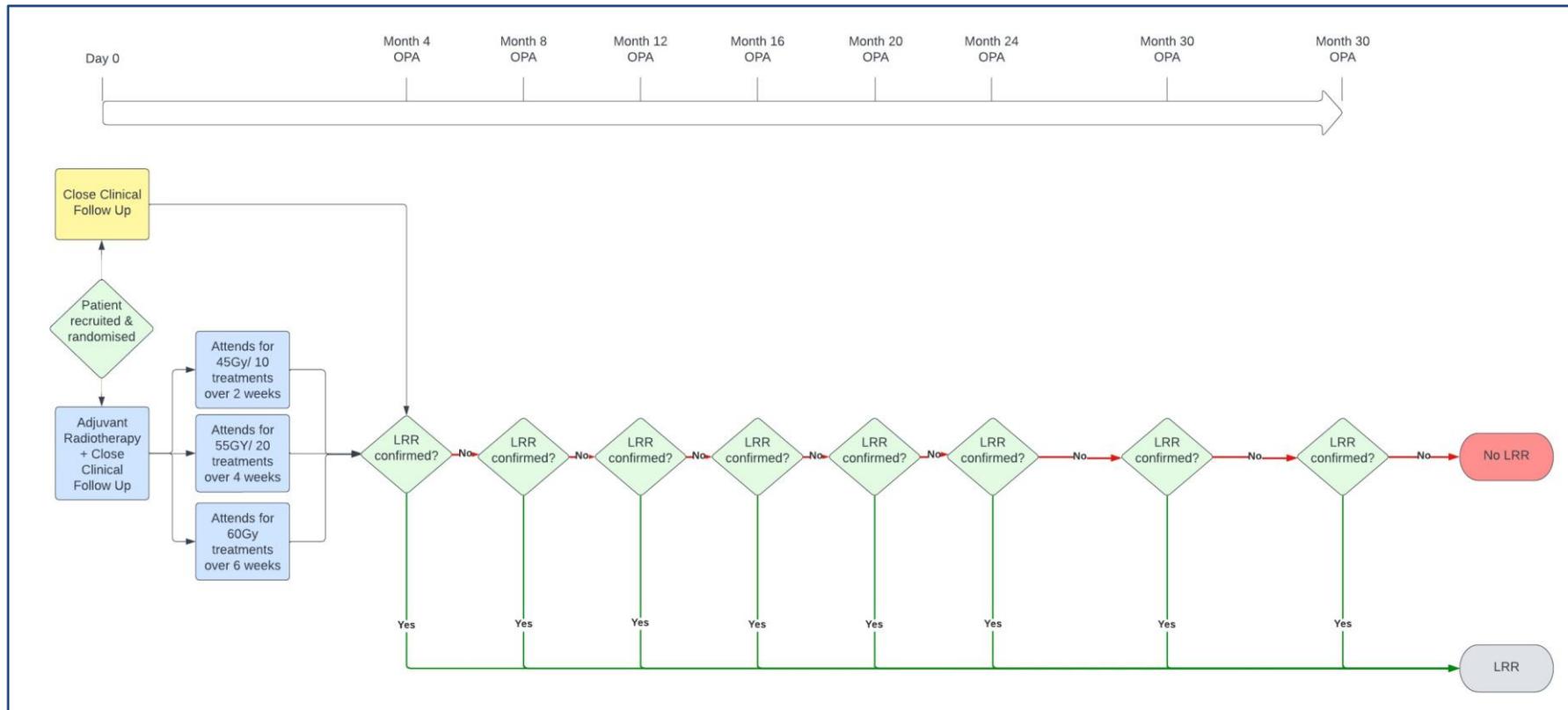
3.1 Schema



INTEGRATED QUINTET RECRUITMENT INTERVENTION (QRI) and INCLUSION SWAP:
Aim:
Optimise recruitment and informed consent
Duration:
First 24 months of recruitment

¹ An internal pilot targeting recruitment of 100 patients within the first 12 months will determine feasibility. See Section 17.2 Table 6.

