The systematic review (appendix 4)

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SCoR
THE SOCIETY & COLLEGE OF RADIOGRAPHERS

The Society and College of Radiographers

Practice Guideline Document

Radiation Dermatitis Guidelines for Radiotherapy Healthcare Professionals

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Contents Page

Oncology Nursing Society (UKONS) colleagues have been involved in the writing of this document and UKONS recognises it as expert guidelines.

Executive summary

The Society and College of Radiographers (SCoR) has a responsibility to provide national guidance promoting equitable and consistent practice across the UK, informing policy and standards. All patients have the right to receive a high standard of evidence-based care irrespective of where they receive their treatment. This guidance is based on an expert consensus and review of the available evidence base; it supports the need for further research into new products before they are recommended for radiotherapy skin care.

Skin reactions from external beam radiotherapy are a common side effect of treatment and may cause distress to some patients; a skin reaction may also be a factor that can limit radiation dose and treatment schedules.

It has been widely acknowledged that despite the publication of a number of best practice guidelines for skin care, radiotherapy departmental practice with respect to the prevention and management of acute radiotherapy and skin toxicity has been slow to change. A wide variety of methods and topical applications are still utilised at a local level, often with very little or no evidence base.

Hence, the purpose of this current review was to determine if new research evidence had emerged that could improve skin care practices in radiotherapy. This systematic review aimed to assess the effectiveness of interventions and practices that may prevent, reduce (or alter) radiation induced skin reactions (RISRs) in patients undergoing external beam radiotherapy for cancer, with an emphasis on research published since November 2014. The review proposal was registered on PROSPERO: International prospective register of systematic reviews (CRD42019148161).

Despite reviewing a significant amount of published evidence, still very few definitive recommendations can be made with respect to the optimal intervention for the management or prevention of radiation induced skin reactions.

The use of steroid-based creams is the one area where evidence shows consistent positive benefit across studies assessed as having a low risk of bias. However, it is important to note that even in cases where positive results were presented, those benefits may not be translated to cases where hypofractionated dose schedules are employed or where the comparator does not include a cream considered to potentially cause irritation. Therefore, the use of steroid-based cream is only recommended for RISR prevention in patients assessed as being at high risk of developing a high-grade radiation dermatitis.

Barrier films and dressings still seem to be widely used. However, the results of studies included in this review are not significant enough to recommend a change in practice. This is partly due to limitations in the design of some of the studies, as well as the variety of products investigated, the high drop-out rate in some cases (due to tolerability of the product), and the limited positive outcomes presented in some studies.

Photobiomodulation therapy (PBMT) is an emerging intervention to reduce RISR. The use of PBMT has been recognised in other areas of radiotherapy toxicity, such as the treatment of oral mucositis and lymphoedema. Further research is needed on the long-term effects of the use of PBMT as a prophylactic intervention for RISRs before it could be recommended for widespread use and future research should consider assessment of patients having modern dose fractionation schedules.

A significant amount of research is still being undertaken to investigate topical emollients, as shown by the number of such studies included in this review and trials currently recruiting participants.

However, these are often single institution studies of one particular product, and as more enter the market the research base is spread across a number of small sample studies of different products. Hence, the review team are unable to draw confident conclusions as it is not possible to pool data in the form of a meta-analysis. Therefore, there is still not enough strong evidence to recommend or endorse any one specific product.

In addition, some of the issues highlighted by the review team with respect to study design and analysis only add to the uncertainty, with a lack of reporting or stratifying for many of the possible patient-related variables as well as variations in radiotherapy technique, planning and dose fractionation regimens.

There may be benefits to risk stratifying patients to allow those at high risk of developing severe (or high-grade) radiation dermatitis to be treated with appropriate interventions. For example, there may be cases where it is appropriate for patients to use steroid cream, but currently there is limited data to confirm exactly which groups of patients with specific levels of risk would benefit. Choice of a control or placebo also requires careful consideration and justification within the research method. As identified in this review, some researchers adopted a cream for the comparator that may exacerbate skin irritation experienced by the control arm and thus may invalidate or limit the usability of the study results.

