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# The SCC-AFTER research study aims to find out whether it is better to use radiotherapy or not to prevent high-risk skin cancer from coming back after it has been removed by surgery


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| **Submission date**<br>04/06/2024 | **Recruitment status**<br>Recruiting | [X] Prospectively registered<br>[X] Protocol<br>[_] Statistical analysis plan<br>[_] Results<br>[_] Individual participant data<br>[X] Record updated in last year |
| **Registration date**<br>02/07/2024 | **Overall study status**<br>Ongoing | |
| **Last Edited**<br>26/08/2026 | **Condition category**<br>Cancer | |


## Plain English summary of protocol

Background and study aims

Some squamous cell cancers are called ‘high-risk’, meaning that there is a higher chance that they could come back after surgery compared to other skin cancers. Around 3 out of 10 people with high-risk skin cancer may experience their cancer coming back within 3 years of the surgery. Radiotherapy (x-ray treatment) is sometimes given to people with high-risk skin cancer after surgery to try and reduce the chances of the cancer coming back. This is called ‘post-operative’ or ‘adjuvant radiotherapy’. It is given to the area of the skin where the cancer was removed. It works by using X-rays to destroy any cancer cells that might be left behind in that area. However, there is no certainty that radiotherapy does stop high-risk skin cancers from coming back. The alternative to radiotherapy is to start a close clinical follow-up to monitor if the skin cancer shows signs of coming back and to treat it if it does. This study aims to find out whether using radiotherapy in people who have had high-risk squamous cell cancer removed by surgery reduces the chances of their skin cancer coming back, or whether radiotherapy is not necessary and only close clinical follow-up is required. The study will also find out what impact it has on quality of life.

Who can participate?

People aged 18 years old and over who have had this type of high-risk skin cancer removed with surgery

What does the study involve?

The study will have two groups of patients:

Radiotherapy and close clinical follow-up:

• Will receive treatment with radiotherapy every weekday for 2-6 weeks, starting within 4 months of the surgery that removed the cancer.

• Will be followed up closely for 3 years to see if the skin cancer shows signs of returning.

• Will be unlikely to have radiotherapy again in the future if the skin cancer does return to the same place.

Close clinical follow-up:
• Will be followed up closely for 3 years to see if the skin cancer shows signs of returning.
• May be able to have radiotherapy in the future if the skin cancer does return to the same place.

There is a linked study that wants to find out more about how patients feel about taking part in the trial. It will involve somebody asking patients questions about their experience and these will be recorded.

What are the possible benefits and risks of participating?
Possible benefits of Radiotherapy followed by close clinical follow-up:
• Radiotherapy may lower the risk of a patient's cancer coming back.

Possible benefits of Close clinical follow-up:
• Patients will not need to attend for daily radiotherapy or experience the side effects that may come with radiotherapy.
• Radiotherapy has not been proven to lower the risk of a patient's cancer coming back.
• Patients may be able to have radiotherapy at a later date if their cancer does come back.

Possible risks of Radiotherapy followed by close clinical follow-up:
• Radiotherapy has not been proven to lower the risk of a patient's cancer coming back.
• Patients would not be able to have further radiotherapy in the same area if the cancer comes back in the same place and would therefore need different treatment.
• Radiotherapy is generally very well tolerated, however, there are possible short-term and long-term side effects from radiotherapy:
Short term: Skin redness, irritation, itching, flaking, peeling, scaling and dryness in the treatment area. The skin may scab over or break down in the treatment area. General tiredness during the treatment period. Some side effects can be specific, such as potential interactions with other medicines a patient may take or with a pacemaker. This may affect the radiotherapy. These will be discussed with the medical team.
Long-term: Permanent skin texture changes in the treatment area are possible and include thicker or thinner skin, skin colour change and rarely a more long-term non-healing ulcer that may require further treatment such as dressings or surgery. If radiotherapy is given to an area on the body where hair grows such as the scalp, it can sometimes cause permanent hair loss.

Possible risks of Close clinical follow-up:
• The cancer may come back even though a patient has had surgery and may require further treatment, such as surgery or radiotherapy.

Where is the study run from?
The study is being co-ordinated by the Centre for Trials Research on behalf of Cardiff University.