3.2 Participant flow diagram



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

3.3 Trial Lay Summary

Cutaneous 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. 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 suggesting 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 perineural Invasion (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 stressed 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://trialssearch.who.int/Default.aspx>) repeated on 10/05/2022 has not identified any clinical trials assessing ART for primary cSCC.

5 Trial objectives 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 (Appendix 4) and clinical frailty (Appendix 2) 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

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; or date of death from loco-regional recurrence.

-‘*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 (England)/RMDT (Scotland and Northern Ireland)/MDT (Wales).

- '*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/(England)/RMDT (Scotland and Northern Ireland)/MDT (Wales).

Detailed information on the estimand framework can be found in Section 17.1.

5.4 Secondary outcomes measures

- QoL – measured using EORTC QLQ-C30, skin-specific Skin Cancer Index (SCI), and Picker Patient Experience 15 questionnaire (PPE-15) (Appendix 4).
- Clinical frailty – measured using Clinical frailty scale (CFS) V2.0 (Appendix 2).
- 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 (Appendix 3).
- 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.

5.5 Tertiary objectives and outcomes

Objectives

- Optimise recruitment and informed consent (Quintet Recruitment Intervention, QRI) particularly among patients historically underserved in trials research (Study within a project, SWAP)

Outcomes

- Eligibility and recruitment challenges minimised for relevant under-served groups (such as older, frailer participants and those with multiple long-term conditions)

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 Northern Ireland 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. An event is defined as the occurrence of, or death due to, local, regional, or loco-regional recurrent disease.

It includes a QuinteT Recruitment Intervention (30) and an INCLUSION Study within a Project (SWAP) (integrated during trial set up and during first phase of recruitment) 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.

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, the pilot and recruitment.

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 CTR 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 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 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 CTR Trial Team before randomisation.

8.1 Inclusion criteria

- 1) High-risk primary cSCC (T2b/T3 by BWH staging criteria) excised with histologically clear peripheral and deep margins (≥ 1 mm by RCPATH criteria*). Surgical excision margins should be consistent with BAD guidelines (peripheral and deep) and will be recorded.
- 2) Time since excision surgery < 3 months (< 4 months acceptable only if necessary).
- 3) ECOG performance status of 0, 1, 2, or 3 at enrolment (Appendix 1).
- 4) Aged 18 years or 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.

*For SCC on the scalp, a deep histological margin of 0.8mm - < 1mm is eligible if the deep margin of excision was confirmed to have resected either galea or galea and periosteum or galea, periosteum

and bone; the galea is not infiltrated by tumour; the peripheral histological margins are 1mm or greater; the SSMDT assesses that surgical treatment is complete

** 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.

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.
- 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. 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 participant 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 be recruited also into other clinical trials, but this should be discussed with the CTR before this is considered.

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 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.

Baseline non-identifiable demographic and health data recorded from medical records for all patients considered for the trial should be entered onto the trial database; 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.

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 (not eligible, 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 patient reported ethnicity.

9.3 Recruitment rates

A total of 840 participants will be recruited into the SCC-After trial over a period of approximately 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) or equivalent legislation in Scotland and Northern Ireland. Where a participant is assessed as lacking capacity to consent to remain in the trial, a consultee (a family member or close friend) or equivalent role in Scotland and Northern Ireland 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 re-consented to remain in the study.

9.5 Randomisation

All eligible and consenting 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 either the close clinical follow up arm or ART and close clinical follow up arm.

A link to the randomisation activates within the database once eligibility and consent is validated.

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, perineural invasion (nerve diameter \geq 0.1 mm)).

Stratification factor	Category
Age	Less than 65
	>=65 to <80
	80 or over
Stage of cancer BWH classification	T2b
	T3
Immunocompromised	Yes
	No
Time since surgery (months)	< Three months
	Three to <= four months
Perineural invasion	Yes
	No

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– 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/RNA from tissue and associated data
 2. Data:
 - a. SCC-AFTER Trial data
 - b. QRI 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 equivalent 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 and 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: Every effort will be made to chase the sites to request missing data during central monitoring and data cleaning, particularly if the patient has attended a visit but the data has not been entered onto the trial database. If there is no evidence the participant has lost capacity, the site can continue to attempt to contact the participant 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. Additional information is

provided in the SCC AFTER Radiotherapy guidance document. The radiotherapy dose and fractionation are dependent on the size of the treatment field. The permitted radiotherapy dose and fractionation schedules are:

- Field diameter 8cm or less: 45Gy in 10 daily fractions over 2 weeks or 55Gy in 20 daily fractions over 4 weeks or 60Gy in 30 daily fractions over 6 weeks
- Field diameter greater than 8cm: 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)

EQD₂ 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.rtrialsqa.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's 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

SCC-AFTER patients are treated as Category 1, defined by The Royal College of Radiologists (RCR), and any unscheduled gaps should be managed in line with the RCR guidance document.

