UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES

MMed Part III (minor dissertation)

Does hair curl variation influence the efficacy of scalp cooling in the prevention of chemotherapy-induced alopecia in breast cancer patients? A randomized controlled pilot study

by

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OBSODI001

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree

Master of Medicine (MMed) in Radiation Oncology

Date of Submission:

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DECLARATION

I, Odirile Obuseng, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Background: Chemotherapy-induced alopecia (CIA) is a common side-effect of breast cancer treatment. Scalp cooling is reported to reduce CIA; however, it is unknown whether the efficacy is influenced by hair curvature.

Methods: This 20-month randomized controlled trial recruited females, (18-65 years) with breast cancer to receive chemotherapy (Adriamycin or Epirubicin and Cyclophosphamide followed by Paclitaxel) with or without scalp cooling. The main outcomes were percentage alopecia (*Severity ALopecia Tool* scored by 3 dermatologists) in straight versus curly hair and treatment retention rates.

Results: Forty-eight patients (24 per group) were randomized; 4 in each group withdrew before study visit1 and photographs of 3 in the cooling group could not be found for severity assessment. Thus 77% constituted the intention to treat population (17 cooling versus 20 control). Agreement on alopecia severity was good overall (ICC=0,94; 95% CI: 0.85 - 0.97) and at 6 of 7 time points. Overall, cooling significantly reduced CIA, relative to no cooling (58.15 ± 28.46 versus 37.29 ± 20.52; p:0.0167), however, percentage alopecia was cosmetically significant. There was no difference in CIA between cooling participants with straight (8) versus curly hair (9), (p:0.0740).

The number of patients completing the various cycles of chemotherapy, declined from 77.1% at cycle 1 to 18.8% at cycle 7 for the whole study; from 100% each to 17.6% and 30% for cooling and control groups, respectively (p:0.451).

Conclusions: This small study suggests that hair curvature has no significant impact on the efficacy of scalp cooling to reduce CIA, however this requires confirmation.

Word count: 250

CAPSULE SUMMARY

- Scalp cooling is reported to be effective in reducing CIA. In previous studies patients with curly hair were under-represented (1% to 12%), thus it is unknown whether cooling is as effective in reducing CIA as in straight hair.

- This investigator initiated study found scalp cooling to be equally effective in patients with straight and curly hair.

Word count: 56

ACKNOWLEDGEMENTS AND CONTRIBUTIONS

I would like to recognize the invaluable contribution of the following persons for making my research successful:

My supervisor, **Professor Nonhlanhla P. Khumalo,** for her vital guidance and assistance. Funding: the NRF SARChI Chair for funding the study

My co-supervisors, **Dr. Thurandrie Naiker and Dr. Tselane Thebe**, whose support was also invaluable.

Sister Juliet Esterhuizen, the study nurse, for her crucial role in the implementation of the study.

Professor Jeannette Parkes, head of the Department of Radiation Oncology, as well as the doctors, nurses, and administration staff in the Breast Clinic for their immense contribution in making the study a success.

The dermatologists in the Division of Dermatology that were involved in the research, **Professor Nonhlanhla P. Khumalo, Dr. Eugene Hirschfeld and Dr. Tonderai Nyika**, for their assistance in scoring participant photographs for alopecia severity.

Lastly, I would like to acknowledge the patients that agreed to participate in this trial, it is through their participation that this study was possible.

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ABBREVIATIONS AND DEFINITIONS

CBC	Combined Breast Clinic
CI	Confidence Interval
CIA	Chemotherapy Induced Alopecia
FEC	A combination of 5 Fluorouracil (also known as 5FU), Epirubicin and Cyclophosphamide chemotherapy
GSH	Groote Schuur Hospital
HPLC	High Performance Liquid Chromatography
LC	Liquid chromatography
MS	Mass Spectrometry
PI	Principle Investigator
QOL	Quality of Life
RR	Relative Risk
TAC	A combination of T – Docetaxel (also called Taxotere), A – Doxorubicin (originally called Adriamycin) and C – Cyclophosphamide chemotherapy
WHO	World Health Organization

Chemotherapy-induced alopecia: hair loss following the administration of chemotherapeutic agents for the treatment of cancer. This may vary from slight thinning of the hair to complete baldness. The extent of hair loss is affected by the choice of drug and its dose.

Hair curvature: Macroscopic classification of hair into two main groups, straight or curly.

Null hypothesis: a hypothesis of "no difference" e.g., no difference between blood pressures in group A and group B

P value: represents the probability that random fluctuations alone could have generated results that differed from the null hypothesis. The p-value is a number between 0 and 1 and interpreted in the following way:

- A small p-value (typically ≤ 0.05) indicates strong evidence against the null hypothesis, so you reject the null hypothesis.
- A large p-value (> 0.05) indicates weak evidence against the null hypothesis, so you fail to reject the null hypothesis.
- p-values very close to the cut-off (0.05) are considered to be marginal (could go either way)

Scalp cooling: A technique used for the prevention of chemotherapy-induced alopecia. This is achieved by causing scalp hypothermia through a cooling agent (ice or gel cap, cold air or cold liquid) using various procedures.

CHAPTER 1

1.1 Introduction and literature review

Breast cancer is the most common malignancy among women worldwide, with nearly 1.7 million new cases diagnosed in 2012[1]. In 2018 the number of newly diagnosed cases were estimated to be 2.1 million, accounting for almost 25% of all cancers in women. Treatment often includes neoadjuvant or adjuvant chemotherapy, which has been shown to reduce the 10-year relative risk of death from breast cancer by approximately 35%[2] as well as the risk of recurrence by treating micrometastatic disease[3].

Chemotherapy works by targeting rapidly dividing cells in the body. This is achieved through damage to mitotic and metabolic cellular processes, making it effective against cancer cells which proliferate rapidly. This treatment is however associated with several toxic effects such as nausea and vomiting, fever related to neutropenia, anaemia, menopausal symptoms, and infertility. Hair follicles, which contain the second fastest dividing cells in the body, are also susceptible to chemotherapy resulting in chemotherapy-induced alopecia (CIA). It is reported that a substantial number of women choose not to receive treatment because of concerns about these side effects[2].

Over the years substantial improvements in supportive care have led to significant improvements in the management of chemotherapy related adverse effects and has allowed clinicians to reassure patients that symptoms can be controlled, helping to persuade them to initiate treatment despite their apprehension and distress about doing so. One of the strongest deterrents however remains the concern about CIA which remains almost universal, with approximately 50% of patients reported to consider hair loss the most traumatic aspect of chemotherapy and approximately 8% reporting that they would decline chemotherapy because of this concern[2].

Throughout history, ‘healthy shiny hair’ has been symbolic of good health, strength, and sexual attractiveness. Conversely, loss of hair may give rise to psychosocial stress, including negative changes in body image, sexuality, self-esteem, and disturbances in social relationships[4].

Hair loss has also been reported to be associated with lower overall Quality of Life (QOL). However, little is known about the effect on specific components of QOL. In qualitative studies, women have reported that alopecia is associated with a loss of privacy because it makes it known/obvious that they are receiving chemotherapy. It is also described as a visible reminder of the disease and confronts patients with the seriousness of cancer. Some patients commented that hair loss had an influence on their willingness to continue working or creating apprehension about returning to work[5]. These negative impacts of CIA may contribute to poor therapeutic outcome, as stress may lower the body’s immune function[6]. Furthermore, hair loss was found to contribute to depression, a disease associated with poor adherence to chemotherapy and risks of cancer progression[7].

Many chemotherapeutic classes, including anthracyclines, taxanes and alkylating agents are well recognized causes of CIA. The onset typically occurs 2 to 4 weeks after the initiation of chemotherapy and most cases resolve within 3 to 6 months after completion of treatment. Rare cases of permanent hair loss have however been reported[8]. The mechanisms of alopecia include treatment induced keratinocyte apoptosis, hair follicle regression, and

impaired metabolic and mitotic processes in hair follicles, most noticeable on the scalp where the majority (up to 90%) of follicles are in the active growth phase (anagen). CIA tends to particularly affect the frontal or occipital areas of the scalp[9].

Various preventive measures have been tried to reduce CIA: scalp compression, for example with a tourniquet, pharmacological agents such as minoxidil & vitamin D3 and scalp cooling[10]. Although each of these techniques has shown promise in animal studies, scalp cooling is the only modality with consistent efficacy in humans and thus preventative measures have mainly focused on this technique. This is accomplished using either a manual cold cap (ice cap or gel cap) which requires frequent changes throughout therapy to maintain scalp hypothermia, or automatic, machine-based cooling systems, which consist of a tightly fitted cap connected to a device that circulates coolant through the cap cooling the scalp to maintain a set temperature throughout treatment[8].

Three mechanisms/ hypotheses have been proposed to explain how scalp cooling works. Firstly, reducing the scalp temperature causes perifollicular vasoconstriction, reduces blood flow to the scalp to 20-40% of the normal rate and results in less chemotherapeutic drug delivery to the hair follicles. Secondly, cooling reduces the rate of drug diffusion across plasma membranes and thus lowers effective drug doses entering cells. Lastly, cell division is metabolism-driven, a process that is decelerated by cooling; this results in a general reduction in exposure of hair follicles to the damaging effects of chemotherapy drugs[4].

Historically, data was largely retrospective and gathered from use of manual methods however recent prospective studies conducted using automatic cooling systems, such as the Dignicap and Paxman Scalp Cooling System, have shed further insights on this technique and associated outcomes. Much of the scalp cooling data available is derived from breast cancer literature however could be applicable for the treatment of other malignancies in which the same chemotherapeutic agents are used[8].

In a review article it was reported that the effectiveness of scalp cooling in preventing CIA depends on many factors, including patient characteristics, chemotherapy characteristics, and the procedure used for scalp cooling. In terms of patient characteristics, this intervention was more effective in younger patients, in male patients, and in patients with a ‘Caucasian type’ of hair. A possible explanation offered for the lower effectiveness in patients with ‘black African’ hair is a thicker hair layer in this population, which may act as an insulating layer between the cooling cap and the scalp. The authors found three studies in which patients were randomized to chemotherapy either with or without scalp cooling. In these studies, minimal or no hair loss was seen in patients who received scalp cooling, in contrast to almost 100% alopecia for patients in the control groups. It was also observed that scalp cooling results were better with certain chemotherapy types, such as taxanes, and less favorable at higher doses of chemotherapy[9].

Scalp cooling was found to be generally well tolerated with results indicating low levels of discomfort and high acceptability with evidence of only minor and reversible side effects. The most common side effects included headaches, complaints of coldness and/or uncomfortable sensations, and claustrophobia[9].

A recent comprehensive systematic review and meta-analysis that included 17 studies, 8 of which were randomized controlled trials (RCTs) with the remainder being controlled clinical trials (CCTs), by Shin et al. found that scalp cooling significantly reduced (RR= 0.38, 95%

CI= 0.32-0.45, p< 0.001) the risk of CIA. This study found that even though most of the studies evaluated did not perform randomization or use a double-blind approach, which is hard to perform with an intervention such as scalp cooling, the relative risk of CIA was reduced by approximately one third. The authors reported doxorubicin, daunorubicin, epirubicin, docetaxel and cyclophosphamide as the main chemotherapeutic agents inducing CIA. Scalp cooling was generally well tolerated but contraindicated in cases with cold sensitivity, cold agglutinin disease, cryoglobulinemia and cryofibrinogenemia. Due to the reported potential risk of scalp metastases the review advised against the use of scalp cooling systems in patients with circulating malignant cells, such as leukemia or lymphoma, who are receiving chemotherapy with curative intent. Caution was further advised in patients with solid tumors with strong skin metastatic potential, such as breast, lung, or gastric cancer. Monitoring the scalp for evidence of disease was recommended in this patient population[(11)].