A wide variation in the timing of the assessment of skin reactions was observed, making it difficult to make comparisons across studies, and very few of the studies reviewed included assessment of inter- and intra-rater reliability of the clinician assessed reactions; where this was undertaken, poor reliability of the assessment process was evident. Furthermore, in the topical emollient studies reviewed, patient adherence to the intervention was rarely assessed; patient compliance is an important consideration when considering changes to practice, along with cost and resource use.

In light of these concerns, the review team have therefore produced a set of recommendations for skin care research design, based on the assessment of the existing literature. In order to move the evidence base forward for interventions to prevent or treat RISRs we need high-quality research studies and we would recommend that researchers in this field try to implement some of the recommendations when designing future studies.

Overall, the evidence base is not strong enough to either support or refute the use of any particular product for topical application.

These clinical practice guidelines are a set of evidence-based recommendations to support radiotherapy healthcare professionals in advising patients about skin care and radiation dermatitis. They have been developed systematically using evidence from research and expert opinions, and have been subjected to peer, professional and lay assessment. They include guidance on assessing and managing radiation induced skin toxicity. These guidelines would be of value to individual practitioners, service managers and academic institutions.

The following eight key principles of effective skin care management are recommended:

1. Knowledge of intrinsic and extrinsic factors that may affect the development and severity of radiation dermatitis. Prior to the start of radiotherapy, patients should be identified as being at low, medium or high risk based on intrinsic and extrinsic factors.

2. Documentation of current skin care regimen and existing skin conditions, including sensitivities and allergies to certain products.

3. Use of a standardised tool for radiation dermatitis assessment of all patients undergoing a course of radiotherapy. Using the agreed validated tool and scoring criteria, radiotherapy departments should standardise the initial assessment and continued regular monitoring of skin reactions, and ensure that these are recorded.

4. Adherence to a standardised assessment process that includes a baseline assessment and weekly assessments during treatment using the standardised assessment tool.

5. Mandatory local training for all staff assessing skin toxicity, to ensure accurate reporting and maintenance of consistent management protocols.

6. Regular audit of skin reactions to collate accurate data on frequency and severity.

7. An emphasis on empowering patients to use products they are familiar with and to self-monitor their skin, being proactive to improve comfort and minimise the risk of developing severe skin reactions. Recording of patient acceptability/satisfaction and compliance with skin care advice is recommended as such information can be used to evaluate the appropriateness of skin care products for future patients.

8. Testing within a well-designed randomised controlled trial any new product or device designed to reduce radiation dermatitis, before its implementation.

1. Introduction

1.1 How was the topic identified?

Since publication in 2015, a variety of new skin care products have emerged on the market, while some previously used products have been removed by pharmacy suppliers. Technological developments, such as proton therapy and innovative treatment techniques, have become more widely used in the UK. Therefore, a review of the 2015 skin care guidelines (SCoR, 2015) was necessary, alongside the recommendation in the guidelines themselves to perform regular reviews in order to remain consistent with current evidence.

1.2 Why is it important?

Skin reactions from external beam radiotherapy are a common side effect of treatment and may cause pain and distress to some patients; a skin reaction may also be a factor that can limit radiation dose and treatment schedules (Royal College of Radiologists, 2008).

Radiotherapy delivered in the megavoltage range using modern equipment has skin sparing properties that significantly reduce the severity of reactions from this type of treatment (Harris, 2002b). The use of immobilisation devices (as frequently used in head and neck radiotherapy) will cause this skin sparing effect to be lost.

The use of accelerated radiation dose schedules and the concurrent use of chemotherapy or biological agents, such as epidermal growth factor receptor (EGFR) inhibitors, will also lead to an increase in skin reactions (Bernier et al., 2008). The most severe reactions tend to be seen in those patients receiving high doses to large fields and where there are folds of skin (for example inframammary fold, groin, axilla) (Porock et al., 1998; Richardson et al., 2005). Bolus material is still frequently used, especially for some breast cancer treatments, and this will also increase skin toxicity rates.