All three radiotherapy schedules, permitted within the trial, include once daily fractionation Monday to Friday and 5 fractions per week. In the event of public holidays, missing treatment(s) should be made up in the same way as for treatment interruptions (see below).

Treatment interruptions should be avoided unless there is severe acute toxicity which cannot be managed conservatively. In the event of a treatment interruption for any reason, the missing dose fraction(s) should be made up by either treatment on a weekend, giving a second treatment on one or more of the remaining treatment days with a minimum 6-hour interfraction interval, provided that no more than 6 fractions are given in any one week, or adding the missed fraction on at the end. Twice-daily treatment is not recommended when fraction size is significantly greater than 2.2Gy.

If the gap is more than one treatment day (excluding expected no standard radiation treatment on Saturday or Sunday) it would be regarded as a protocol deviation and the SCC-AFTER team needs to be informed. The reason for any treatment interruption must be documented.

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 36 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, which includes also a breakdown of the QoL questionnaires and clinician and patient reported toxicity timepoints. All procedures will be carried out by clinical and/or research team at the participating site, according to the site delegation log.

Clinician reported toxicity may be completed by an appropriately qualified member of the medical team who is delegated to carry out these assessments.

14.1 Screening (baseline) assessments

Randomisation should be within 3 months of surgery. A window up to 4 months post-surgery will be allowed. Where additional time has been needed to heal or for other reasons, this should be discussed with the SCC-AFTER trial team before the patient is consented.

Participants 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 (Appendix 1)
- Clinical frailty scale (Appendix 2)
- Toxicity Assessment (Appendix 3)
- QoL Questionnaires : EQ-5D-5L, EORTC QLQ30, health utilisation (Appendix 4)

Toxicity should be assessed according to CTCAE 5.0.

14.2 Pre-treatment assessments (additional to screening assessments for patients randomised to the radiotherapy arm)

Participants should undergo the following assessments at the time of trial entry and before treatment with radiotherapy. Physical Examination

- Pregnancy test in people of childbearing potential who are randomised to the Radiotherapy treatment arm as per local practice.
- Key concomitant medication check

All baseline assessments and pre-treatment assessments must be completed prior to the start of any radiotherapy treatment. Radiotherapy should start within one month of randomisation.

14.2 Assessments during radiotherapy

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

Clinician reported toxicity assessments can be performed by any appropriately trained and delegated member of the medical team as per standard practice at site i.e. Research Nurse, radiographer etc.

Note: There 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 (Appendix 4) EQ-5D-5L, EORTC QLQ-C30, SCI, and health utilisation at the end of radiotherapy treatment. Participants 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, 24, and 36 months following randomisation)

The participant 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
- Clinical frailty scale (annually) (Appendix 2)
- Toxicity Assessment (4, 8, 16, 24, 36 months) (Appendix 3)
- QoL Questionnaires (4, 12, 24, 36 months) (Appendix 4) EQ-5D-5L, EORTC QLQ-C30, SCI, PPE-15 (12 months only), and health utilisation (4, 12, 24, 36 months). See table 2 for table of QoL questionnaires and clinician and patient reported toxicity timepoints.

For all participants, who have completed the post-treatment assessments at 36 months post randomisation, any further recurrence and vital status data will be collected from routine visits until the end of the trial (see Section 21 End of Trial Definition).