Results of a Dutch scalp cooling registry comprising of 1411 patients from 28 hospitals treated with chemotherapy and scalp cooling (using the Paxman systems) between 2006 and 2009, the majority of whom were women (96%) with breast cancer (86%), and treated in the adjuvant setting (69%), showed that alopecia requiring head cover (including wigs, scarves, hats, beanies, turbans, and bandanas) did not occur in 50% of patients who received chemotherapy regimens that normally cause severe CIA. The authors suggest that faced with a 50% chance to keep their hair during chemotherapy, many patients would opt for scalp cooling. It is to be noted that the outcome parameters, head cover use at the time of the final cooling session and WHO Alopecia and Central Alopecia Severity Score, were used as key metrics of scalp cooling success in preventing CIA[(12)].

Use of head covering varied according to type and dose of chemotherapy. Results were best for monotherapy with low dose taxanes, in which 94% and 81% of patients on docetaxel and paclitaxel chemotherapy respectively wore no head cover. Results were worst for TAC chemotherapy (8%), despite the relatively low dose of taxane and anthracycline used in the combination therapy. Longer 5-Fluorouracil, Epirubicin and Cyclophosphamide (FEC) infusion times were found to reduce the use of head covering; this observation had not been reported previously. Poorer protective scalp cooling results were shown in patients older than 65 years and those with ‘Asian type’ of hair. It is worth noting that patients with ‘African hair types’ comprised 1% (11) of the total patient number on the registry. Scalp cooling was stopped because of intolerance in only 3% of patients and notably no scalp skin metastases were reported[(12)].

Table 1: WHO Alopecia and Central Alopecia Severity Score

WHO Scale	Hair loss
0	No hair loss
1	Minimal hair loss
2	Severe hair loss
3	Total alopecia

Two prospective trials, both published in the United States in the last year, have shed further insights on the efficacy and safety of scalp cooling. The first trial titled SCALP (Scalp Cooling

Alopecia Prevention) is a multicenter, randomized, non- blinded study[3]. The second is a multicenter, cohort study[13].

Table 2: A comparative summary table of the design of the studies follows: [8]

First author	Device used	Cooling schedule	Study population	Type of chemotherapy
Nangia *et al. 2017*[3]	Orbis Paxman Hair Loss Prevention System	30 minutes before treatment, during chemotherapy, and 90 minutes after treatment	Early-stage breast cancer (I or II)	Taxane or anthracycline (including both agents sequentially)
Rugo *et al. 2017*[13]	DigniCap scalp-cooling device	30 minutes before treatment, during chemotherapy, and 90- 120 minutes after treatment	Early-stage breast cancer (I or II)	Taxane based (anthracycline based allowed, but no enrolled patients treated with anthracycline)

In the SCALP trial, in which patients received chemotherapy either neoadjuvant or in the adjuvant setting, the primary objective was to evaluate the efficacy of the Paxman Hair Loss Prevention System. Success was defined as grade 0 (no hair loss) or grade 1 (<50% hair loss, not requiring a wig) alopecia after 4 cycles of chemotherapy. Assessment of hair loss was done by a clinician that was blinded to the patient treatment group allocation. At the time of interim analysis 50.5% of the patients in the scalp-cooling arm had hair preservation versus 0% in the control group. It was found that chemotherapy type, with taxanes less likely to cause hair loss compared to anthracyclines, and technique of use of the scalp cooling system had an impact on hair preservation success. In this trial 'Black or African American' participants constituted 12% of the study population.

Only grade 1 or 2 adverse events related to scalp cooling were reported. Quality of life (QOL) end points, including emotional and social functioning as well as anxiety/ depression scores, were found to be comparable between both groups. Study accrual was stopped early as the P value of the difference in hair preservation had crossed the predefined superiority boundary at the time of interim analysis[3].

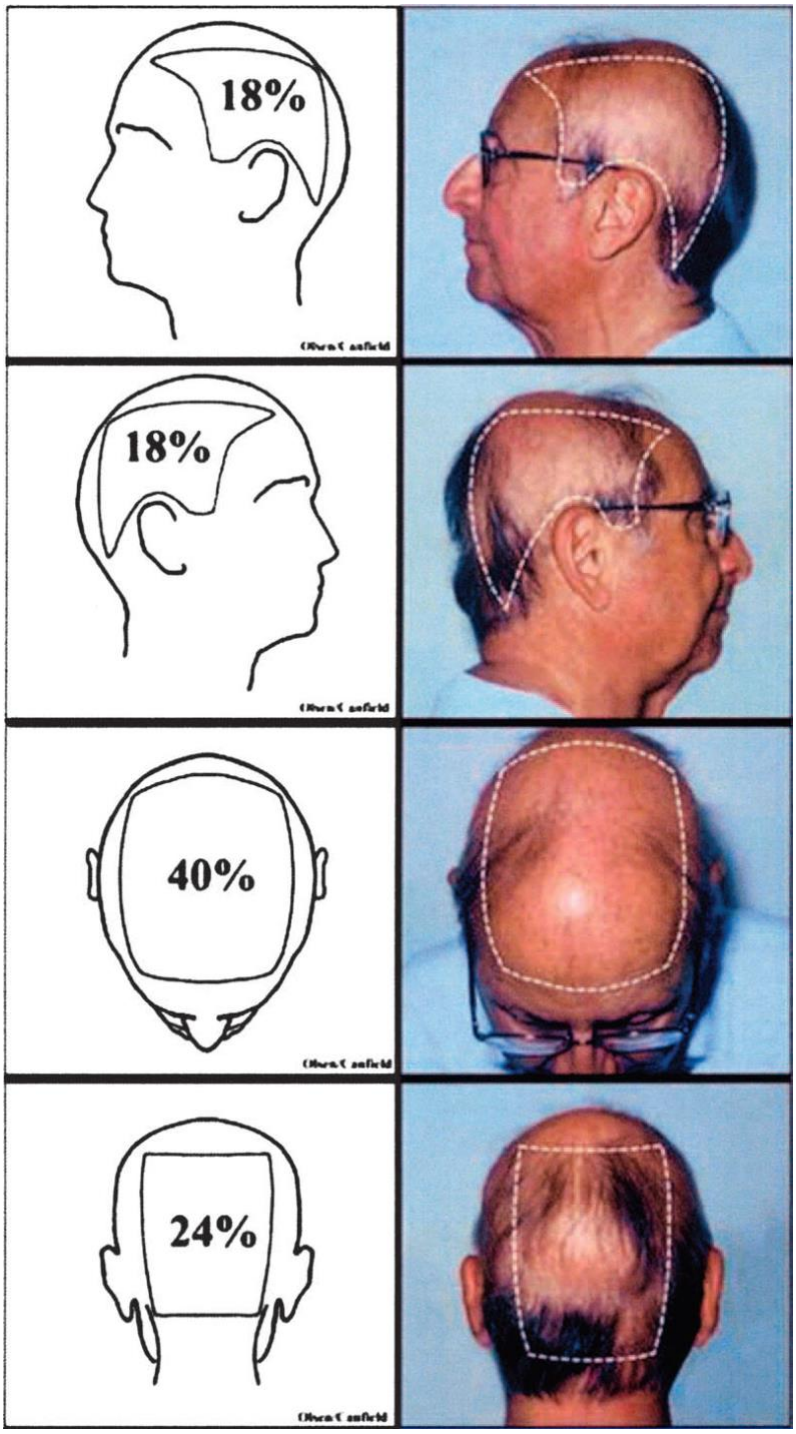
The primary end point in a study by Rugo, H.S et al. was defined as prevention of hair loss 4 weeks after completion of neoadjuvant or adjuvant chemotherapy, with success defined by patient self-assessment using the Dean scale. A score of 2 or less (corresponding to hair loss of 50% or less) was considered successful hair preservation. 66% of the patients in the scalp cooling group versus 0% in the control arm experienced hair preservation success. Even though 'Black' women constituted only 10.4% of the study population it is reported that hair thickness did not seem to affect the incidence of hair loss [13].

In contrast to the SCALP study, differences in some QOL end points were identified between the control and cooling groups. Of note, patients in the cooling group were (statistically) significantly less likely to report feeling less physically attractive because of their disease or treatment and less likely to be dissatisfied with their body compared with those in the control

group. The control group was more likely to report being upset about hair loss. As with the SCALP study no major safety concerns were identified[13].

The *Severity ALopecia Tool* (SALT) is widely use in dermatology to estimate percentage alopecia. The SALT score was developed and validated for use in patients with alopecia areata, the most common cause of diffuse alopecia. The progression of CIA is very similar to that of alopecia areata; hence the SALT score would be suitable to assess severity [14].

Figure 1: *Severity ALopecia Tool* (SALT) used to score alopecia



The SALT score equals the sum of the scalp hair loss in each area. (a) Top (left side view) = 95% X 0.18 = 17.1 (b) Second (right side view) = 90% X 0.18 = 16.2 (c) Third (top of scalp)

= 95% X 0.40 = 38 (d) Bottom (back of scalp) = 55% X 0.24 = 13.2. The total (a+b+c+d) = 17.1 + 38 + 16.2 + 13.2 = 84.5% hair loss or SALT 84.5 [14].

The University of California San Francisco (UCSF) Penguin Cold Cap Registry study was also recently published. The aim of the study was to assess the efficacy and tolerability of manual cold cap technology, using the Penguin Cold Caps, in women undergoing commonly utilized chemotherapy regimens in the United States for early or advanced stage breast cancer. Hair loss was assessed by both patients, using a 100-point Visual Analog Scale (VAS), and physician, using the 5-point Dean Scale. Assessments were done at baseline, every 3–4 weeks during chemotherapy, and at least 1 month after completion of chemotherapy. The primary efficacy endpoint for success was defined as ≤50% hair loss by patient report (VAS) at all measured time points.

Overall, 61% of patients successfully retained hair during treatment, with the best outcomes noted for those receiving taxanes compared to those with anthracycline containing regimens. This intervention was well tolerated and viewed favorably by most patients, with all patients that completed therapy reporting that they would recommend the cold cap system to other patients receiving chemotherapy. Other than chemotherapy regimen administered, no other factors were found to affect the success of scalp cooling in this study. Similar to other publications 'Black' patients were under-represented in this study constituting only 3% of the overall population[15]. Thus, it is unknown whether scalp cooling is as effective in reducing CIA in patients with curly as in those with straight hair.

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CHAPTER 2 – Publication Ready Manuscript

Does hair curl variation influence the efficacy of scalp cooling in the prevention of chemotherapy-induced alopecia in breast cancer patients? A randomized pilot trial

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Author contributions: Odirile Obuseng and Nonhlanhla Khumalo contributed to the design and implementation of the research and the writing of the manuscript. Thurandrie Naiker and Tselane Thebe contributed to data interpretation after analysis done by a private company and reviewed several versions of the manuscript. All authors agreed on the final version of the manuscript.

Funding sources: The NRF SARChI Chair in Dermatology and Toxicology and the South African Medical Research Council.

Conflicts of Interest: This is an investigator-initiated study, NPK requested loan of Paxman Hair Loss Prevention System for the study.

IRB approval status: Reviewed and approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee; approval #892/ 2016

Manuscript word count: 4157
Abstract word count: 250
Capsule summary word count: 56
References: 350
Figures: 1
Supplementary figures: 0
Tables: 4
Supplementary tables: 0

Keywords: alopecia; breast cancer; chemotherapy; chemotherapy-induced alopecia; efficacy; hair curvature; scalp cooling

ABSTRACT

Background: Chemotherapy-induced alopecia (CIA) is a common side-effect of breast cancer treatment. Scalp cooling is reported to reduce CIA; however, it is unknown whether the efficacy is influenced by hair curvature.

Methods: This 20-month randomized controlled trial recruited females, (18-65 years) with breast cancer to receive chemotherapy (Adriamycin or Epirubicin and Cyclophosphamide followed by Paclitaxel) with or without scalp cooling. The main outcomes were percentage alopecia (*Severity ALopecia Tool* scored by 3 dermatologists) in straight versus curly hair and treatment retention rates.