When is the study starting and how long is it expected to run for?
January 2024 to January 2031

Who is funding the study?
National Institute for Health and Care Research (NIHR)

Who is the main contact?
SCCAFTER@cardiff.ac.uk

# Contact information

**Type(s)**
Public, Scientific

**Contact name**
Ms Ann White

**ORCID ID**
https://orcid.org/0000-0001-7317-6304

**Contact details**
Centre for Trials Research (CTR) – Cancer Group
College of Biomedical & Life Sciences
Cardiff University
6th Floor, Neuadd Meirionnydd
Heath Park
Cardiff
United Kingdom
CF14 4YS
+44 (0)2920687465
SCCAFTER@cardiff.ac.uk

**Type(s)**
Principal investigator

**Contact name**
Prof Catherine Harwood

**ORCID ID**
https://orcid.org/0000-0002-1375-0965

**Contact details**
The Royal London Hospital
Barts Health NHS Trust
London
United Kingdom
E1 1BB
+44 (0)20 7882 2332
SCCAFTER@cardiff.ac.uk

**Type(s)**
Principal investigator

**Contact name**
Prof Agata Rembielak

**ORCID ID**
https://orcid.org/0000-0003-2351-7179

**Contact details**

The Christie NHS Foundation Trust
Wilmslow Road
Manchester
United Kingdom
M20 4BX
+44 (0)161 446 8583
SCCAFTER@cardiff.ac.uk

# Additional identifiers

### Integrated Research Application System (IRAS)
331136

### Central Portfolio Management System (CPMS)
62841

### Protocol serial number
SPON1924-22

# Study information

### Scientific 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

### Acronym
SCC-AFTER

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

### Ethics approval required
Ethics approval required

### Ethics approval(s)
Approved 11/04/2024, East of England - Essex Research Ethics Committee (2 Redman Place, London, EC20 1JQ, United Kingdom; +44 (0)207 104 8106; Essex.REC@hra.nhs.uk), ref: 24/EE/0049

### Primary study design
Interventional

### Study design
Multicentre interventional open-label two-arm Phase III randomized controlled trial

### Study type(s)
Treatment

## Health condition(s) or problem(s) studied
Adjuvant radiotherapy in patients with high-risk primary cutaneous Squamous Cell Carcinoma (a non-melanoma skin cancer) after surgery

## Interventions
This study aims to find out whether using radiotherapy in people who have had high-risk skin cancer removed by surgery reduces the chances of their skin cancer coming back, or whether radiotherapy is not necessary and only close clinical follow-up is required. This is an open-label, multicentre, two-arm, phase III randomised control trial to evaluate superiority, cost-effectiveness, and effects on quality of life (QoL) of adjuvant radiotherapy (ART) in completely resected high-risk (BWH T2b/3) primary cutaneous squamous cell carcinoma (cSCC).

Patients will be randomised to either the ART followed by close clinical follow-up (ART arm) or close clinical follow-up only (comparator arm and current standard care). Patients will be assessed following UK guidance at baseline, mid-ART (ART arm only), 4 monthly for 2 years, then 6-monthly for year 3. During the follow-up period, QoL and Health Economics (HE) will be assessed twice for year 1, and annually in years 2 and 3. Progression and survival data will be collected throughout the trial.

Participants will be randomised using unweighted minimisation with a 20% random element. The stratification/balancing variables are detailed below.
STRATIFICATION/BALANCING VARIABLES
The balancing factors will be:
• Age
o Less than 65
o >=65 to <80
o 80 or over
• Stage of cancer BWH classification
o T2b
o T3
• Immunocompromised
o Yes
o No
• Time since surgery (months)
o < Three months
o Three to ≤ four months
• Perineural invasion (nerve diameter >=0.1mm)
o Yes
o No
Each factor will have equal weighting.

An internal pilot targeting the 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-ups. Otherwise, the trial will be analysed when at least 194 events have been reported.

A Quintet Recruitment Intervention (QRI) and INCLUSION Study Within a Project (SWAP) are integrated within the trial to optimise recruitment and inclusion of people with multiple long-term conditions, safeguard informed consent, address clinician equipoise, and identify organisational barriers.