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 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)			End of ART To coincide with final assessment on ART	Comparator Arm Only Comparator arm= 7 weeks (+/- 4 weeks) from randomisation	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	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	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	x	x	x	x	x	x
Clinical frailty scale^		x								x				x		x
QRI	x	x						x								
ART planning ⁵			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

[^]Questionnaire to assess the score will be provided to the sites and should be kept at the site as source data

[§]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-5L	✓	*	*	*	✓	✓	✓	*	✓	*	*	✓	*	✓	
EORTC QLQ-C30	✓	*	*	*	✓	✓	✓	*	✓	*	*	✓	*	✓	
SCI	✓	*	*	*	✓	✓	✓	*	✓	*	*	✓	*	✓	
PPE-15	*	*	*	*	*	*	*	*	✓	*	*	*	*	*	
Patient Reported Toxicities	✓	✓	✓	✓	*	✓	✓	✓	*	✓	*	✓	*	✓	
<u>To be completed by Clinicians:</u> Clinician Reported Toxicities	✓	✓	✓	✓	*	✓	✓	✓	*	✓	*	✓	*	✓	
<u>Clinical Frailty Score</u>	✓	*	✓	*	*	*	*	*	✓	*	*	✓	*	✓	

<u>To be completed by research team (in conjunction with patient):</u> 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 - <ul style="list-style-type: none"> • 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 with partial or complete loss of graft 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 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.

SAE reporting should continue 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 Investigators (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 Research Ethics Committee.

15.9 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigators or Principal Investigator may carry out in order to protect the trial participants 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. An event is defined as occurrence of, or death due to, local, regional, or loco-regional recurrent disease. 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 randomised to each group with a fixed ratio of 1:1 using a centralised internet randomisation. Randomisation will be by minimisation with a random element. Randomisation stratification factors will be: age category, stage of cancer, immunocompromised

status, time since surgery, and perineural invasion. The trial is open-label, since participants in the intervention arm will receive radiotherapy.

16.2 Sample size

We assume a conservative LRR of 20% for T2b and 50% for T3 cSCC (16, 17), with UK data confirming 92% of recurrence 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). The 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 armenu 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% (with two interim analysis and a final analysis; this is split into 0.001, 0.007 and 0.042) 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.

As a sensitivity analysis 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

Full detail will be provided in the Statistical Analysis Plan (SAP). There will be no data imputation for missing data in the primary endpoint. Imputation methods may be proposed for purposes of sensitivity analysis—imputation methods for missing data in the primary endpoint and secondary endpoints will be fully documented in the SAP.

Time to event data will be censored at the date the participant was last seen if no event is recorded during the trial.

The EORTC QLQ30 module allows for some items to be imputed if at least 50 % of responses have been provided.

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 analysed when at least 194 events have been reported and data cleaning completed. All participants from both arms will receive close clinical follow up for 3 years from date of randomisation or until a primary event has occurred. After these periods of close clinical follow up, follow up will continue so that any further recurrence and vital status data will be collected from routine visits until the end of the trial (see Section 21 End of Trial Definition).

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 (see section 17.1) and a “composite endpoint” strategy will be used for dealing with the competing risks of death from other causes, permanent skin damage or amputation prior to loco-regional recurrence. Participants that withdraw completely or are lost to follow-up will be censored at the date last known to be recurrence free and participants that die due to other causes will be censored at the time of death.

17 Analysis

17.1 Main analysis

Estimand framework

Treatment condition of interest vs alternative treatment condition(s): Assignment to ART plus close clinical follow up at the selected dose and frequency of administration vs close clinical follow up only

Target population: Patients aged 18 years or over with an excised 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 (≥ 1 mm by RCPATH criteria). Patients must comply with all inclusion and exclusion criteria.

Variable: 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.

Population-level summary: Loco-regional recurrence (LRR)-free survival time

Estimand: Difference in loco-regional recurrence (LRR)-free survival time between patients from the target population assigned to ART plus close clinical follow up at the selected dose and frequency of administration vs close clinical follow up only, and treatment and follow up regardless of:

- any adverse events that may occur
- development of distant metastases or a new malignancy
- other co-morbidities that could lead to death or treatment non-compliance
- non-adherence to protocol and/or discontinuation of radiotherapy treatment due to:
 - other treatments or concomitant medications that interact with the radiotherapy treatment or reduce the amount of radiotherapy treatment that can be given
 - patient withdrawing consent after randomisation allocation
 - diagnosis of distant metastases that may require another treatment
 - use of an alternative treatment
 - any other potential intercurrent event (such as a fall at home, any other medical events that stop treatment, skin infection, haematoma, seroma, graft failure, post-surgical complications)

and as if death from other causes, permanent skin damage or amputation of the primary cSCC area before loco-regional recurrence may occur but will not be counted as primary events.