Results: Forty-eight patients (24 per group) were randomized; 4 in each group withdrew before study visit1 and photographs of 3 in the cooling group could not be found for severity assessment. Thus 77% constituted the intention to treat population (17 cooling versus 20 control). Agreement on alopecia severity was good overall (ICC=0,94; 95% CI: 0.85 - 0.97) and at 6 of 7 time points. Overall, cooling significantly reduced CIA, relative to no cooling (58.15 ± 28.46 versus 37.29 ± 20.52; p:0.0167), however, percentage alopecia was cosmetically significant. There was no difference in CIA between cooling participants with straight (8) versus curly hair (9), (p:0.0740).

The number of patients completing the various cycles of chemotherapy, declined from 77.1% at cycle 1 to 18.8% at cycle 7 for the whole study; from 100% each to 17.6% and 30% for cooling and control groups, respectively (p:0.451).

Conclusions: This small study suggests that hair curvature has no significant impact on the efficacy of scalp cooling to reduce CIA, however this requires confirmation.

CAPSULE SUMMARY

- Scalp cooling is reported to be effective in reducing CIA. In previous studies patients with curly hair were under-represented (1% to 12%), thus it is unknown whether cooling is as effective in reducing CIA as in straight hair.

- This investigator initiated study found scalp cooling to be equally effective in patients with straight and curly hair.

2.2 Background

Breast cancer is the most commonly diagnosed malignancy and the leading cause of cancer death among women worldwide. In 2018 the number of newly diagnosed cases were estimated to be 2.1 million, accounting for almost 25% of all cancers in women[1]. Treatment often includes neoadjuvant or adjuvant chemotherapy, which has been shown to reduce the 10-year relative risk of death from breast cancer by approximately 35%[2] as well as the risk of recurrence by treating micrometastatic disease[3].

Chemotherapeutic agents work by targeting rapidly dividing cells in the body. This is achieved through damage to mitotic and metabolic cellular processes, making it effective against cancer cells, which proliferate rapidly. This treatment is however associated with unintended effects on other normal cells such as hair follicles, which may result in alopecia.[2]

Chemotherapy-induced alopecia (CIA), although reversible, has been described as one of the most common and distressing side effects of cancer therapy, affecting approximately 65% of all patients and influencing treatment decisions in some women who want to avoid hair loss.[4] Hair loss has also been associated with lower overall Quality of Life (QOL)[5] and was found to contribute to depression, a condition associated with poor adherence to chemotherapy and risks of cancer progression[6]. In the first study of its kind, Lemieux et al.[5] compared mortality among women with non-metastatic breast cancer treated with chemotherapy who used scalp cooling to reduce CIA compared to similar women who did not. They found no negative impact on survival for women who used scalp cooling with their chemotherapy.

Scalp cooling has been proven effective in reducing CIA[7]. In a recent review of three studies as well as 2 prospective trials, in which patients were randomized to chemotherapy either with or without scalp cooling, minimal or no hair loss was seen in patients who received scalp cooling in contrast to almost 100% alopecia for patients in the control groups. The effectiveness of this intervention is reported to depend on many factors including hair curvature, with improved outcomes suggested in patients with a 'Caucasian type of hair[4]. This claim has never been validated in a randomized prospective trial and prior outcomes are derived mainly from patients with straight hair, therefore it remains unclear whether these results can be generalized to patients with curlier hair curvature.

In a randomized prospective clinical study, the Scalp Cooling Alopecia Prevention (SCALP) trial, the cooling system was significantly more likely to cause less hair loss. In this trial, although no multivariate analysis by hair type is stipulated, demographic information shows that only 12% of the study population was Black or African American[3]. In another prospective study, the use of scalp cooling was associated with less hair loss after chemotherapy. In this study, as with previous trials, Black women constituted a minority of the study population with only 10.4% representation[8].

2.3 Objectives

In this pilot trial, the research aims were to evaluate whether hair curvature influences the ability of scalp cooling to reduce chemotherapy-induced hair loss in breast cancer patients and to assess feasibility of conducting a definitive trial. The objectives of the study were as follows:

1. To verify findings from previous research indicating that the severity of CIA is less in participants receiving scalp cooling versus those that are not, and to determine whether

scalp cooling is less effective in patients with curly hair compared to those with straight hair.

2. To assess and establish procedures for recruitment and retention in a future study.

2.4 Methods

2.4.1 Trial design

The trial was a pilot monocentric, prospective, investigator initiated, randomized (patient) controlled single blind (three independent dermatologists) study of scalp cooling versus no cooling in breast cancer patients receiving neoadjuvant or adjuvant chemotherapy in a 21-day cycle. Equal randomization (1:1) was employed to provide the greatest power for testing effectiveness in a future definitive randomized controlled trail (RCT).

After obtaining institutional approval to conduct the study, the investigator was made aware that the Groote Schuur hospital (GSH) departmental breast cancer clinical protocol had been updated to offer neoadjuvant chemotherapy to a select group of patients depending on their breast cancer molecular subtype. The trial protocol was therefore amended to recruit patients receiving both neoadjuvant and adjuvant chemotherapy.

The study was conducted in cooperation between the Department of Radiation Oncology Breast Clinic and the Dermatology Division at GSH.

2.4.2 Participants

Fifty-three eligible female patients with breast cancer were recruited from the GSH specialist breast clinic between May 2017 and November 2018. The inclusion criteria included: (i) female gender, (ii) aged 18 to 65 years, (iii) had breast cancer surgery: mastectomy or breast conserving methods, with or without lymph node removal, <12 weeks before inclusion or planned surgery after neoadjuvant chemotherapy, (iv) had planned antineoplastic therapy with chemotherapy, Adriamycin or Epirubicin and Cyclophosphamide followed by Paclitaxel (AC/EC -P), including written consent. Participants were not deemed eligible if they had: (i) evidence of alopecia at baseline, (ii) planned radiation therapy of the skull before or during the study, antineoplastic therapy within 6 months prior to baseline, inadequately treated hypo or hyperthyroidism, known cold sensitivity, cold agglutinin disease, cryoglobulinemia and cryofibrinogenemia, enrolled in another study at the time of recruitment, refused to participate in the study or withdrawn consent before the first post-treatment assessment.

At the end of each week, the investigator collected and scanned the files of all patients seen for their post-operative visit as well as new patients seen at the combined breast clinic within that week. These files were then pre-screened to determine eligibility. All eligible patients were then called by the investigator to schedule a screening appointment prior to commencement of chemotherapy. Once eligibility was confirmed informed written consent was obtained. The investigator, together with the study nurse, then conducted a thorough scalp examination to exclude baseline alopecia before obtaining pictures and hair samples. Hair samples were then sent to the University of Cape Town Hair and Skin Lab for analysis and Geometric Classification.

2.4.3 Interventions

At the first chemotherapy treatment visit participants were notified of their study group allocation prior to being asked questions relating to haircare, specifically use of cosmetic hair chemicals that alter hair curl such as relaxers, hair dyes and highlights and timing of most recent use. These questions were also asked at all subsequent visits.

For participants randomized to receive scalp cooling, the appropriately sized cooling cap was selected ensuring good contact with the scalp. The scalp was then pre-cooled for 30 minutes prior to commencement of treatment. Scalp cooling was then continued throughout the administration of chemotherapy and for 90 minutes afterwards. Patients randomized to the control group received chemotherapy only. In this study chemotherapy was either administered neo-adjuvantly or adjuvantly, as per the departmental protocol.
At all subsequent visits patients were asked to complete a hair loss questionnaire and had to mention if they needed to cover their head (e.g. with a wig) as a result of alopecia. This was followed by obtaining standardized clinical photographs and hair sampling.

2.4.4 Outcomes

Recruitment and retention were assessed by the ability to enrol the pre-set number of participants and the number of patients retained through each subsequent cycle of chemotherapy, respectively. Efficacy of scalp cooling, including in patients with curly versus straight hair, was determined by objective comparative percentage hair loss analysis between the groups: three dermatologists not involved in (and blinded to) the trial were chosen to grade photographs using the *Severity ALopecia Tool* (SALT). A mean score between the dermatologists was used to allocate severity, intraclass correlation coefficient (ICC) was used to assess agreement between the 3 dermatologists.

2.4.5 Sample size

Using an online sample size calculator, Clincal.com (https://clincalc.com), it was estimated that forty-six participants would be a large enough sample to provide a measure of the impact of hair curl variation on scalp cooling. This was based on the following assumptions: mean hair loss of 95% and 50% within the non-cooling and cooling groups respectively; 0.05 probability of a type 1 error and powered at 95% to detect a difference between the two groups. Fifty-two patients were included to account for attrition.

2.4.6 Randomization

Prior to commencement of recruitment, sequence generation was done using the online program ‘Research Randomizer’ (https://www.randomizer.org). The total number of participants were divided into 2 groups of 26 each, curly and straight hair. For each of these groups this number was inputted into the program with resultant generation of a randomized sequence of the letters A and B, in a 1:1 ratio. It was already decided before randomization that A would represent allocation to the cooling arm and B the control arm. After recruitment and hair type testing patients were allocated to either the straight or curly group and assigned to either undergo cooling or not based on the corresponding letter (A or B) alongside their sequential listing within the relevant group.

2.4.7 Analytical methods

The research statistician encoded the data in MS Excel. Stata MP version 14 software was used for data processing and analysis. Intraclass correlation coefficient was calculated to determine the inter-rater reliability. Continuous data were presented as mean and standard deviation while categorical variables were presented as frequency and percentages. Comparison of continuous data across groups were performed using the following tests: Independent t test, One Way ANOVA, paired t test, and Two-Way Repeated Measures ANOVA. Significant ANOVA results were further analyzed using Scheffe's test (Repeated Measures) and Tukey HSD (One Way). Categorical variables were compared across groups using Chi square test or Fisher's exact test. McNemar's test was used to compare the proportions by time period. P values ≤0.05 were considered statistically significant.