### Intervention Type
Procedure/Surgery

### Primary outcome(s)
Loco-regional recurrence (LRR)-free survival time, time to LRR is defined as the time from randomisation to date of clinical detection of what is subsequently confirmed to be local, regional, or loco-regional recurrent disease, measured using physical examination at a skin clinic at 4, 8, 16, 12, 24, and 36 months following randomisation until the end of the study

### Key secondary outcome(s)
1. Quality of life (QOL) measured using EORTC QLQ C30, skin-specific Skin Cancer Index, Picker Patient Experience 15 questionnaire and EQ-5D at 4, 12, 24, and 36 months post-randomisation
2. Distant metastasis-free survival, defined as days from randomisation to the date of distant metastasis or death from any cause, measured using data reported by completion of recurrence CRF from randomisation until the point of recurrence is confirmed or death
3. Overall survival, defined as days from randomisation to death for any reason, measured using data reported by completion of a death CRF at the date of death
4. Safety/toxicity as assessed by common terminology criteria for adverse events (CTCAE) V5.0 scoring system and serious adverse events, including patient-reported outcomes version of the CTCAE, measured using adverse event CRFs at 4, 8, 16, 24, 26 months post-randomisation
5. Cost-effectiveness measured using health utility using EQ-5D-5L and recording health resource use at 4, 12, 24, and 36 months post-randomisation. The primary economic outcome is cost per quality-adjusted life year (QALY). The secondary economic outcome is resource use and costs.

### Completion date
01/01/2031

## Eligibility

### Key inclusion criteria
Current inclusion criteria as of 20/08/2026:
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.
If, after surgical excision with curative intent (either wide local excisions with predetermined margins or Mohs micrographic surgery) the deep histological margin is <1 mm, the patient is eligible if ALL of the following are met:
1.1. For scalp cases only: the galea aponeurotica (or galeal aponeurosis) must be resected with no evidence of tumour infiltration. If infiltration of the galea is present, the deep histological excision margin must be ≥1 mm).
1.2. All cases: the MDT is in agreement that surgical treatment is complete;
1.3. All cases: the pathological size of the deep margin is 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

* 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.

Previous inclusion criteria as of 18/02/2026:
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 0.8 mm - <1 mm 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

Previous inclusion criteria:
1. High-risk primary cSCC (T2b/T3 by BWH staging criteria) excised with adequate peripheral and deep surgical margins (according to BAD guidelines) with histologically clear margins (≥1 mm by Royal College of Pathology criteria
2. Time since excision surgery < 3 months (<2 months is preferred)
3. ECOG performance status of 3 or less at enrolment
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

## Participant type(s)
Patient

## Healthy volunteers allowed
No

## Age group
Mixed

## Lower age limit
18 Years

## Upper age limit
100 Years

## Sex
All

## Total final enrolment
0

## Key exclusion criteria
Current exclusion criteria as of 20/08/2026:
1. Any current clinicopathological evidence of loco-regional recurrence of the index tumour
2. Previous (within 2 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

Previous 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 in the same area
6. Patients with reproductive potential who are not willing to use contraception for the duration from trial consent until the last dose of radiotherapy if they are randomised to the ART arm
7. Unable to lie still unattended for the duration of ART (estimated to be around 5 minutes)
8. Participation in another interventional clinical study that may affect the recurrence of cSCC (primary endpoint)
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

## Date of first enrolment
31/07/2024

## Date of final enrolment
14/06/2027

# Locations

## Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

## Study participating centre
**The Christie**
550 Wilmslow Road
Withington
Manchester
England
M20 4BX

## Study participating centre
**Kings Mill Hospital**
Sherwood Forest NHS Trust
Mansfield Rd
Sutton-in-Ashfield
England
NG17 4JL

## Study participating centre
**Velindre Cancer Centre**
Velindre Road
Cardiff
Wales
CF14 2TL

## Study participating centre
**Nottingham University Hospitals NHS Trust - City Campus**
Nottingham City Hospital
Hucknall Road
Nottingham
England
NG5 1PB

**Study participating centre**
**Sheffield Teaching Hospitals NHS Foundation Trust**
Northern General Hospital
Herries Road
Sheffield
England
S5 7AU

**Study participating centre**
**Tayside**
Ninewells Hospital
Dundee
Scotland
DD1 9SY

**Study participating centre**
**Cambridge University Hospitals NHS Foundation Trust**
Cambridge Biomedical Campus
Hills Road
Cambridge
England
CB2 0QQ