A composite strategy approach to deaths will be used, whereby deaths from loco-regional recurrence will be coded 1 (for primary event) and deaths from other causes without a primary event will be coded 0 (censored at date of death). The same approach will be used for permanent skin damage or amputation of the primary cSCC area before loco-regional recurrence.

Participants that withdraw completely or are lost to follow-up will be censored at the date last known to be recurrence. Participants that withdraw before starting treatment will be censored at day+1.

Full details on the estimand framework and handling of missing data will be provided in the statistical analysis plan (SAP). The estimand framework for the secondary endpoints distant metastasis-free survival and overall survival will be described in the Statistical Analysis Plan.

The trial will be analysed when at least 194 events have been reported and data cleaning completed (see Section 16.5).

A full statistical analysis plan will be finalised prior to the first formal analysis of this group sequential trial. The trial uses a group sequential design with three planned analyses to allow early stopping for efficacy while maintaining the overall two-sided Type I error rate at 0.05. 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 O'Brien-Fleming alpha-spending function was applied to allocate the cumulative alpha across analyses. The nominal significance levels for the analyses are approximately 0.001 at the first interim, 0.007 at the second interim, and 0.048 at the final analysis, corresponding to cumulative alpha spending of 0.001, 0.008, and 0.05 respectively. 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.

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 6 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) and clinical frailty

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 and clinical frailty scale (Appendix 2) 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. Exploratory statistical significance tests will be carried out if clinically meaningful differences are observed. 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, and 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 Investigators 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 CIs/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 trial 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 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 CIs 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 database user guide.

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.

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

Sites will be provided with a guide on using the 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-5L) (Appendix 4) and patient reported toxicities (Appendix 3). 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 scanned any identifiable data must be redacted, transferred via secure file transfer to the CTR 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 (the last participants recruited will be followed up for 3 years; the first participants recruited may be followed up for more than 3 years). Progression/death data for all patients will continue to be collected until the last participant has completed 3 years follow up. All participants from both arms will receive close clinical follow up for 3 years from date of randomisation or until a primary event has occurred. After these periods of close clinical follow up, follow up will continue so that any further recurrence and vital status data will be collected from routine visits until the end of the trial.

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 after completion of data cleaning.

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 Trial Site Files (TSFs) 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 2018.
- 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, CIs, 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 CIs 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 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.