2.5 Results

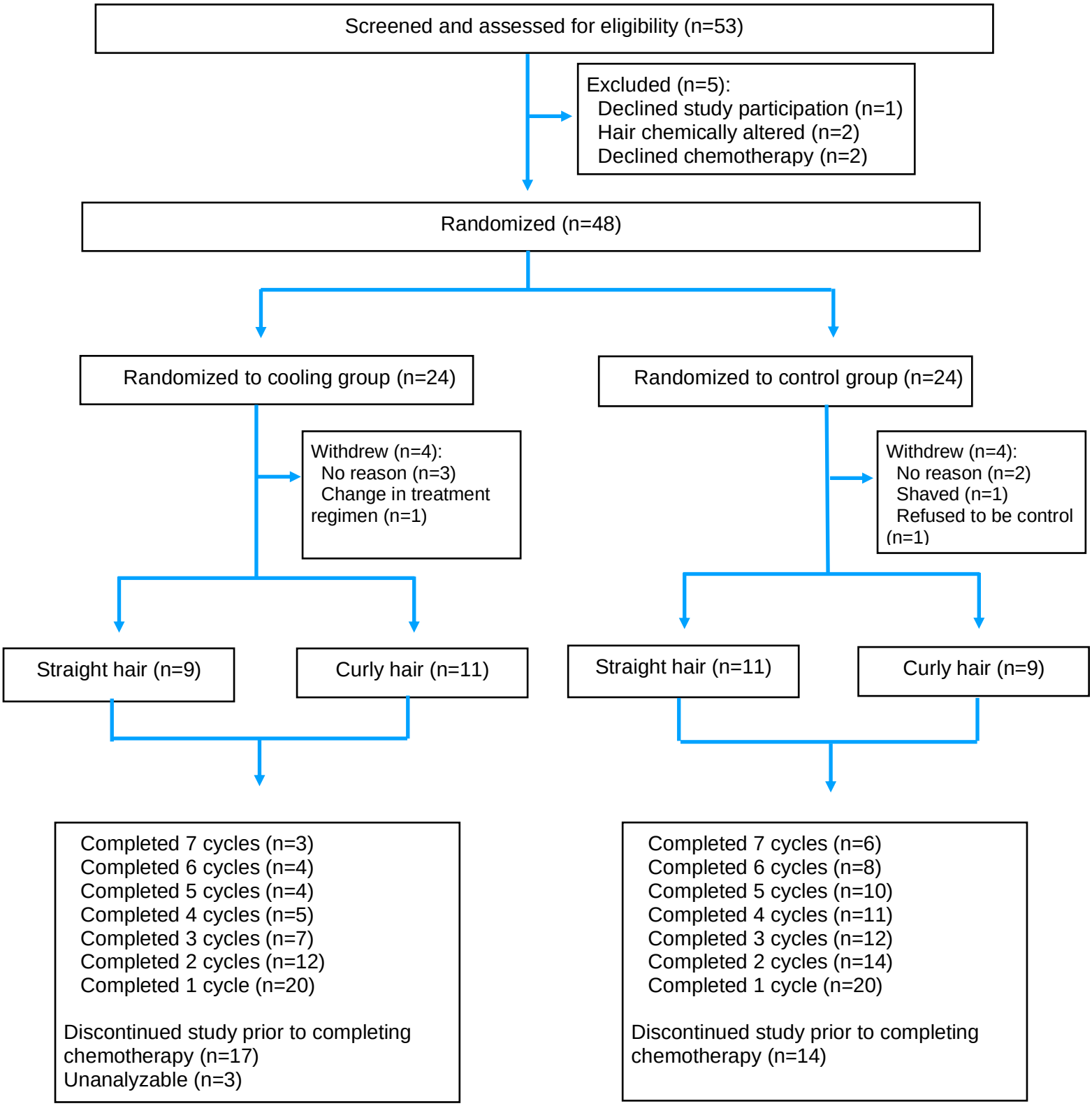

Figure 2: Flow diagram of progress through phases of pilot trial

Reasons for withdrawal through the various cycles of chemotherapy include the following:

Reason	Total	Cooling	No Cooling
Shaved hair	6	2	4
Scalp cooling side effects	7	7	0
Defaulted chemotherapy	4	1	3
Chemotherapy stopped	1	1	0
No reason provided	13	6	7
Total	**31**	**17**	**14**

Table 3: Reasons for withdrawal

Recruitment

Patient enrolment started in May 2017 and was completed in November 2018. The study closed at the end of the recruitment period once the intended sample size had been reached.

Baseline data

Characteristics	Categories	Cooling (n=17) frequency (%)	No Cooling (n=20) frequency (%)	p value
Hair type	Straight	8 (47)	11 (55)	p=0.630
	Curly	9 (53)	9 (45)	
Hair relaxer or color use	Yes	7 (41)	10 (50)	p=0.591
	No	10 (59)	10 (50)	
Smoker	Yes	3 (18)	3 (15)	p=0.811
	No	12 (71)	12 (60)	
	Ex-smoker	1 (6)	3 (15)	
	Unknown	1 (6)	2 (10)	
	No	8 (47)	16 (80)	
	No	9 (53)	4 (20)	
*IDC subtype	Yes	17 (100)	18 (90)	p=0.489
	No	0	2 (10)	
**Chemotherapy regimen	EC-P	9 (53)	7 (35)	p=0.331
	AC-P	8 (47)	13 (65)	

Characteristics	Cooling (n=17) Mean ± SD	No Cooling (n=20) Mean ± SD	p value
Age (in years)	47.76 ± 10.28	49.35 ± 7.56	0.5930
No. of cycles completed	2.94 ± 2.36	4.05 ± 2.58	0,1846

*IDC: Invasive Ductal Carcinoma- the most common type of breast cancer
**EC or AC-P: Epirubicin or Adriamycin and Cyclophosphamide followed by Paclitaxel

Table 4: Baseline characteristics by treatment group

Intra-class correlation coefficient (ICC) value for the observation of three dermatologists on percentage alopecia severity using the SALT score

Table 5: Intra-class correlation coefficient (ICC) values through the chemotherapy cycles

Cycle	ICC	95% CI
Overall	0,94	0.85 - 0.97
Baseline	0,94	0.89 - 0.97
Cycle 1	0,94	0.89 - 0.97
Cycle 2	0,91	0.80 - 0.96
Cycle 3	0,91	0.77 - 0.97
Cycle 4	0,64	0.17 - 0.86
Cycle 5	0,89	0.61 - 0.97
Cycle 6	0,90	0.69 - 0.97
Cycle 7	0,93	0.68 - 0.99

Interpretation: based on the 95% confident interval of the ICC estimate, values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively.

Numbers analyzed

Out of the 53 eligible patients screened, 48 (90.6%) fulfilled the randomization criteria and agreed to participate in the study. Study retention figures through the chemotherapy cycles are reflected in figure 1 above. 37 (77.1%) of the randomized patients completed at least one cycle of chemotherapy, with analyzable pictures, and were included in the final ITT analysis, including: 17 (45.9%) and 20 (54.1%) in the scalp cooling and control arms respectively of which 18 (48.6%) and 19 (51.4%) had curly and straight hair, respectively.

Outcomes and estimation

Photographs of alopecia severity were blindly, individually, assessed for each participant and time point by 3 dermatologists using the *Severity ALopecia Tool* (SALT) score. The overall intra-class correlation coefficient (ICC) value for the observation of the three assessors was estimated to be 0,94 (95% CI: 0.85 - 0.97), this is indicative of good to excellent reliability. Further, agreement on alopecia severity was good in 6 of 7 time points (Table 6).

When the mean overall change in alopecia severity post-chemotherapy was compared in the ITT population, no statistically significant difference in CIA severity was found between participants with curly (9) and straight (8) hair, 36.11 ± 18.33; 50.89 ± 37.04; 38.63 ± 23.98; 64.09 ± 18.84 in the curly-cooling, curly no-cooling, straight-cooling and straight no-cooling groups respectively p value= 0.0740. However further analysis, using Tukey HSD, showed that the mean change in alopecia severity at cycles 2 and 3 were significantly higher in participants with curly hair randomized to the control group compared to those with curly hair that underwent scalp cooling. P-values were 0.0138 and 0.0347, respectively.

The mean change in alopecia severity post-chemotherapy (overall) was significantly higher in the non-cooling group compared to the cooling group, 58.15 ± 28.46 and 37.29 ± 20.52, respectively with p value = 0.0167. This result supports previously reported evidence for the efficacy of scalp cooling to reduce the severity of CIA. When results were analyzed by cycle (data from Table 6), statistically significant differences were also found at cycles 2, 3 and 5,

80.79 ± 17.63 versus 42.90 ± 34.26; 89.25 ± 13.66 versus 57.43 ± 11.43 and 79.50 ± 27.21 versus 44.25 ± 26.42; with p values of 0.0018, 0.0055 and 0.0477, respectively.

	Cooling Mean ± SD	**No cooling Mean ± SD**	**p value**
Overall post-chemo	**(n=17)**	**(n=20)**	0.0167*
	37.29 ± 20.52	58.15 ± 28.46	
Cycle 1	**(n=17)**	**(n=20)**	0.3555
	25.18 ± 20.28	33.40 ± 30.97	
Cycle 2	**(n=10)**	**(n=14)**	0.0018*
	42.90 ± 34.26	80.79 ± 17.63	
Cycle 3	**(n=7)**	**(n=12)**	0.0055*
	57.43 ± 11.43	89.25 ± 13.66	
Cycle 4	**(n=5)**	**(n=11)**	0.1255
	66.40 ± 18.73	82.45 ± 18.08	
Cycle 5	**(n=4)**	**(n=10)**	0.0477*
	44.25 ± 26.42	79.50 ± 27.21	
Cycle 6	**(n=4)**	**(n=8)**	0.1322
	26.75 ± 30.25	62.63 ± 37.85	
Cycle 7	**(n=3)**	**(n=6)**	0.4188
	29 ± 17.47	51.33 ± 39.07	

Table 6: Comparative CIA through each cycle of treatment in the cooling versus non-cooling groups

Ancillary analyses

Among patients who completed at least 5 cycles of chemotherapy, 4 cycles of Adriamycin or Epirubicin and Cyclophosphamide followed by at least 1 cycle of Paclitaxel, there was insufficient evidence to suggest a difference between the severity of alopecia caused by the chemotherapy regimens, 68.64 ± 15.90 versus 52.24 ± 38.02 and 58.25 ± 22.66 versus 70.60 ± 29.55; with p-values of 0.1581and 0.3005 for AC versus P and EC versus P, respectively.

Harms

Participants in the two groups, cooling, and non-cooling, were similar in terms of age, mean number of chemotherapy cycles completed, hair relaxer or color use, smoking history, breast cancer subtype and prescribed treatment regimen. However, a higher proportion of patients in the cooling group were given adjuvant chemotherapy compared to the non-cooling group (53% vs 20%) and conversely, a higher proportion of patients in the non-cooling group were given neo-adjuvant chemotherapy compared to the cooling group (80% vs 40%). This is not expected to affect outcomes as the chemotherapy regimens are similar and the timing of administration of chemotherapy is not known to influence susceptibility to CIA.

An unexpected finding in this study was 7/17 (41.18%) of patients in the scalp cooling arm withdrawing from the study due to device- related side effects, previous studies have reported rates of between 2.8 and 6.18%. Of these, 6/17 (35.29%) cited headaches as the main reason for withdrawal whilst 2/17 (11.76%) and 1/17 (5.88%) withdrew due to feeling cold and scalp tenderness, respectively. However, overall, the true dropout rate was similar

in the cooling versus control groups (17 versus 14), p-value: 0.451. A comparison of the attrition rate between the two groups found a non-significant difference after all cycles except cycle 5 where there was a significantly higher dropout rate in the cooling group relative to the no-cooling group (80% versus 50%, p-value: 0.047).
Unfortunately, clinical photographs of 3 participants from the cooling group were accidentally deleted from the study camera further reducing analyzable data.

2.6 Discussion

Interpretation

Findings from this small study seem to be in keeping with previous findings demonstrating a significant reduction in alopecia in patients who used scalp cooling while receiving chemotherapy regimens that normally cause severe CIA, relative to those that did not use scalp cooling during treatment. In this pilot trial an overall risk reduction of 35.87% was demonstrated. Despite this benefit some patients reported that the percentage, as well as pattern and distribution, hair loss was still large and made it cosmetically difficult to conceal, with some opting to rather shave their heads instead. Although no previous trials defined comparative CIA outcomes by hair curvature as a study objective, in one of the trials a multivariate analysis failed to show that hair type had a statistically significant impact. However, in that study patients with 'African hair' type constituted only 1% of the registry[11]. This analysis seems to be in keeping with our findings of no statistically significant difference in CIA reduction in CIA between curly versus straight hair. Although the mean change in alopecia severity at cycles 2 and 3 were significantly higher in participants with curly hair randomized to the control group compared to those with curly hair that underwent scalp cooling these are to be interpreted with caution as the overall risk reduction was not statistically significant, with a risk ratio of 0.94 (95%CI: 0.77 - 1.14) and 1.08 (95%CI: 0.93 - 1.27).

The results of this trial support the feasibility of conducting a larger definitive randomized trial involving breast cancer patients due to receive chemotherapy (neo-adjuvant or adjuvant) as part of their radical treatment. Despite the inability to meet all predetermined criteria and timelines we believe this trial still demonstrates feasibility albeit with a need for protocol and resourcing amendments to improve recruitment and retention rates. With regard to recruitment, we believe we were probably too confident when targeting a 2-month recruitment period, however with faster hair classification turnaround times an improvement can be made on the 18-month timeline attained. To address both the shortfall in recruitment and retention in a future trial we believe the solution is an improvement in human resourcing as well as securing more scalp coolers.