The use of intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) offers the potential to reduce skin toxicity in some cases by increasing the number of beams and simultaneously reducing the dose contribution from each beam. The reduction in rates of dry and moist desquamation when using IMRT is particularly well demonstrated when treating cancers in the head and neck region (Freedman et al., 2004; Harsolia et al., 2006; Price et al., 2006; Freedman et al., 2006; Harsolia et al., 2007; Pignol et al., 2008; Freedman et al., 2009; Ciammella, et al., 2014). Despite these reductions, significant acute toxicity is still often observed when treating head and neck cancers.

Proton beam therapy has the potential to cause more severe skin reactions due to loss of the skin sparing effect when using protons, and protons can be used for dose escalation. The difference in skin reactions compared to photons is due to the variations in beam characteristics, beam dosimetry and beam arrangement. With the opening of proton beam centres in the UK, it is expected that reported toxicities associated with proton therapy will be researched and published.

Results from large scale multicentre trials have led to adoption of hypofractionation (using fewer doses of radiotherapy at higher dose per fraction), particularly in the common cancers of breast and prostate, will also change the pattern of observed skin toxicity.

Despite changes in radiotherapy practice and numerous published skin care guidelines (NHS Quality Improvement Scotland, 2004; SCoR, 2001; NHS Quality Improvement Scotland, 2010; SCoR, 2011a, 2015), patient skin care appears to have changed little over time, with no consensus among centres

on product use, approaches, and skin care regimens (Barkham, 1993; Harris, 2002a; Harris et al., 2012).

Complete prevention of skin reactions seems unlikely, but there should be a constant drive to delay onset and minimise the severity of a reaction, to reduce discomfort and prevent further complications. Radiobiologically, skin reactions tend to peak towards the end of the treatment course and are often at their worst in the first two weeks after treatment has completed. Skin reactions may be acute or chronic, but currently there is insufficient data to indicate if acute reactions are more common than chronic. The extent of a skin reaction is often dependent upon clinical factors (see section 1.5.2), making patients more vulnerable to intensified skin reactions and possible interruptions in radiotherapy, which can have a detrimental effect on treatment outcome (RCR, 2008).

Radiation may cause chronic late effects as well as acute reactions. Late skin reactions may be characterised by fibrosis of subcutaneous tissues, and telangiectasia. Advice on the management of late effects is beyond the scope of this document. However, there is a lack of evidence that links acute reaction severity to the risk of chronic late effects and this would merit further investigation.

1.3 How does it fit with existing radiotherapy practice?

The SCoR and the United Kingdom Oncology Nursing Society (UKONS) offer advice and guidance for professional development to promote patient-centred care and the highest quality services. The SCoR document library contains policies, advice and guidance on a range of topics.

1.4 The policy context

The SCoR has a responsibility to provide national guidance promoting equitable and consistent practice across the UK, informing policy and standards. All patients have the right to receive a high standard of evidence-based care irrespective of where they receive their treatment. This guidance is based on an expert consensus and review of the available evidence base; it supports the need for further research into new products before they are recommended for radiotherapy skin care.

As part of NHS England specialised commissioning, the SCoR supports the reduction of variation in quality by adopting standardised best practice protocols and so improving user outcomes, including quality of life, mortality and morbidity from adverse side effects. Access to high-quality, protocol-driven services focused around patients' needs must be equitable, and the review of radiotherapy skin care advice works towards this.

The results of surveys (SCoR, 2011b; Harris et al., 2012; SCoR, 2014) conducted by the Society and College of Radiographers and Nisbet et al. (2018, 2019) identified variance in practices in UK radiotherapy departments with respect to both the prevention and management of radiation induced skin reactions. These surveys highlighted that, despite the published guidance, not all departments were following recommendations for baseline skin assessments and the prevention/management of skin reactions, or recording potential risk factors; much of the existing evidence base was contradictory and many references were old, with a disappointing scarcity of contemporary evidence. Audit and data collection are too limited to provide an accurate record of radiotherapy reactions across clinical departments. This makes quantifying the extent of the problem difficult.

The evidence base was not found to be strong enough to make definitive recommendations around any specific interventions; however, recommendations have been made around practice to alleviate symptoms and promote comfort.

The UK is not alone in facing difficulties in standardising guidance and advice – a survey in Canada also demonstrated variance in managing radiotherapy skin reactions across departments (Bolderston et al., 2018).

