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Cardiff University Prifysgol Caerdydd | Centre for Trials Research Canolfan Ymchwil Treialon

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.

Thank you for your interest in taking part in the SCC-AFTER clinical trial. Below is a brief synopsis of the rationale behind the trial and its objectives, details of the intended patient cohort, inclusion and exclusion criteria and a summary of the trial pathway.

Cutaneous squamous cell carcinoma (cSCC) is a common skin cancer and high-risk cases (defined as BWH staging system T2b/3) are usually cured by surgery. Unfortunately, it is estimated that 1 in 3 of these patients may develop recurrent disease in the surgical site or nearby lymph glands (loco-regional recurrence) which can lead to significant morbidity, impaired quality of life and mortality attributable to cSCC.

Currently, it is not well established if treating high-risk patients with adjuvant radiotherapy (ART) after their surgery leads to better outcomes. Our feasibility work confirmed clinical equipoise around the best approach for standard of care, which differs between clinicians and hospital trusts.

The SCC-AFTER trial aims to definitively show whether giving ART plus close clinical follow up (versus close clinical follow up alone) is beneficial in reducing loco-regional recurrence of high-risk primary cSCC following surgery. The outcomes from this study will hopefully provide robust and reliable evidence to guide future national treatment recommendations and improve patient outcomes.

PRIMARY OBJECTIVE

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

SECONDARY OBJECTIVES

- Quality of life (QoL) - measured using EORTC QLQ C30, Skin-specific Skin Cancer Index, Picker Patient Experience 15 questionnaire
- Clinical frailty – measured using Clinical frailty scale (CFS)V2.0
- Distant metastasis-free survival
- Overall survival
- Safety and toxicity
- Cost-effectiveness of ART

Participants

The SCC-AFTER trial is designed to be both representative of the population affected by high-risk cSCC, and inclusive of those patients historically under-represented in trial participation, including older, frailer patients, those with multiple long-term conditions including the immunocompromised and from socio-economically disadvantaged groups. To that aim, within the trial design we have incorporated the Quintet Recruitment Intervention (QRI) and the INCLUSION SWAP to help identify barriers to recruitment and optimise involvement of under-served groups, through exploratory interviews and analysis of recruitment processes.

The trial aims to recruit 840 participants over 25 UK wide sites over 4 years.

Please contact SCCAfter@cardiff.ac.uk with any queries

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INCLUSION CRITERIA

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. If, after surgical excision with curative intent (either wide local excisions with predetermined margins or Mohs micrographic surgery) the deep histological margin is <1mm, the patient is eligible if ALL of the following are met:**
   a) **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 ≥ 1mm).**
   b) **All cases: the MDT is in agreement that surgical treatment is complete;**
   c) **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.**
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.**

EXCLUSION CRITERIA

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.*****

* 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

**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

Trial Design

Following surgery to excise their cSCC and confirmation of eligibility, participants will be randomised to either the ART followed by close clinical follow up arm or the close clinical follow up arm.

Those assigned to the ART arm will receive ART as follows, to begin within 4 months of their surgery:

- 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.

It is estimated that the majority of trial patients would be treated with electrons/direct skin apposition. Physical examination, toxicity and QoL assessments will be completed as per the schedule of assessments, with progression and survival data collected throughout the trial.

Follow up will be 4 monthly for the first 2 years and then 6 monthly in year 3 to align with standard of care for this group of patients.