One of the goals of this pilot study was to investigate the feasibility of a future definitive trial based on study recruitment and retention. It was anticipated that trial recruitment would begin soon after institutional approval was granted however this had to be delayed as a result of a change in the departmental chemotherapy treatment protocol, which necessitated a subsequent ethics application for approval of the minor change in the trial protocol. We initially envisioned that recruitment would run over a 2-month period with the trial completed within 10 months of commencement. The recruitment time target was not met, with the number of eligible patients only being recruited after 18 months and the study concluded after approximately 20 months of commencement.

The reasons for the delay in recruitment include: a higher than anticipated proportion of patients receiving neo-adjuvant chemotherapy, which was prioritized for a faster than usual

treatment start date, this often meant that hair sampling and classification could not be completed in time for chemotherapy commencement. If the turnaround time for hair classification was accelerated this could potentially reduce the recruitment time period in a future definitive trial. Another reason is that only 2 scalp cooling devices were available for the trial and if patients were booked to start chemotherapy on a day on which 2 trial patients randomized to scalp cooling were already booked these patients had to be excluded due to the possibility of them being randomized to scalp cooling, as a machine would not be available. In a future trial the use of more scalp cooling devices could help to reduce recruitment timelines.

Once randomized, eight patients declined to actively participate before even beginning the intervention. To avoid early withdrawal in a definitive study, a suggestion would be to spend more time explaining the trial and the implications of the outcomes, including potential benefits for future patients, during the consent process. A further 31 patients dropped out of the study (through the subsequent 7 cycles of chemotherapy) for various reasons after receiving at least 1 cycle of chemotherapy. Due to time constraints, as the investigator was in an active clinical training program at the time of the pilot trial, patient counselling sessions were often brief. For the definitive trial we believe retention rates may be improved by allocating a dedicated investigator to ensure adequate counselling of patients at each treatment visit. An emphasis would need to be placed on addressing the potential reasons for study withdrawal, as identified in the pilot trial, including highlighting the possibility of device-related side effects and encouraging patients to report these as soon as they occur to allow early management, examples include the early use of analgesics and body warmers. Dedicating more time to probing reasons for patient withdrawal (from the pilot trial) may have assisted in determining such in the patients that chose not to offer a reason for withdrawal, however this had to be balanced with the ethics of respecting the right for patients not to offer a reason. Most of the patients that chose to shave their hair did so due to patchy CIA patterns that had a negative cosmetic effect, encouraging patients to use head covers instead of shaving may have reduced the need to shave in these patients. With regard to the missing pictures, the camera used for the trial was a shared resource within the department and some information was lost during the camera exchange process. A suggestion for a future trial is to obtain a camera that is solely dedicated to the study so as to limit the risk of losing information.

Generalizability

Although our data reflect the activities of only a single pilot trial; we believe that the findings and methods used are well suited to serve as a template for a future, definitive RCT as well as for analyzing other studies with different designs in other research settings.

Limitations

There are several limitations to this trial. It was a single-blinded design (because of the cooling) that had a relatively small sample size. Although it was determined that a relatively small number of patients (46) were required to provide adequate data, given that the chemotherapy regimens used are known to cause marked alopecia, we were unable to attain 46 as the intention- to- treat (ITT) sample size. Eight participants (4 in each group) dropped out before study initiation and clinical pictures of 3 participants in the cooling group could not be found leaving only 37 with analyzable results at the end of the trial. There was additional patient drop out through the cycles of chemotherapy, with a differential attrition noted in favour of the non-cooling group. It was not determined if this differential dropout led to biased results.

Conclusion
Our study findings suggest that scalp cooling is effective and hair curvature does not seem to impact the effectiveness of this intervention. A larger study is required to verify these findings.

2.7 Other information
Protocol
The protocol for this pilot trial, attached as supporting information, is based on the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Ethical approval
The University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (HREC) approved the study, HREC REF: 892/ 2016.

2.8 References

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2.9 Appendices

2.9.1 Study protocol

2.9.2 University of Cape Town Human Research Ethics Committee approval

2.9.3 CONSORT Checklist

2.9.1 Study Protocol

Does hair curl variation influence the efficacy of scalp cooling in the prevention of chemotherapy-induced alopecia in breast cancer patients? **A randomized controlled pilot study**

MMED Project: Dr Odirile Obuseng

Collaboration: Department of Radiation Oncology and Division of Dermatology, Groote Schuur Hospital and the University of Cape Town

Background

Chemotherapy is commonly administered as a treatment for cancer. It works by targeting all rapidly dividing cells in the body. Hair follicles contain the second fastest dividing cells in the body and thus many chemotherapy drugs induce hair loss.

The aim of chemotherapy is to damage mitotic and metabolic processes in cancer cells. Hair follicle cells are inadvertently affected resulting in significant alopecia most noticeable on the scalp where the majority (up to 90% of follicles) are in the active growth phase (anagen). The mechanism of alopecia includes treatment induced keratinocyte apoptosis, hair follicle regression, impaired metabolic and mitotic processes in hair follicles, all of which can result in rapid and extensive alopecia approximately 2 weeks after the commencement of treatment, particularly affecting the frontal or occipital areas of the scalp. (Komen, 2013:885)

Throughout history, 'healthy shiny hair' has been symbolic of good health, strength and sexual attractiveness. Conversely, loss of hair may give rise to psychosocial stress, including negative changes in body image, sexuality, self-esteem and disturbances in social relationships. (Massey, 2004:122) Chemotherapy Induced Alopecia (CIA), although reversible (with spontaneous recovery 3–6 months post chemotherapy in most cases), is still described as one of the most common and distressing side effects of cancer therapy, affecting approximately 65% of all patients and reportedly driving 8% of women to either reject chemotherapy or choose potentially less effective regimens that do not cause hair loss. (Kanti[i] et al., 2014:644)

Hair loss has also been reported to be associated with lower overall Quality Of Life (QOL). However, little is known about the effect on specific components of QOL. In qualitative studies, women have reported that alopecia is associated with a loss of privacy because it makes it known/obvious that they are receiving chemotherapy. It is also described as a visible reminder of the disease and confronts patients with the seriousness of cancer. Some patients commented that hair loss had an influence on their willingness to continue working or creating apprehension about returning to work. (Lemieux, Maunsell & Provencher, 2008:326) These negative impacts of CIA may contribute to poor therapeutic outcome, as stress may lower the body's immune function. (Luanpitpong & Rojanasakul 2012:53) Furthermore hair loss was found to contribute to depression, a disease associated with poor adherence to chemotherapy and risks of cancer progression. (de Souza et al., 2013:62)

Various preventive measures have been tried to reduce CIA: the tourniquet, pharmacological agents and scalp cooling. (Luanpitpong & Rojanasakul 2012:59) Currently, preventative measures mainly focus on scalp cooling. This is done either by using of a cooling agent (ice cap or gel cap) which is changed frequently or by continuous cooling of the scalp with cold air or liquid. (Grevelman & Breed, 2005:352)
Three mechanisms have been proposed to explain how scalp cooling works. Firstly, reducing the scalp temperature causes perifollicular vasoconstriction, reduces blood flow to the scalp to 20-40% of the normal rate and results in less chemotherapeutic drug delivery to the hair follicles. Secondly, cooling reduces the rate of drug diffusion across plasma membranes and thus lowers effective drug doses entering cells. Lastly, cell division is metabolism-driven, a process that is decelerated by cooling; this results in a general reduction in the cytotoxicity of chemotherapy drugs localized to the scalp. (Massey, 2004:123)

Results of a Dutch scalp cooling registry comprising of 1411 chemotherapy patients treated between 2006 and 2009, the majority of whom were women (96%) with breast cancer (86%), and treated in the adjuvant setting (69%), showed that alopecia requiring head cover (including wigs, scarves, hats, beanies, turbans and bandanas) did not occur in 50% of patients who received chemotherapy regimens that normally cause severe CIA. The authors suggest that faced with a 50% chance to keep their hair during chemotherapy, many patients would opt for scalp cooling. It is to be noted that the outcome parameters, head cover use and WHO Alopecia and Central Alopecia Severity Score, were used as a measure of scalp cooling efficacy in preventing CIA.

Use of head covering varied according to type and dose of chemotherapy. Results were best for monotherapy with low dose taxanes, in which 94% and 81% of patients on docetaxel and paclitaxel chemotherapy respectively wore no head cover. Results were worst for TAC chemotherapy (8%), despite the relatively low dose of taxane and anthracycline used in the combination therapy. Poorer protective scalp cooling results were shown in patients older than 65 years and those with 'Asian type' of hair. Longer 5-**F**luorouracil, **E**pirubicin and **C**yclophosphamide (FEC) infusion times were found to reduce the use of head covering; this observation had not been reported previously. Scalp cooling was stopped because of intolerance in only 3% of patients and notably no scalp skin metastases were reported. (van den Hurk et al., 2012:498)

Komen (2013:886) found that the effectiveness of scalp cooling in preventing CIA depends on many factors, including patient characteristics, chemotherapy characteristics, and the procedure used for scalp cooling. In terms of patient characteristics, this intervention was more effective in younger patients, in male patients, and in patients with a 'Caucasian type' of hair. A possible explanation offered for the lower effectiveness in patients with 'black African' hair is a thicker hair layer in this population; which may act as an insulating layer between the cooling cap and the scalp. The authors found three studies in which patients were randomized to chemotherapy either with or without scalp cooling. In these studies, minimal or no hair loss was seen in patients who received scalp cooling, in contrast to almost 100% alopecia for patients in the control groups. It was also observed that scalp cooling results were better with certain chemotherapy types, such as taxanes, and less favorable at higher doses of chemotherapy.

Scalp cooling was found to be generally well tolerated with results indicating low levels of discomfort and high acceptability with evidence of only minor and reversible side effects. The most common side effects include headaches, complaints of coldness and/or uncomfortable sensations, and claustrophobia.

A theoretical risk of scalp metastases has been highlighted with the theory being that any tumor cells that may have seeded in the scalp might not receive adequate chemotherapy during hypothermia, thus allowing them to grow at a later date. However, this side effect has rarely been reported in the literature. (Komen et al., 2013:886) In a review article by Breed et al. (2011:18) scalp skin metastases were found in nine patients out of a total of approximately 2500 patients in 56 scalp cooling studies. The authors concluded that it was very unlikely that scalp metastases were a result of scalp cooling. In a direct comparison, with a median follow-up of more than 5 years the incidence of scalp metastases was not significant in cooled versus non-cooled patients where 6 out of 553 (1.1%) and 1 out of 87 (1.2%) respectively developed scalp metastases.

In the first study of its kind, Lemieux et al. (2015:267) compared mortality among women

with non-metastatic breast cancer treated with chemotherapy who used scalp cooling to that of similar women who did not. They found no negative impact on survival for women who used scalp cooling with their chemotherapy. This data was deemed important as it provides new information about the safety of scalp cooling to clinicians, patients and health care system decision makers.

A recent comprehensive systematic review and meta-analysis that included 17 studies, 8 of which were randomized controlled trials (RCTs) with the remainder being controlled clinical trials (CCTs), by Shin et al. (2015:E442) found that scalp cooling significantly reduced (RR= 0.38, 95% CI= 0.32-0.45, p< 0.001) the risk of CIA. This study found that even though most of the studies evaluated did not perform randomization or use a double-blind approach, which is hard to perform with an intervention such as scalp cooling, the relative risk of CIA was reduced by approximately one third. The authors reported doxorubicin, daunorubicin, epirubicin, docetaxel and cyclophosphamide as the main chemotherapeutic agents inducing CIA. Scalp cooling was generally well tolerated but contraindicated in cases with cold sensitivity, cold agglutinin disease, cryoglobulinemia and cryofibrinogenemia. Due to the reported potential risk of scalp metastases the review advised against the use of scalp cooling systems in patients with circulating malignant cells, such as leukemia or lymphoma, who are receiving chemotherapy with curative intent. Caution was further advised in patients with solid tumors with strong skin metastatic potential, such as breast, lung, or gastric cancer. Monitoring the scalp for evidence of disease was recommended in this patient population.