1.5 Background information

1.5.1 Radiobiology

The timing of acute skin reactions has been extensively studied, with well-documented experiments dating back to the 1920s. Early radiotherapy treatment times were determined by the time it took for the skin to become erythematous. The timing of acute skin reactions relates to cell turnover and the relatively rapid turnover of skin cells, leading to early (within weeks) manifestations of radiotherapy effect (Hopewell, 1990).

Skin toxicity is radiation-dose dependent although threshold levels will vary between patients. Ryan et al. (2012) described erythema at doses of 10–12Gy and moist desquamation occasionally occurring at doses of 30–40Gy (when giving 2Gy per fraction).

Various attempts have been made to produce dosimetric guidance as to the likelihood of radiotherapy effects, but usually only late effects. The original National Cancer Institute (NCI) study by Emami et al. (1991) calculated a five-year risk of a 5% increase of necrosis and ulceration when a 30cm^2 area of skin receives a dose of 60Gy (V60) or a 10cm^2 area of skin receives a dose of 70Gy (when giving 2Gy per fraction). The updated quantitative analyses of normal tissue effects in the clinic (QUANTEC) dosimetric guidance (Bentzen et al., 2010) does not consider effects on skin at all.

There have been subsequent efforts in the current era to produce normal tissue complication probabilities (NTCPs), almost exclusively in the breast. The possibility to model and calculate NTCPs arises from the potential of modern treatment planning systems (TPSs) to outline the skin as an organ at risk. Many commercially available TPSs have calculation grid sizes of 3mm, which approximates to the thickness of skin, and if grid sizes are reduced then calculations will become more accurate. In a study of 55 patients of average body mass index (BMI) who had breast treatment with intensity modulated radiotherapy (IMRT), an NTCP calculation determined that skin volume receiving a dose >35Gy (V35) should be limited to <85.7mL to keep the incidence of radiation dermatitis (RD) grade 2$^+$ toxicity below 50% (Lee, 2018).

Turesson et al. (1996) demonstrated that the number of basal cells in the epidermis declines during fractionated radiotherapy due to increased cell cycle arrest and reduced mitosis. The reduction in basal cells causes a thinning of the epidermis and an inflammatory reaction, and variation in the reaction appears to be a genetic predisposition related to individual DNA repair capacity (Tucker et al., 1992; Lopez et al., 2002; Twardella et al., 2003; Popanda et al., 2003; Chang-Claude et al., 2005; Pinar et al., 2007; Andreassen and Alsner, 2009), to genetic radiosensitivity (Barber et al., 2000; Burrill et al., 2000; Suga et al., 2007), and/or to intravascular thrombin generation (Lincz et al., 2009).

1.5.2 Clinical factors

Certain clinical factors (Table 1) can aid in the prediction of which patients are more likely to experience a significant radiation reaction (Russell et al., 1994; Russell, 2010). Extrinsic factors, which are treatment related, include: dose, volume, fractionation, adjuvant treatment, treatment in a skin fold area (e.g. inframammary fold or anal cleft), use of bolus material, type of immobilisation, and treatment technique (Porock and Kristjanson, 1999). In the last decade, there have been rapid changes and progressive developments in the technology used for planning and delivery of radiotherapy. Intensity modulated radiotherapy (IMRT) and rotational intensity modulated radiotherapy (RIMRT),

including volumetric modulated arc therapy (VMAT) and tomotherapy are now commonly implemented for clinical use (Miles and Venables, 2012).

Intrinsic factors, which are individually patient related, include: larger breast size (only relevant when treating the breast) (Porock and Kristjanson, 1999; Harris, 2002b; Goldsmith et al., 2011); higher body mass index (BMI) (Kouvaris et al., 2001; Twardella et al., 2003; Wells et al., 2004); and/or pre-existing conditions and comorbidities, such as diabetes (Turesson et al., 1996; Porock et al., 1999). Such intrinsic factors may enhance an individual's propensity to experience a skin reaction and therefore should be recorded when taking baseline observations and closely monitored throughout, and after, a course of radiotherapy (Porock et al., 1998; Fisher et al., 2000; Richardson et al., 2005; NHS Quality Improvement Scotland, 2010). Smoking has also been shown to be an independent risk factor; patients should be advised about this and supported to change behaviours wherever possible (Wells et al., 2004; Kraus-Tiefenbacher et al., 2012; Sharp et al., 2013 (a) and (b)).