28 References

1. Keohane SG, Botting J, Budny PG, Dolan OM, Fife K, Harwood CA, et al. British Association of Dermatologists guidelines for the management of people with cutaneous squamous cell carcinoma 2020. *Br J Dermatol.* 2021;184(3):401-14.
2. Stratigos AJ, Garbe C, Dessinioti C, Lebbe C, Bataille V, Bastholt L, et al. European interdisciplinary guideline on invasive squamous cell carcinoma of the skin: Part 2. Treatment. *Eur J Cancer.* 2020;128:83-102.
3. National Comprehensive Cancer Network Squamous Cell Skin Cancer Guidelines for Patients 2019 NCCN2023 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/squamous_blocks.pdf]
4. Gibbons E, Casañas i Comabella C, Fitzpatrick R. A structured review of patient-reported outcome measures for patients with skin cancer, 2013. *Br J Dermatol.* 2013;168(6):1176-86.
5. Klein J, Livergant J, Ringash J. Health related quality of life in head and neck cancer treated with radiation therapy with or without chemotherapy: a systematic review. *Oral Oncol.* 2014;50(4):254-62.
6. Dakin H, Abel L, Burns R, Yang Y. Review and critical appraisal of studies mapping from quality of life or clinical measures to EQ-5D: an online database and application of the MAPS statement. *Health and Quality of Life Outcomes.* 2018;16(1):31.
7. Kwiatkowska M, Ahmed S, Ardern-Jones M, Bhatti LA, Bleiker TO, Gavin A, et al. An updated report on the incidence and epidemiological trends of keratinocyte cancers in the United Kingdom 2013-2018. *Skin Health Dis.* 2021;1(4):e61.
8. Venables ZC, Nijsten T, Wong KF, Autier P, Broggio J, Deas A, et al. Epidemiology of basal and cutaneous squamous cell carcinoma in the U.K. 2013-15: a cohort study. *Br J Dermatol.* 2019;181(3):474-82.
9. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. *N Engl J Med.* 2001;344(13):975-83.
10. WHO Global Cancer Observatory [Available from: <https://gco.iarc.fr/>].
11. Way M, Marquart L, Chambers DC, Hopkins P, Miura K, Jiyad Z, et al. Skin cancer multiplicity in lung transplant recipients: a prospective population-based study. *Br J Dermatol.* 2020;183(3):503-8.
12. Lansbury L, Bath-Hextall F, Perkins W, Stanton W, Leonardi-Bee J. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. *Bmj.* 2013;347:f6153.
13. Eigentler TK, Leiter U, Häfner HM, Garbe C, Rösen M, Breuninger H. Survival of Patients with Cutaneous Squamous Cell Carcinoma: Results of a Prospective Cohort Study. *J Invest Dermatol.* 2017;137(11):2309-15.
14. Venables ZC, Autier P, Nijsten T, Wong KF, Langan SM, Rous B, et al. Nationwide Incidence of Metastatic Cutaneous Squamous Cell Carcinoma in England. *JAMA Dermatol.* 2019;155(3):298-306.
15. Sahovaler A, Krishnan RJ, Yeh DH, Zhou Q, Palma D, Fung K, et al. Outcomes of Cutaneous Squamous Cell Carcinoma in the Head and Neck Region With Regional Lymph Node Metastasis: A Systematic Review and Meta-analysis. *JAMA Otolaryngol Head Neck Surg.* 2019;145(4):352-60.

16. Karia PS, Jambusaria-Pahlajani A, Harrington DP, Murphy GF, Qureshi AA, Schmults CD. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. *J Clin Oncol*. 2014;32(4):327-34.
17. Ruiz ES, Karia PS, Besaw R, Schmults CD. Performance of the American Joint Committee on Cancer Staging Manual, 8th Edition vs the Brigham and Women's Hospital Tumor Classification System for Cutaneous Squamous Cell Carcinoma. *JAMA Dermatol*. 2019;155(7):819-25.
18. Schmitt AR, Brewer JD, Bordeaux JS, Baum CL. Staging for cutaneous squamous cell carcinoma as a predictor of sentinel lymph node biopsy results: meta-analysis of American Joint Committee on Cancer criteria and a proposed alternative system. *JAMA Dermatol*. 2014;150(1):19-24.
19. Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. *N Engl J Med*. 2018;379(4):341-51.
20. Rischin D, Khushalani NI, Schmults CD, Guminski A, Chang ALS, Lewis KD, et al. Integrated analysis of a phase 2 study of cemiplimab in advanced cutaneous squamous cell carcinoma: extended follow-up of outcomes and quality of life analysis. *J Immunother Cancer*. 2021;9(8).
21. Likhacheva A, Awan M, Barker CA, Bhatnagar A, Bradfield L, Brady MS, et al. Definitive and Postoperative Radiation Therapy for Basal and Squamous Cell Cancers of the Skin: Executive Summary of an American Society for Radiation Oncology Clinical Practice Guideline. *Pract Radiat Oncol*. 2020;10(1):8-20.
22. Ruiz ES, Koyfman SA, Que SKT, Kass J, Schmults CD. Evaluation of the utility of localized adjuvant radiation for node-negative primary cutaneous squamous cell carcinoma with clear histologic margins. *J Am Acad Dermatol*. 2020;82(2):420-9.
23. Stevenson ML, Criscito MC, Wilken R, Doudican NA, Bain EE, 3rd, Parashar B, et al. Use of Adjuvant Radiotherapy in the Treatment of High-risk Cutaneous Squamous Cell Carcinoma With Perineural Invasion. *JAMA Dermatol*. 2020;156(8):918-21.
24. Ruiz ES, Kus KJB, Smile TD, Murad F, Zhou G, Ilori EO, et al. Adjuvant radiation following clear margin resection of high T-stage cutaneous squamous cell carcinoma halves the risk of local and locoregional recurrence: A dual-center retrospective study. *J Am Acad Dermatol*. 2022;87(1):87-94.
25. Kim Y, Lehrer EJ, Wirth PJ, Khesroh EA, Brewer JD, Billingsley EM, et al. Adjuvant radiotherapy may not significantly change outcomes in high-risk cutaneous squamous cell carcinomas with clear surgical margins: A systematic review and meta-analysis. *J Am Acad Dermatol*. 2022;86(6):1246-57.
26. Clinician survey conducted at the Centre of Evidence Based Dermatology (CEBD), Nottingham [Available from: <https://www.nottingham.ac.uk/research/groups/cebd/projects/4non-melanoma/index.aspx>].
27. Thomson J. Management of high-risk primary cutaneous Squamous Cell Carcinoma in the head and neck region after surgery (SCC-AFTER): Results of a feasibility survey of cancer multidisciplinary teams. *Br J Dermatol*. 2019;181 (Suppl S1):DS05.
28. Witham MD, Anderson E, Carroll C, Dark PM, Down K, Hall AS, et al. Developing a roadmap to improve trial delivery for under-served groups: results from a UK multi-stakeholder process. *Trials*. 2020;21(1):694.