Study Rationale

There is currently very good evidence for the efficacy of scalp cooling to prevent or reduce chemotherapy-induced alopecia in patients with breast cancer. However, it is not clear from published literature whether hair curl variation influences the efficacy of this intervention. Curly hair, which is generally associated with ‘African hair’ compared to the less curly ‘Asian and Caucasian hair’, (Bryant, Porter & Yang, 2012:8) contains higher amounts of internal lipids than straight hair which may influence incorporation of lipid soluble drugs and alopecia severity. (Robbins, 2012:143) Further, most published studies are from communities with very few participants who have tightly curly hair typical of African ancestry.

Aim

The aim of this study is to evaluate whether hair curvature influences the ability of scalp cooling to reduce chemotherapy-induced hair loss in breast cancer patients.

Objectives

The objectives are to assess whether:

1. The severity of alopecia after chemotherapy is less in participants receiving scalp cooling versus those that are not
2. The severity of alopecia after chemotherapy in the scalp cooling group is worse in those with curly compared to straight hair.
3. The severity of alopecia correlates with hair chemotherapy levels and drugs levels are lower in patients receiving scalp cooling versus those that are not

Significance of study

This study is a pilot that initiates the exploration of whether hair curvature has an impact on the efficacy of scalp cooling. It is also potentially a step towards extending to Africans a technology that has benefited patients in developed countries for more than a decade especially in Europe. In America, scalp cooling has not been routinely offered mainly because of concerns about cost, its efficacy in preventing hair loss and potential risks of increased scalp metastases and thermal injury. Thus, scalp cooling is not recommended with chemotherapy as standard of care in international guidelines; however, this is likely to change with the recent FDA approval (2015) (U.S. Food & Drug Administration [FDA], 2015. The outcomes of this study are expected to provide early insights on whether currently published results of this intervention can be generalized and whether improved access to this treatment would benefit patients with Afro-textured hair.

Definitions

Chemotherapy-induced alopecia: Hair loss following the administration of chemotherapeutic agents for the treatment of cancer. This may vary from slight thinning of the hair to complete baldness. The extent of hair loss is affected by the choice of drug and its dose.

Hair curvature: Allocation was made based on macroscopic appearance of hair as naturally straight or curly.

Scalp cooling: A technique used for the prevention of chemotherapy-induced alopecia. This is achieved by causing scalp hypothermia through a cooling agent (ice or gel cap, cold air or cold liquid) using various procedures.

Abbreviations:

CBC: Combined Breast Clinic
CI: Confidence Interval
CIA: Chemotherapy Induced Alopecia
FEC: A combination of 5 **F**luorouracil (also known as 5FU), **E**pirubicin and **C**yclophosphamide chemotherapy
GSH: Groote Schuur Hospital
HPLC: High Performance Liquid Chromatography
LC: Liquid chromatography
MS: Mass Spectrometry
PI: Principle Investigator
QOL: Quality Of Life
RR: Relative Risk
TAC: A combination of **T** – Docetaxel (also called **T**axotere), **A** – Doxorubicin (originally called **A**driamycin) and **C** – **C**yclophosphamide chemotherapy
WHO: World Health Organization

Keywords: alopecia, breast cancer, chemotherapy, chemotherapy-induced alopecia, efficacy, hair curvature, scalp cooling

Methods

Study Design

This is a pilot monocentric, prospective, investigator initiated, randomized (patient) controlled single blind (three independent dermatologists) study of scalp cooling versus no cooling in breast cancer patients receiving adjuvant chemotherapy in a 21-day cycle. Equal randomization (1:1) will be employed. The study will be conducted in cooperation between the Department of Radiation Oncology Breast Clinic and the Division of Dermatology at Groote Schuur Hospital.

Study Population

52 female patients with breast cancer, who are due to receive similar adjuvant chemotherapy (AC and Paclitaxel), as outpatients, will be enrolled in this study from the Groote Schuur Hospital breast clinic. The treating Radiation Oncology doctor (consultant, registrar or medical officer), based on the departmental protocol, will determine and prescribe the chemotherapy regimen for each patient.

Inclusion criteria:

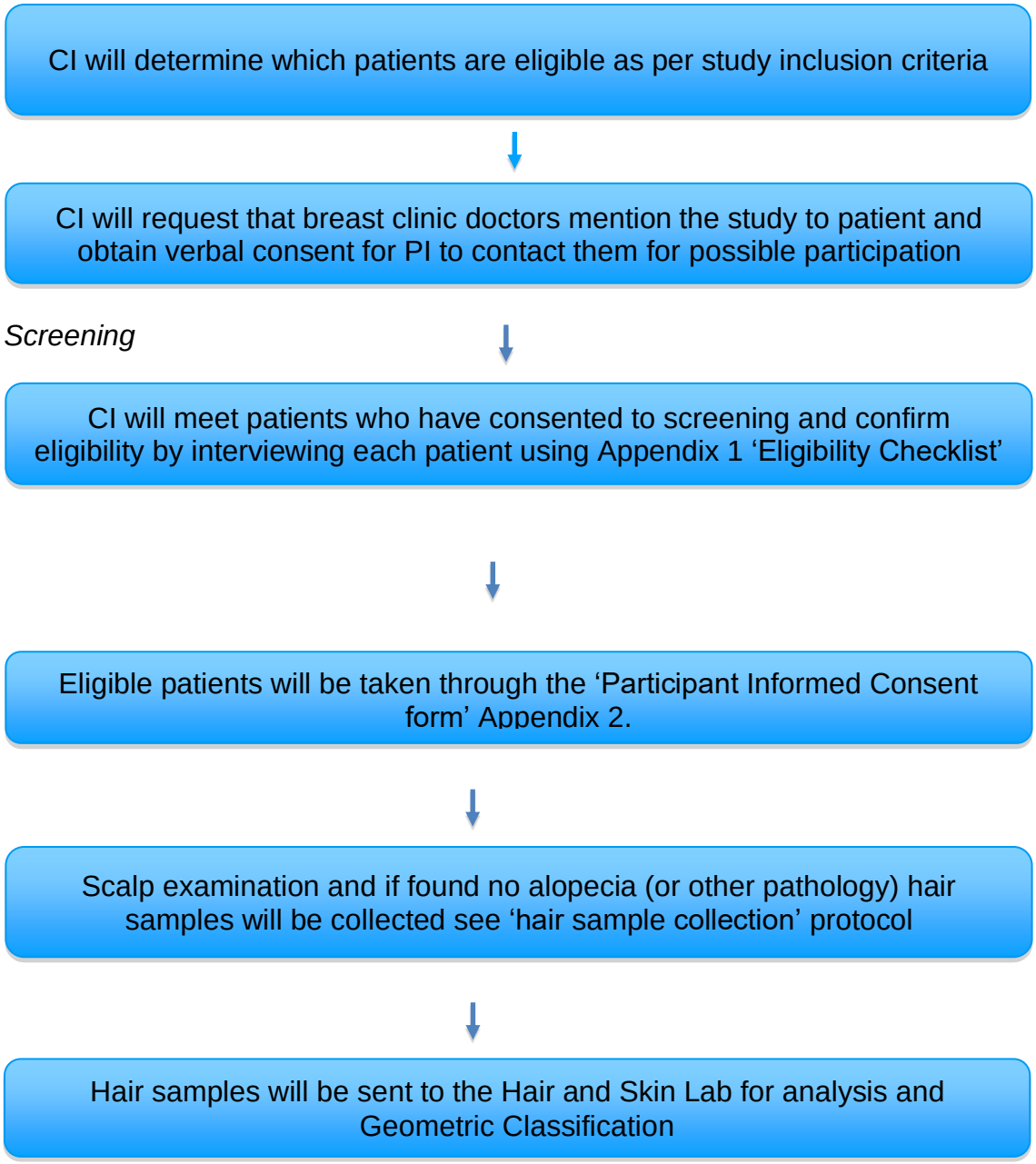
(i) Female sex
(ii) Age 18–65 years
(iii) Removal of a breast cancer through mastectomy or breast conserving methods (with or without lymph node removal) < 12 weeks before inclusion
(iv) Planned antineoplastic therapy with chemotherapy (Adriamycin and Cyclophosphamide followed by Paclitaxel) including written consent

Exclusion criteria:

(i) Evidence of alopecia at baseline
(ii) Planned radiation therapy of the skull before or during the study
(iii) Antineoplastic therapy within 6 months prior to baseline
(iv) Inadequately treated hypo or hyperthyroidism
(v) Known cold sensitivity, cold agglutinin disease, cryoglobulinemia and cryofibrinogenemia.
(vi) Participation in another study.
(vii) Unwillingness to participate in the study or withdrawal of consent before the first post treatment assessment. All post treatment data will be included in the analysis.

Method of recruitment and Pre-screening

Co- Investigator (CI) will request, from the breast clinic secretary, the files of all Post-operative patients. This will take place on Mondays (the day prior to the scheduled bookings for these patients

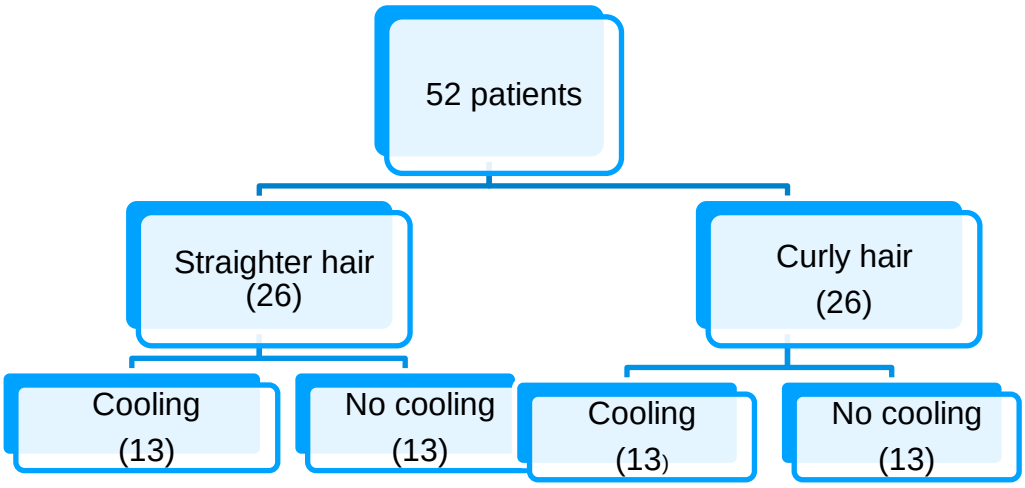


Randomization

From the literature review no specific risk factors for CIA could be identified. However, the following patient characteristics were found to influence the effectiveness of scalp cooling: age- it was found to be more effective in younger patients with inferior protective results shown in patients older than 65 years, gender and hair type- it was more effective in males and participants with a 'Caucasian hair' type. Komen (2013:886) In this study, gender will not have an impact as only women will be recruited. Hair type assessment at inclusion be macroscopically (straight/wavy or Afro-textured) and later in the lab will be determined

objectively using the 'Geometric Classification' and the rate and severity of alopecia within the different hair types forms the primary objective of the study. As age was found to have an impact on the efficacy of scalp cooling patients will be randomized between the groups through stratified randomization. After the participants have been assigned a group, based on their hair type, they will be randomized to scalp cooling or no scalp cooling. Sequence generation will be done using the online program 'Research Randomizer' (https://www.randomizer.org). Sequences will then be concealed in numbered, sealed, opaque envelopes.