Table 1: Intrinsic and extrinsic factors that may influence the severity of skin reactions

Intrinsic factors	**Extrinsic factors**
Demographic or disease-related characteristics	Treatment-related characteristics
Age, ethnic origin, smoking, obesity, breast size, hormonal status, presence of infection, co-existing diseases (such as diabetes, cardiovascular disease**,** hypermobile Ehlers**–**Danlos syndrome, autoimmune conditions e.g. systemic lupus erythematosus and scleroderma), skin type.	Technique, dose, volume, fractionation, beam energy, use of bolus, immobilisation devices, addition of systemic anti-cancer therapies (SACTs). Clinical site of treatment, e.g. areas containing skin folds, such as the head and neck, breast and axilla.

Based on Porock and Kristjanson, 1999

The 2015 skin care guidelines (SCoR, 2015) showed a significant amount of research being undertaken, but that very few definitive recommendations could be made with respect to the optimal intervention for the management of, and potential to reduce, radiation induced skin reactions. Gosselin (2010) noted that some skin care products showed promising results but comparing data across studies is difficult because of the wide variety of assessment tools used.

The use of a validated skin assessment tool on at least a weekly basis is recommended. This practice allows monitoring and recording of an individual patient's skin reaction. An example of a validated assessment scale recommended by these guidelines is that developed by the Radiation Therapy Oncology Group (RTOG) (Cox et al., 1995). The use of an effective monitoring system (Campbell and Lane, 1996; O'Shea et al., 2003) would assist in a robust approach to radiation skin care management, aiding product evaluation and justification of practice.

Another important aspect of skin care during radiotherapy is quality of life. Patients often have fears and misconceptions about radiotherapy; therefore, consistent, current and relevant reinforced information can help to alleviate some of these concerns (Harris, 1997). It may not be possible to stop or reduce the rates of skin reactions, but skin care products may provide comfort and enhance self-care (Gosselin, 2010).

Studies have showcased the benefits of utilising a patient reported outcome measure (PROM) in skin care evaluation studies. Recording of patient symptoms, acceptability/satisfaction and compliance, as incorporated into some existing scales (Noble-Adams, 1999), would also be helpful indicators of how appropriate a product will be for future use.

Of significant note is the identification of certain products contraindicated for use on radiotherapy skin reactions:

- topical antibiotics, unless there is a proven infection (Sitton, 1992; Campbell and Lane, 1996; Korinko and Yurick, 1997)
- gentian violet, due to potential carcinogenic side effects (Campbell and Lane, 1996; Rice, 1997; Boot-Vickers and Eaton, 1999)
- aqueous cream – now classified in the British National Formulary (BNF) (Joint Advisory Committee, 2019) as a soap substitute.

Petroleum (Sitton, 1992; Blackmar, 1997; Korinko and Yurick, 1997) and silver sulfadiazine (Fackrell, 2013; Fackrell et al., 2015) based products have been considered to create a build-up effect due to their radiation attenuation properties. However, more recent evaluation (Morley et al., 2013) of dosimetric considerations has shown that the amount of product layering required to cause a problem would be far in excess of normal skin care use. Zinc oxide creams (e.g. Sudocrem^{R}) still do not appear to be suitable for use (Fackrell et al., 2015).

2. Scope and purpose

The practice guideline is for the whole professional radiotherapy workforce, including students and learners. This encompasses clinical and non-clinical, registered and other practitioners, service managers, educationists, and researchers. The population covered in the guideline is patients receiving external beam radiotherapy. The setting for the guideline is radiotherapy departments in the United Kingdom.

3. Guideline question

What current evidence is there to assist radiotherapy healthcare professionals giving the optimal skin care advice to patients undergoing radical external beam radiotherapy?