**Study participating centre**
**Clatterbridge Cancer Centre**
Clatterbridge Hospital
Clatterbridge Road
Wirral
England
CH63 4JY

**Study participating centre**
**James Cook University Hospital**
Marton Road
Middlesbrough
England
TS4 3BW

**Study participating centre**
**Barking, Havering and Redbridge University Hospitals NHS Trust**
Queens Hospital
Rom Valley Way
Romford
England
RM7 0AG

**Study participating centre**
**East Lancashire Hospitals NHS Trust**
Royal Blackburn Hospital
Haslingden Road
Blackburn
England
BB2 3HH

**Study participating centre**
**Maidstone & Tunbridge Wells NHS Trust Hq**
Maidstone Hospital
Hermitage Lane
Maidstone
England
ME16 9QQ

**Study participating centre**
**Churchill Hospital**
Churchill Hospital
Old Road
Headington
Oxford
England
OX3 7LE

**Study participating centre**
**Barts and the London NHS Trust**
Alexandra House
The Royal London Hospital
Whitechapel
London
England
E1 1BB

**Study participating centre**
**Singleton Hospital**
Sketty Lane
Sketty
Swansea
Wales
SA2 8QA

**Study participating centre**
**Mount Vernon Cancer Centre**
Rickmansworth Road
Northwood
England
HA6 2RN

**Study participating centre**
**Norfolk and Norwich University Hospitals NHS Foundation Trust**
Colney Lane
Colney
Norwich
England
NR4 7UY

**Study participating centre**
**Northampton General Hospital**
Cliftonville
Northampton
England
NN1 5BD

**Study participating centre**
**Queen Elizabeth Hospital**
Queen Elizabeth Medical Centre
Edgbaston
Birmingham
England
B15 2TH

**Study participating centre**

**Royal Surrey NHS Foundation Trust**
Egerton Road
Guildford
England
GU2 7XX

**Study participating centre**
**Derriford Hospital**
Derriford Road
Derriford
Plymouth
England
PL6 8DH

**Study participating centre**
**University Hospitals Dorset NHS Foundation Trust**
Management Offices
Poole Hospital
Longfleet Road
Poole
England
BH15 2JB

**Study participating centre**
**Musgrove Park Hospital**
Musgrove Park
Taunton
England
TA1 5DA

**Study participating centre**
**Beatson West of Scotland Cancer Centre**
1053 Great Western Road
Glasgow
Scotland
G12 0YN

**Study participating centre**
**Glan Clywd Hospital**
Rhuddlan Rd, Bodelwyddan
Rhyl

Wales
LL18 5UJ

**Study participating centre**
**Belfast City -Northern Ireland Cancer Centre**
10 Jubilee Road
Belfast
Northern Ireland
BT9 7JL

**Study participating centre**
**Royal Sussex County Hospital**
Eastern Road
Brighton
England
BN2 5BE

**Study participating centre**
**Sussex Partnership NHS Foundation Trust**
Trust Hq
Swandean
Arundel Road
Worthing
England
BN13 3EP

**Study participating centre**
**Royal Berkshire NHS Foundation Trust**
Royal Berkshire Hospital
London Road
Reading
England
RG1 5AN

# Sponsor information

**Organisation**
Cardiff University

**ROR**
https://ror.org/03kk7td41

# Funder(s)

**Funder type**
Government

**Funder Name**
National Institute for Health and Care Research

**Alternative Name(s)**
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

**Funding Body Type**
Government organisation

**Funding Body Subtype**
National government

**Location**
United Kingdom

# Results and Publications

**Individual participant data (IPD) sharing plan**
The final datasets generated and analysed during the trial will be available upon request directly from the sponsor subject to review using SCCAFTER@cardiff.ac.uk.

**IPD sharing plan summary**
Available on request

**Study outputs**

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Protocol file | version 1.1 | 18/03/2024 | 01/07/2024 | No | No |
| Protocol file | version 3.0 | 09/12/2025 | 18/02/2026 | No | No |
| Protocol file | | 11/02/2026 | 20/08/2026 | No | No |
| Study website | | 11/11/2025 | 11/11/2025 | No | Yes |