Study allocation



Assessments

Visit 1

a. Questions relating to hair-care (use of temporary and permanent cosmetic hair chemicals) will be completed by participants. These will specifically include: most recent use of chemicals that alter hair curl and/or curl (relaxers, hair dyes and high-lights) and frequency within the last year.

b. Standardized clinical photographs of 4 views of participants' heads (forward with chin touching chest, left, right and back views with head straight ahead); taken with a black background. The camera should be on the macro setting, the flash on automatic and the distance of the camera from the participants' head at 50cm.

c. Scalp cooling

- The Paxman Scalp Cooling system will be switched on and allowed to reach operating temperature. This takes approximately 30 to 40 minutes.
- The appropriate sized cooling cap will be selected for each patient, ensuring good contact with the scalp
- The cap will be connected to the system and placed on the patient's head.
- The scalp will be pre-cooled for 30 minutes prior to commencement of drug infusion. This ensures the scalp is at the required temperature before chemotherapy is administered. The cap will be worn throughout the administration of chemotherapy

and for 90 minutes afterwards.

See Appendix 4: 'The Paxman Scalp Cooling System Overview and Clinical Efficacy Studies' for full details on the system.

Visit 2 – Visit 8

1. All participants will answer the following questions:
   a. Have you noticed hair loss?
   b. Do you have to cover your hair because of hair loss?
   c. Have you experienced any side effects since your last chemotherapy session? If so, please indicate these
   d. Have you dyed, bleached of chemically straightened your hair since the visit

2. Hair sample collection

   Approximately 150 - 200mg of proximal hair of at least 6 cm long will be sampled from the vertex of the scalp. The hair will be cut as close to the scalp as possible and the collected samples aligned in the same direction from root to end, labelled with a unique identifier code and stored in a dry place at ambient temperature in aluminum foil, an envelope or a plastic bag. Sample collection will be performed by a skilled clinician and a skilled scientist. Before sample analysis, hair will be decontaminated using standard protocols of washing and drying.

3. Standard photography (b. above – ideally at each visit)

4. Scalp cooling (c. above)

The above data will be captured on a 'Visit Data Sheet' (Appendix 5)

Clinical photographs (alopecia severity grading)

A photograph-based scale will be used to grade submitted clinical photographs from study sites for alopecia severity. Three dermatologists not involved in (and blinded to) the study will grade photographs using the *Severity ALopecia Tool* (SALT) Score Agreement in 2/3 or all 3/3 will be used to allocate severity. (Olsen et al., 2004:442)

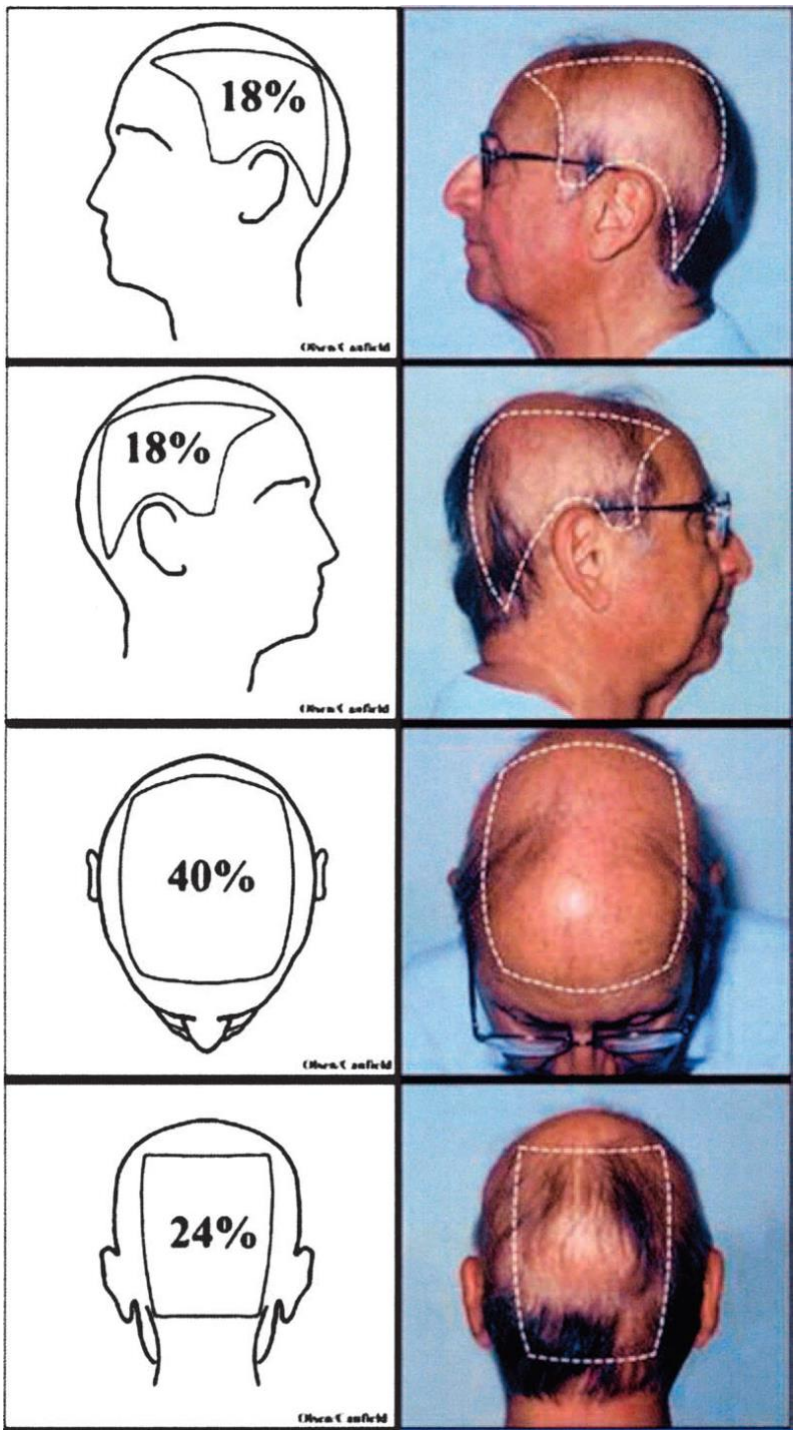


Image (Olsen et al., 2004:443). *Right: Photographs will be taken of the four views for analysis by the evaluators. Left:* Severity ALopecia Tool *(SALT) score. The percentage of hair loss in any one of the four views (areas) of the scalp = the percentage hair loss X percent surface area of the scalp in that area. The SALT score then equals the sum of the scalp hair loss in each area.*
(a) Top (left side view) = 95% X 0.18 = 17.1
(b) Second (right side view) = 90% X 0.18 = 16.2
(c) Third (top of scalp) = 95% X 0.40 = 38
(d) Bottom (back of scalp) = 55% X 0.24 = 13.2
a+b+c+d = 17.1 + 38 + 16.2 + 13.2 = 84.5% hair loss or SALT 84.5

Data Management and Analysis

Sample size calculation

A sample size of 44 participants (power 80% at 5% significance level. Based on a 50% reduction in the incidence of CIA. (Trüeb, 2010; van den Hurk et al., 2012:500). Fifty two patients will be included to accommodate potential study dropout.

Results will be entered into the Stata program and be cross tabulated to analyze results between the groups.

Relative Risk (RR) calculation
The RR will be calculated (95%CI) using the STATA software.

Intention-to-treat analysis
Data from all randomized participants will be included in the analysis. Participants will all be retained in the group to which they were allocated.

Outcomes/ Endpoints
The primary combined endpoint of the study is the incidence and severity of alopecia after each cycle of chemotherapy. Further endpoints will comprise the correlations of alopecia severity with hair chemo levels and hair curl variation. incidence and severity of alopecia after completion of 4 cycles of each regimen (i.e. AC and Paclitaxel.),

Ethical considerations

Scalp cooling is an established safe method of reducing and even preventing chemotherapy induced alopecia. The method is associated with minimal adverse effects (related to the cold cap), the intervention is not associated with scalp metastasis or poorer treatment outcome. All patient personal and clinical data will be kept confidential. No participants below the age of 18 will be enrolled in the study and thus all participants will be able to sign their own written consent. The consent form (Appendix 2) will be translated into isiXhosa and Afrikaans for the study.

Participants will be able to, at any time during the study period, terminate their participation without any negative consequences to them. The study is Investigator Initiated and no monetary sponsorship will be provided by a third party. Paxman Coolers Ltd. have agreed to engage in a loan agreement for two Paxman Scalp Cooling Systems for the duration of the study.

Informed Consent

In the recruitment stage, patients will be informed of the purpose of the study, eligibility, the procedure, expected risks, benefits and time commitment. Patients will be informed that participation is voluntary and that they have the right to withdraw without reason at any stage of the study. As recruitment will be done by a health professional in the clinic, patients may be subject to institutional vulnerability and may feel obligated to participate. To address this, participants will be informed that whether or not they choose to participate in the study, their current and future treatment will not be impacted. Patients will be given time to consider all the information presented before they provide written consent. No participants below the

age of 18 will be enrolled in the study and thus all participants will be able to sign their own written consent.

Risks and Benefits
Scalp cooling is an established safe method of reducing and even preventing chemotherapy induced alopecia. The method is associated with minimal adverse effects (related to the cold cap), the intervention is not associated with scalp metastasis or poorer treatment outcome.

The benefit to the patient is hair preservation, while on a larger scale, the findings of this study will add to the body of knowledge on scalp cooling from an African setting.

Privacy and confidentiality
All patient personal and clinical data will be kept confidential. A unique identifier code will be assigned to each participant and all data collected for the study i.e. questionnaires and hair samples. A database maintaining participant names and the unique identifier codes assigned to them will be kept and made accessible only to the principal investigator. All forms and questionnaires will be filed in a locked cabinet.

The approval of the Health Sciences Human Research Ethics Committee will be sought before data collection commences.

The study is Investigator Initiated and no monetary sponsorship will be provided by a third party. Paxman Coolers Ltd. have agreed to engage in a loan agreement for two Paxman Scalp Cooling Systems for the duration of the study.

Remuneration

All participants will be attending routine clinic and will not be paid, but will receive an equivalent of transport money or lunch.

Time frame

Once approval has been granted by the University of Cape Town Ethics Committee and the GSH Hospital Research Directorate the study start date will be agreed upon by the various role players including the relevant staff in the Department of Radiation Oncology and Division of Dermatology. Patient recruitment will run over a 4-8 week period. The study will be completed approximately 7-8 months after the recruitment phase. This timeframe is consistent with the treatment period (of 6 months) for the chemotherapy regimen stipulated in the inclusion criteria i.e. AC and Paclitaxel, with a 1-2-month provision period factored in for any unanticipated delays in therapy.

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Appendix 1: Eligibility checklist

Date (dd/mm/yy) **Participant screening ID**

Introduction
I am Dr Odirile Obuseng, a Medical Officer in the Department of Radiation Oncology at Groote Schuur Hospital. I am part of a research team that hopes to learn more about an intervention to prevent hair loss caused by chemotherapy called scalp cooling. I am asking women with breast cancer, who have recently had surgery and will be receiving chemotherapy as part of their treatment, if they would be willing to participate in this study

Question	**Response**	
May I ask you a few questions to see if you are able to participate in the study?	Yes □	No □ If no, stop here.
Are you between the ages of 18 and 65 years?	Yes □	No □ If no, stop here.
Are you comfortable speaking in English, Afrikaans or isiXhosa?	Yes □ Preferred language: _____	No □ If no, stop here.
Was your operation for breast cancer less than 12 weeks ago?	Yes □	No □ If no, stop here.
Have you agreed to and signed consent to receive chemotherapy (Adriamycin and Cyclophosphamide followed by Paclitaxel) for your breast cancer?	Yes □	No □ If no, stop here.
Have you had any Radiation Therapy to your skull in the past? Have you been told by a doctor that you will Radiation Therapy to your skull whilst you are receiving chemotherapy?	Yes □	No □ If no, stop here.
Have you received any treatment for cancer in the last 6 months?	Yes □	No □ If no, stop here.
Have you ever been told by a doctor that you have thyroid disease?	Yes □	No □ If no, stop here.