Trial Management

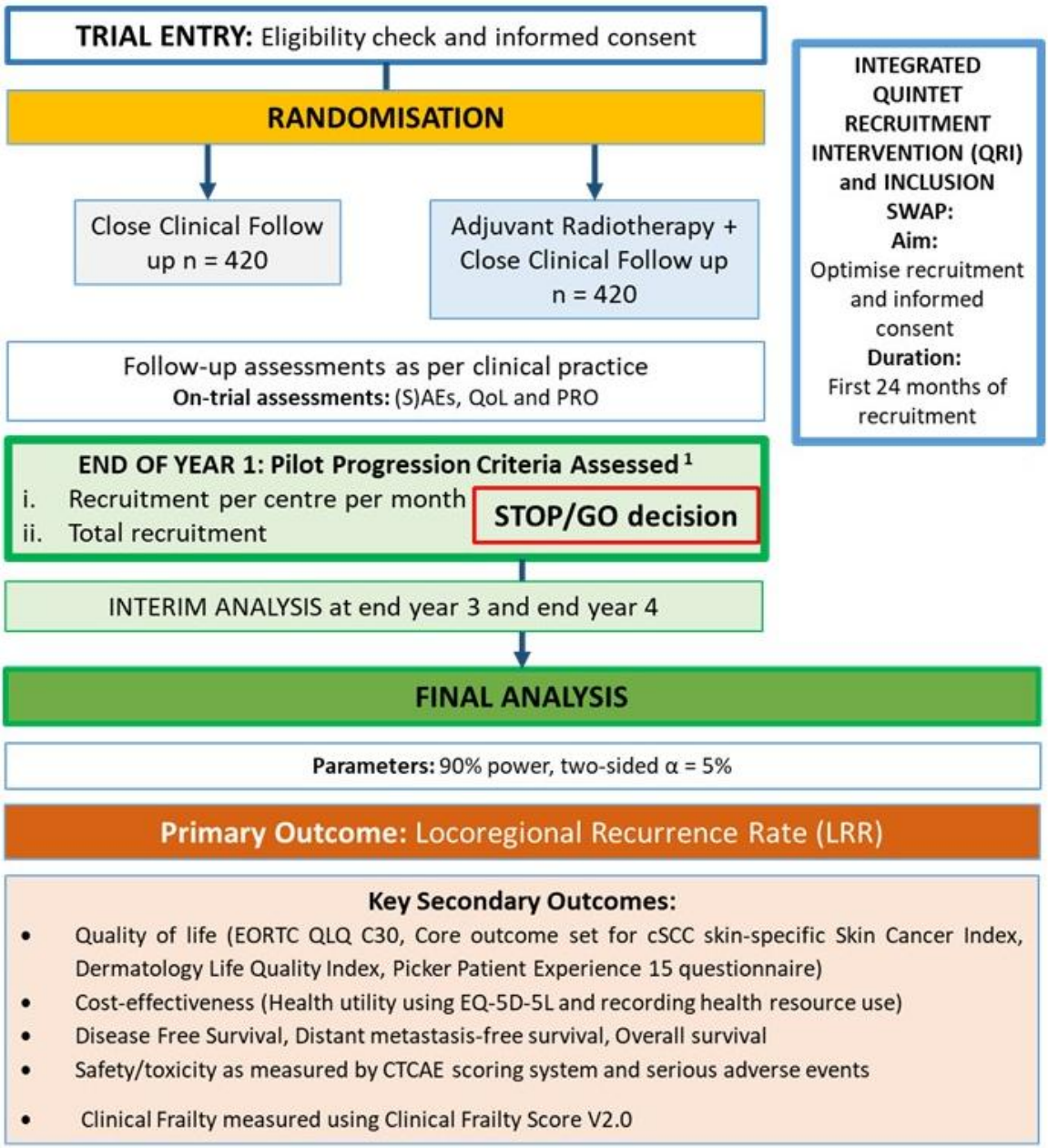
Chief Investigators: Prof. Agata Rembielak, Prof. Catherine Harwood

The Centre for Trials Research, Cardiff University are managing the trial and Cardiff University are Sponsor.

NIHR have funded this trial (NIHR151760) to enable this important research to be carried out.

Please contact SCCAfter@cardiff.ac.uk with any queries

Trial Schema



Key Secondary Outcomes:

- Quality of life (EORTC QLQ C30, Core outcome set for cSCC skin-specific Skin Cancer Index, Dermatology Life Quality Index, Picker Patient Experience 15 questionnaire)
- Cost-effectiveness (Health utility using EQ-5D-5L and recording health resource use)
- Disease Free Survival, Distant metastasis-free survival, Overall survival
- Safety/toxicity as measured by CTCAE scoring system and serious adverse events
- Clinical Frailty measured using Clinical Frailty Score V2.0