4. Guideline development process

4.1 Core group

The core group of nine was established in March 2019 by the lead professional officer, who is also the core group leader. The remaining eight members were: three experienced academics (two therapeutic radiographers and one nurse) who led the systematic review; an academic and clinical radiographer who led the updates to the background information; two patients and a lay person who ensured there was a patient voice throughout and who led on the review of the patient information.

4.2 Stakeholder group

The stakeholder group comprised thirty-two members: eighteen therapeutic radiographers, two oncology nurses, two clinical oncologists, one dosimetrist, three therapeutic radiographer representatives from Canada to compare across country reviews, and six patients/users. Several of the 'professional members' were also radiotherapy service users and brought that perspective to their feedback. The names of both core and stakeholder group members are listed in ***Appendix 1***.

4.3 Peer review and consultation process

The 2015 practice guidelines were circulated to the stakeholder group for comment in May 2019. Most stakeholders responded and their comments were assimilated in an action log. The form to record comments can be found in ***Appendix 2***. Sub-teams then worked on: updating the background information; undertaking an updated systematic review; updating staff information; and updating patient information. A second round of consultation, including the systematic review report, was conducted at the end of November 2019. Drafts of the patient and staff infographics were shared at the *College of Radiographers Annual Radiotherapy Conference* in January 2020; feedback received from delegates was positive. A third round of consultation, comprising a draft of the practice guideline, was conducted in February 2020. A final and fourth round of consultation to the core group to agree final consensus occurred in March 2020. Final consensus was achieved via email discussion and evaluation of the evidence.

Further guideline versions were updates on wording and minor amendments that did not affect the recommendations agreed by the core and stakeholder groups.

The SCoR Patient Advisory Group (PAG), SCoR Radiotherapy Advisory Group (RAG), SCoR Information, Support and Review Radiographer Forum, Macmillan Cancer Support, Breast Cancer Now and Cancer Research UK (CRUK) were sent the draft guidelines and appendices and asked to review and comment on them during February to March 2020. The form to record comments can be found in ***Appendix 3***.

SCoR UK Council signed off the work in April 2020.

4.4 Funding arrangements

An academic researcher on the core group was paid £500 to conduct and assimilate the literature review. Patient and lay representatives were each offered a gift voucher of thanks to the value of £70. All other core and stakeholder group members gave their time and expertise voluntarily.

4.5 Conflict of interest

The SCoR policy and procedures for managing conflicts of interest was adhered to (Process Manual for Practice Guideline Development (Appendix G)). All members of the core and stakeholder groups have signed the conflicts of interest declaration form. No conflicts of interest were declared.

4.6 SCoR approval process

The finalised practice guideline was submitted to the UK Council of the SCoR in April 2020.

5. Guideline methodology

5.1 Literature search

The current review included a search of multiple databases, as well as a hand search of a number of relevant journals, and was supplemented by searches of the 'grey literature' to include ongoing trials.

The results and discussion covered 33 studies. All included research was assessed for quality, with recommendations based on the studies assessed as having low opportunity for bias. Ongoing clinical trials were also listed, demonstrating a number of investigations that should be considered for inclusion in any future updates to this review.

The review identified a number of key areas that have been or are currently being researched, including the use of topical prophylactic steroids, a wide variety of topical emollients and photobiomodulation therapy. However, significant challenges still arise with respect to the breadth of research methods adopted, the skin care practices used in the control arms, methods of data analysis and stratification of results for the plethora of confounding patient and radiotherapy treatment related variables, all of which can have significant impact on the risk of bias and hence the reliability of the results being presented.

5.2 Introduction and background to systematic review

It has been widely acknowledged that despite the publication of a number of best practice guidelines for skin care, radiotherapy departmental practice with respect to the prevention and management of acute radiotherapy and skin toxicity has been slow to change. A wide variety of methods and topical applications are still utilised at a local level, often with very little or no evidence base (Harris et al., 2012).