Do you have any conditions which are worsened by cold conditions?	Yes □	No □ If no, stop here.
Are currently taking part in any other clinical trial/ study?	Yes □	No □ If no, stop here.
Eligibility	□ **Eligible**	□ **Ineligible**
Researcher Name		
Signature		

A 'no' response to any of the following questions means an individual is ineligible to participate in the study.
If an individual is eligible, informed consent will be obtained.

Appendix 2: Participant Informed Consent Form

Participant informed consent form

Explanation of the study

The Department of Radiation Oncology and the Hair Clinic (part of the Division of Dermatology) at Groote Schuur Hospital hopes to study the prevention of hair loss caused by chemotherapy treatment for breast cancer by using a new method called scalp cooling. The equipment works by reducing the temperature of the scalp during chemotherapy infusions and has been in used successfully for more than 10 years in Europe where patient using scalp cooling had reduced hair loss from cancer treatment. Scalp cooling studies have included mostly patients with straight hair and we would like to test whether it can help to prevent hair loss to the same extent in patients with curly hair, the majority of patients in our clinic. We are inviting women with breast cancer, who will be receiving chemotherapy as part of their treatment to participate in this study.

Study procedure

In this study, you will be asked to complete a brief questionnaire with some personal information, containing short questions about your background and your hair. At each subsequent visit, you will be asked if you are experiencing hair loss. Detailed information regarding your disease and treatment will be obtained from your file. A few hair strands will be cut from your head today and at each chemotherapy visit and these will be sent to the laboratory to analyze your hair type and chemotherapy levels in your hair. Based on your hair type you will be assigned to a group and allocated a unique number. Depending on your group you may or may not be using scalp cooling equipment during your chemotherapy treatment. If you are in the group that will undergo scalp cooling the following process will apply:

- The cooling system will be switched on and allowed to reach the correct temperature.
- The correct size cooling cap will be selected for you, ensuring good contact with the scalp
- The cap will be connected to the system and placed on your head.
- The scalp will be pre-cooled for 30 minutes before the chemotherapy. You will keep wearing the cap throughout the administration of chemotherapy and for 90 minutes afterwards.

If you are not in the group that will undergo scalp cooling, you will receive only routine chemotherapy treatment.

Photographs of your head will be taken at each treatment visit and these will be sent to a group of dermatologists who will assess if and how much hair loss you experience due to chemotherapy.

Participants' rights
Your choice to participate (or not participate) in this study is voluntary and the responses you provide will not have any influence on the treatment you are receiving and/or follow-up care in the future. I will be taking notes and recording our discussion to make sure I have a record of everything we have discussed. All the notes and recordings will be kept confidential and your name will not be used with the results of this study.

Expected benefits
We hope this study will further improve healthcare standards, by allowing the health and scientific community to gain information about whether scalp cooling can help to prevent chemotherapy related hair loss in patients with curly hair to the same extent as it has been shown to do so in patients with straight hair. While we intend that this research will further increase knowledge regarding this intervention in our setting, it may not benefit you directly.

Expected risk and discomfort
Scalp cooling has been shown to be a safe method of reducing and even preventing chemotherapy induced hair loss. Although side effects are not common with scalp cooling some patients may experience headaches, feel cold and/or have an uncomfortable sensation and claustrophobia (a fear of being in a confined space). In theory there is also a small risk of cancer spread to the scalp because during cooling the amount of blood carrying chemo to the scalp is reduced; however published studies have not reported patients in whom this occurred.

Expected time commitment
The first visit which includes written consent, completion of a questionnaire and hair sampling is expected to take a maximum of one hour. Subsequent visits are expected to last approximately 4.5. to 5 hours as they include scalp cooling.

Costs
All participants will be attending routine clinic and will not be paid, but will receive R50 at each visit, an equivalent of transport money or lunch.

Confidentiality
Your information will always be kept confidential and will only be identified by a unique study number and your initials. Your name or any other personal identifying information will never be used in reports or publications resulting from this study. Moreover, some information about your treatment and background will be checked against your clinical records only by the researcher. By signing this informed consent form, you authorize the researcher to obtain some information from your medical record.

Right to refuse or withdraw
The choice to enter or not to enter this study is yours only. If you participate in the study, you always have the right to withdraw at any time without penalty or loss of the benefits or the rights as a patient at this health facility.

Additional information

This research has been assessed and approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee. For any further information, you may contact Dr Odirile Obuseng- Medical Officer: Department of Radiation Oncology. (021) 404 4280 or odiobu@gmail.com
In case you have any ethical concerns or questions about your rights or welfare as a participant in this research, you may contact Professor Marc Blockman, Chairperson, Human Research Ethics Committee, University of Cape Town, 021 406 6626 or marc.blockman@uct.ac.za

……
If you wish to participate in this study, please sign below:
Participant

_____ _____
Name and surname Signature

_____
Date

If unable to write a thumb-print is requested
A witness (preferably selected by the participant with no connection to the research team) could sign on behalf of the participant.

I have witnessed the process and confirm that participant has given consent freely.

Print name of witness_____ **AND** **Thumb print of participant**

Signature of witness _____

Date _____
Day/month/year

Researcher

_____ _____
Name and surname Signature

_____
Date

Appendix 3: Data Capture Form

Participant enrolment number	**Participant Initials**

Date of enrolment (dd/mm/yyyy)

1. **Age**
    a) Date of birth (dd/mm/yyyy) _____
    b) Age at diagnosis_____
2. **Gender**
    a) Male
    b) Female
3. **Past medical history**
4. **Have you used chemicals that alter your hair curl in the last 3 months?**
    a) Yes – (please tick: relaxers or perms)
    b) No
5. **Have you used chemicals that alter hair color in the last 3 months?**
    - Yes – (please tick: dye or bleach/high-lights)
    - No
6. **Surgical procedure (From hospital records)**
    (i) Date of surgery
    (ii) Surgical procedure:
        a) Mastectomy with no sentinel lymph node biopsy or nodal clearance
        b) Mastectomy and sentinel lymph node biopsy
        c) Mastectomy and axillary nodal clearance
        d) Wide local excision with no sentinel lymph node biopsy or nodal clearance
        e) Wide local excision and sentinel lymph node biopsy
        f) Wide local excision and axillary nodal clearance
7. **Histological type**
        a) Ductal carcinoma in situ (DCIS)
        b) Lobular carcinoma in situ (LCIS)
        c) Invasive
        g) Infiltrating Ductal Carcinoma (IDC)
        h) Infiltrating Lobular Carcinoma (ILC)
        d) Primary lymphoma
        e) Angiosarcoma
        f) Malignant phylloides
        g) Carcinosarcoma/metaplastic
8. **Stage (pathological)**
    a) Stage 0
    b) Stage I
    c) Stage II

i) IIA
j) IIB

d) Stage III
k) IIIA
l) IIIB
m) IIIC

e) Stage IV

9. Immunohistochemistry subtype

a) Luminal A
b) Luminal B Her2 negative
c) Luminal B Her2 positive
d) Her2 overexpressed
e) Triple Negative
f) Indeterminate
g) Other

10. Tumour grade

a) Grade 1
b) Grade 2
c) Grade 3

11. Performance status

a) 0- normal
b) 1- Symptomatic but ambulant
c) 2- In bed <50% of the day
d) 3- In bed > 50% of the day
e) 4- In bed 100% of the day
f)

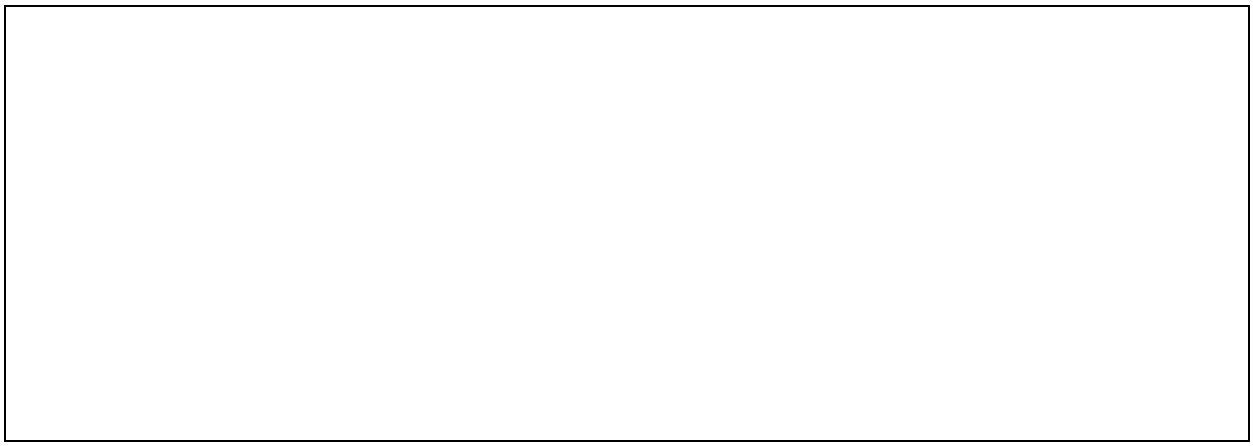
12. Smoking history

a) Non-smoker
b) Current smoker
c) Ex-smoker

13. Chemotherapy regimen and dose prescribed (check √)

	1. AC (Adriamycin 60mg/m^2 and Cyclophosphamide 600 mg/m^2)
	2. Paclitaxel 175mg/m^2

14. Additional notes



Appendix 4: Visit Data Sheet

Visit Data Sheet

Participant enrolment number **Participant Initials _____**

Visit Number (circle) 2 3 4 5 6 7 8

Date (dd/mm/yyyy)

1. Procedures completed during visit (tick all that apply):

	Hair sample collection
	Standard photography
	Scalp cooling

2. Have you noticed hair loss?

a) Yes
b) No

3. Do you have to cover your hair because of hair loss?

a) Yes
b) No

4. Have you dyed or bleached of chemically straightened your hair since the visit?

a) Yes

b) No

5. Have you chemically straightened or permed your hair since the visit?

a) Yes

b) No

6. **Did you experience any side effects? If yes, record below:**

2.9.2 HREC approval

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences

Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone (021] 406 6492
Email: sumayah.ariefdlennuct.ac.za
Website: www.health.uctac.za/fhs/research/humanethics/forms

13 December 2016

HREC REF: 892/2016

Prof N Khumalo
Division of
Dermatology G-
23
NGSH

Dear Prof Khumalo

PROJECT TITLE: DOES HAIR CULR VARIATION INFLUENCE THE EFFICACY OF SCALP COOLING IN THE PREVENTION OF CHEMOTHERAPY-INDUCED ALOPECIA IN BREAST CANCER PATIENTS? A RANDOMIZED CONTROLLED PILOT STUDY (MMeD-candidate-Dr 0 Obuseng)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study, subject to adding the UCT FHS no Fault Insurance clause.

Approval is granted for one year until the 30 DECEMBER 2017.

Please submit a progress form, using the standardized Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF In all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal Investigator.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON. FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number:
IRB00001938

HREC 892/2016

2.9.3: CONSORT Checklist

CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance seeCONSORT abstract extension for pilot trials)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilottrial	3
	2b	Specific objectives or research questions for pilot trial	4
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	4
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
	4c	How participants were identified and consented	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they wereactually administered	5
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	6
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	N / A
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	N / A
Sample size	7a	Rationale for numbers in the pilot trial	6

	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers),describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	1
	11b	If relevant, description of the similarity of interventions	5
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	8
	13b	For each group, losses and exclusions after randomisation, together with reasons	9
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the pilot trial ended or was stopped	9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	10
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbersshould be by randomised group	11
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	11
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	13

Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	13
	19a	If relevant, other important unintended consequences	14
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	16
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	16
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, andconsidering other relevant evidence	14
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	16
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	1
Protocol	24	Where the pilot trial protocol can be accessed, if available	17
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1
	26	Ethical approval or approval by research review committee, confirmed with reference number	1