29. Harwood CA, Mesher D, McGregor JM, Mitchell L, Leedham-Green M, Raftery M, et al. A surveillance model for skin cancer in organ transplant recipients: a 22-year prospective study in an ethnically diverse population. *Am J Transplant*. 2013;13(1):119-29.
30. Donovan JL, Rooshenas L, Jepson M, Elliott D, Wade J, Avery K, et al. Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI). *Trials*. 2016;17(1):283.
31. Wilson C, Rooshenas L, Paramasivan S, Elliott D, Jepson M, Strong S, et al. Development of a framework to improve the process of recruitment to randomised controlled trials (RCTs): the SEAR (Screened, Eligible, Approached, Randomised) framework. *Trials*. 2018;19(1):50.
32. Mental Capacity Act 2005, c.9 [Available from: <https://www.legislation.gov.uk/ukpga/2005/9/contents/enacted>].
33. Radiologists RCo. Timely delivery of radical radiotherapy: guidelines for the management of unscheduled treatment interruptions, fourth edition. BFCO(19)1 2019 [Available from: <https://www.rcr.ac.uk/publication/timely-delivery-radical-radiotherapy-guidelines-management-unscheduled-treatment>].
34. Ridyard CH, Hughes DA. Development of a database of instruments for resource-use measurement: purpose, feasibility, and design. *Value Health*. 2012;15(5):650-5.
35. Garfield K, Husbands S, Thorn JC, Noble S, Hollingworth W. Development of a brief, generic, modular resource-use measure (ModRUM): cognitive interviews with patients. *BMC Health Services Research*. 2021;21(1):371.
36. NHS Reference Costs [Available from: <https://www.gov.uk/government/collections/nhs-reference-costs>].
37. Unit Costs of Health and Social Care programme (2022 – 2027) [Available from: <https://www.pssru.ac.uk/project-pages/unit-costs/>].
38. Dakin H, Abel, L, Burns, R, Yang, Y. Review and critical appraisal of studies mapping from quality of life or clinical measures to EQ-5D: an online database and application of the MAPS statement. In: *Outcomes HaQoL*, editor. 16:31 ed2018.
39. Realpe AX, Foster NE, Dickenson EJ, Jepson M, Griffin DR, Donovan JL. Patient experiences of receiving arthroscopic surgery or personalised hip therapy for femoroacetabular impingement in the context of the UK fashion study: a qualitative study. *Trials*. 2021;22(1):211.
40. Rooshenas L, Paramasivan S, Jepson M, Donovan JL. Intensive Triangulation of Qualitative Research and Quantitative Data to Improve Recruitment to Randomized Trials: The QuinteT Approach. *Qual Health Res*. 2019;29(5):672-9.
41. Research NifHaC. Multiple long-term conditions - Studies within a project (SWAP) v1.2 2023 [Available from: <https://www.nihr.ac.uk/documents/multiple-long-term-conditions-studies-within-a-project-swap/27818>].
42. Corbin J, Strauss A. *Basics of Qualitative Research (3rd ed.): Techniques and Procedures for Developing Grounded Theory*. Thousand Oaks, California 2008. Available from: <https://methods.sagepub.com/book/basics-of-qualitative-research>.
43. Thorn JC, Davies CF, Brookes ST, Noble SM, Dritsaki M, Gray E, et al. Content of Health Economics Analysis Plans (HEAPs) for Trial-Based Economic Evaluations: Expert Delphi Consensus Survey. *Value Health*. 2021;24(4):539-47.

44. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ.* 2005;14(5):487-96.
45. Hardy WAS, Hughes DA. Methods for Extrapolating Survival Analyses for the Economic Evaluation of Advanced Therapy Medicinal Products. *Hum Gene Ther.* 2022;33(17-18):845-56.

29 Appendices

Appendix 1 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



Appendix 2 Clinical Frailty Scale

CLINICAL FRAILTY SCALE		
	1	VERY FIT People who are robust, active, energetic and motivated. They tend to exercise regularly and are among the fittest for their age.
	2	FIT People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g., seasonally.
	3	MANAGING WELL People whose medical problems are well controlled, even if occasionally symptomatic, but often are not regularly active beyond routine walking.
	4	LIVING WITH VERY MILD FRAILITY Previously "vulnerable," this category marks early transition from complete independence. While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up" and/or being tired during the day.
	5	LIVING WITH MILD FRAILITY People who often have more evident slowing, and need help with high order instrumental activities of daily living (finances, transportation, heavy housework). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, medications and begins to restrict light housework.
	6	LIVING WITH MODERATE FRAILITY People who need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (ouling, standby) with dressing.
	7	LIVING WITH SEVERE FRAILITY Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).
	8	LIVING WITH VERY SEVERE FRAILITY Completely dependent for personal care and approaching end of life. Typically, they could not recover even from a minor illness.
	9	TERMINALLY ILL Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise living with severe frailty. (Many terminally ill people can still exercise until very close to death.)

SCORING FRAILITY IN PEOPLE WITH DEMENTIA	
<p>The degree of frailty generally corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.</p>	<p>In moderate dementia, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting. In severe dementia, they cannot do personal care without help. In very severe dementia they are often bedfast. Many are virtually mute.</p>
<p>DALHOUSIE UNIVERSITY www.geriatrionline.ca</p>	<p>Clinical Frailty Scale ©2005–2020 Rockwood, Version 2.0 (EN). All rights reserved. For permission: www.geriatrionline.ca Rockwood K et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:400–405.</p>

Appendix 3 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 4 : 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

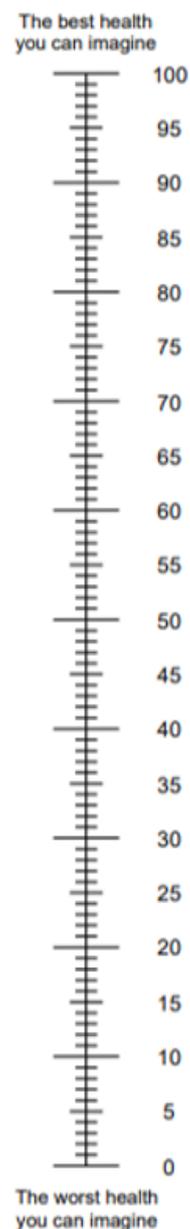
1. I am not anxious or depressed
2. I am slightly anxious or depressed
3. I am moderately anxious or depressed
4. I am severely anxious or depressed
5. I am extremely anxious or depressed

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 =



© 2009 EuroQol Research Foundation.
EQ-5D™ is a trade mark of the EuroQol Research Foundation. UK (English) v1.2

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	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	3	4	5	6	7

Skin Cancer Index (SCI)

Date Completed:

D	D	M	M	Y	Y	Y	Y
---	---	---	---	---	---	---	---

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	Moderately	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