The last skin care guidelines were published by the Society and College of Radiographers in 2015 (SCoR, 2015). The 2015 guidelines were informed by a systematic review of the literature from 2011 to 2014 (***Appendices 4, 5 and 6***). The guidelines recognised that there is often a disparity between the evidence base and clinical practice and the literature reviewed as part of the 2015 guidelines demonstrated that although additional research had been published in the field, the scope of this research and the results were quite wide-ranging, both in their methods and in the aspect of radiation induced skin reaction being researched. Many of the studies published between 2011 and 2014 focused on a topical application, with some studies focused on the benefits of dressings to minimise discomfort and speed healing once a high-grade skin reaction had occurred. While the research published between 2011 and 2014 was potentially valuable to the radiotherapy community, only 30% of the research reviewed for the 2015 guidelines was assessed as high quality (i.e. assessed as having limited opportunity for bias that may affect the research results). The SCoR 2015 guidelines listed nine key recommendations as well as several best practice suggestions. Recommendations for further research were also published, which included the need to consider specifically the impact of proton therapy. It was also acknowledged within the 2015 guidelines that national guidelines need to be regularly reviewed and revised to ensure they are consistent with emerging evidence (Faithfull et al., 2002).

Hence, the purpose of the current review (2019) was to determine if new research evidence had emerged that could improve skin care practices in radiotherapy. This systematic review aimed to assess the effectiveness of interventions and practices that may prevent, reduce (or alter) radiation induced skin reactions (RISRs) in patients undergoing external beam radiotherapy for cancer, with an emphasis on research published since November 2014. The review proposal was registered on PROSPERO: International prospective register of systematic reviews (CRD42019148161).

5.3 Method

Initially a search question was formulated using the Population, Intervention, Control, Outcome (PICO) method (Table 2).

Table 2: PICO method

Population	Patients undergoing external beam photon radiotherapy Patients undergoing proton beam radiotherapy Patients undergoing electron beam radiotherapy
Intervention	Preventative measures including the use of topical applications, use of barrier films and deodorant guidance Management measures – dressings, topical and medical applications
Control	Standard skin care practice including normal washing and use of non-specific moisturisers
Outcome	Radiation induced skin reactions (RISRs), skin reactions, radiation dermatitis, erythema, dry and moist desquamation, Radiation Therapy Oncology Group (RTOG)/Common Terminology Criteria for Adverse Events (CTCAE) and radiation induced skin reaction assessment scale (RISRAS) scores

5.3.1 The overarching guiding question for this systematic review

How effective are preventative practices and management interventions compared with the 2015 skin care guidelines (SCoR, 2015) for reducing radiation induced skin reactions (RISRs) in cancer patients undergoing external beam photon, proton beam or electron beam therapy?

5.3.2 The review aimed to answer the following questions:

- Is there new research evidence to support a change in advice given to patients undergoing radiotherapy about how to care for their skin before, during and after a course of radiotherapy in terms of washing, drying, deodorant or cream use?
- Is there new evidence to support the use of topical agents to reduce RISRs?
- Is there new evidence to support the use of dressings, medical devices, oral medications or barrier films to reduce RISRs?

The review was based on a systematic search of a variety of resources. As evidence from 2011 to 2014 was reviewed in the previous systematic review (***Appendices 4, 5 and 6***), and this is a continuation of that work, it was deemed appropriate to map out and replicate the initial search strategy and then, where appropriate, include any additional resources.

A modified 'pearl growing' method was employed to support the development of the search terms for the review. This method uses multiple key documents to inform the bank of search terms and is deemed an appropriate method to be used for yielding results in a systematic review (Schlosser et al., 2006). Table 3 identifies the two key documents used.

Table 3: Pearl documents

Skin care advice for patients undergoing radical external beam megavoltage radiotherapy (2015) https://www.sor.org/learning/document-library/skin-care-advice-patients-undergoing-radical-external-beam-megavoltage-radiotherapy-0 Key terms: radiotherapy, radiation therapy, skin care, radiation dermatitis, skin reactions, evidence-based practice
Chan, R., Webster, J., Chung, B., Marquart, L., Ahmed, M. and Garantziotis, S. 2014. Prevention and treatment of acute radiation-induced skin reactions: a systematic review and meta-analysis of randomized controlled trials. *BMC Cancer*. 14: 53. Keywords: radiation induced skin reactions, radiation dermatitis, systematic review, meta-analysis, randomised controlled trials

5.3.3 Search strategy

A systematic search of the literature was undertaken using the following databases:

- MEDLINE
- CINAHL
- PreMEDLINE
- ScienceDirect
- Index to Theses.

A search of clinical trials included the following databases:

1. The ISRCTN clinical trials database (http://www.controlled-trials.com)
2. The U.S. National Institutes of Health trials register (http://www.clinicaltrials.gov)
3. The Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au)
4. The World Health Organization International Clinical Trials Registry Platform (http://www.who.int/trialsearch).

Individual journal searches were performed on the following key journals:

- *Journal of Radiotherapy in Practice (JRP)*
- *European Journal of Cancer (EJC)*
- *Radiography*
- *Journal of Medical Imaging and Radiation Sciences (JMIRS)*
- *Journal of Medical Radiation Sciences (JMRS)*
- *International Journal of Radiation Oncology • Biology • Physics (IJROBP)*
- *Radiotherapy & Oncology*
- *Practical Radiation Oncology*.

A secondary evaluation of the 2014 systematic review clinical trials table was undertaken to identify if any of the trials still open at the time of the last review had now been published.

A search of the grey literature, including Index to Theses and conference papers, was undertaken to ensure publication bias was minimised, and a search of Google Scholar using a selection of the key search terms was also carried out to ensure no additional relevant research had been missed.

5.3.4 Key terms

Key terms were searched using standard Boolean operators, wildcards and truncations (Table 4).

Table 4: Key terms

Aspect	Key terms
Radiotherapy	Radiotherapy, radiation therapy, irradiation Proton radiotherapy, proton therapy, proton beam therapy Photon therapy Electron therapy Stereotactic ablative radiotherapy (SABR) Immunotherapy in combination with radiotherapy
Interventions	<u>Preventative measures</u> washing with soap, deodorant, antiperspirant, topical agents, creams, oils, gels, emollients, E45®, aqueous cream, *Calendula officinalis*, steroidal cream, non-steroidal cream, StrataXRT®, Mepitel®, Mepilex®, barrier film, hyaluronic acid and trolamine, mometasone furoate cream, betamethasone cream, methylprednisolone, dexpanthenol, RadiaCare® gel, Aquaphor® ointment, qingdiyou medication, wheatgrass extract cream, sucralfate cream, shaving (dry) and electric shaving <u>Management measures</u> dressings, topical and medical applications, foam dressing, colloid dressings, hydrogel dressings, silver nylon dressings, Wobe-Mugos E®, oral zinc supplements, oral pentoxifylline, oral antioxidant, oral sucralfate suspensions, DermaSilk®
Outcomes	<u>Skin reactions</u> radiation effect, adverse effect, radiation dermatitis, erythema, moist (or dry) desquamation, skin reactions, RISR, radiation induced skin reaction, RTOG acute toxicity, Radiation Therapy Oncology Group toxicity, CTC, common toxicity criteria score, pain, itch(ing), redness, soreness, ulceration, burning, rash, swelling

Table 5: Inclusion/exclusion criteria

Criteria	Inclusion	Exclusion
Date range	All literature from November 2014 to October 2019	Skin reactions caused by a pre-existing genetic or medical disposition
Language	All papers that have an English abstract	Papers where either the full text is not available in English or the required detail of the study cannot be obtained directly from the authors in a translated format
Focus of the research	Papers that assess the use of a topical agent, dressing or intervention, and where the primary focus is skin reaction to photon or electron beam radiotherapy or proton beam therapy	Rare skin reactions caused by topical agents or chemotherapy drugs Papers where the primary focus is the impact of an immobilisation device or radiotherapy planning technique on the skin reaction
Types of studies	Systematic reviews (SRs), randomised controlled trials (RCTs), non-randomised trials and case series	Discussion papers and single case studies

5.3.5 Quality assessment, data synthesis

For the purpose of review, the following quality assessment approaches were used:

- The RoB (Risk of Bias) tool was used to assess the quality of randomised trials and the ROBINS-I tool to assess the quality of non-randomised studies (Higgins and Thomas, 2019).
- Case studies were not assessed for quality and not included in the summary tables. This data has only been used to inform further research recommendations.
- Systematic reviews were assessed using the Scottish Intercollegiate Guidelines Network (SIGN, 2019) checklist for systematic reviews.

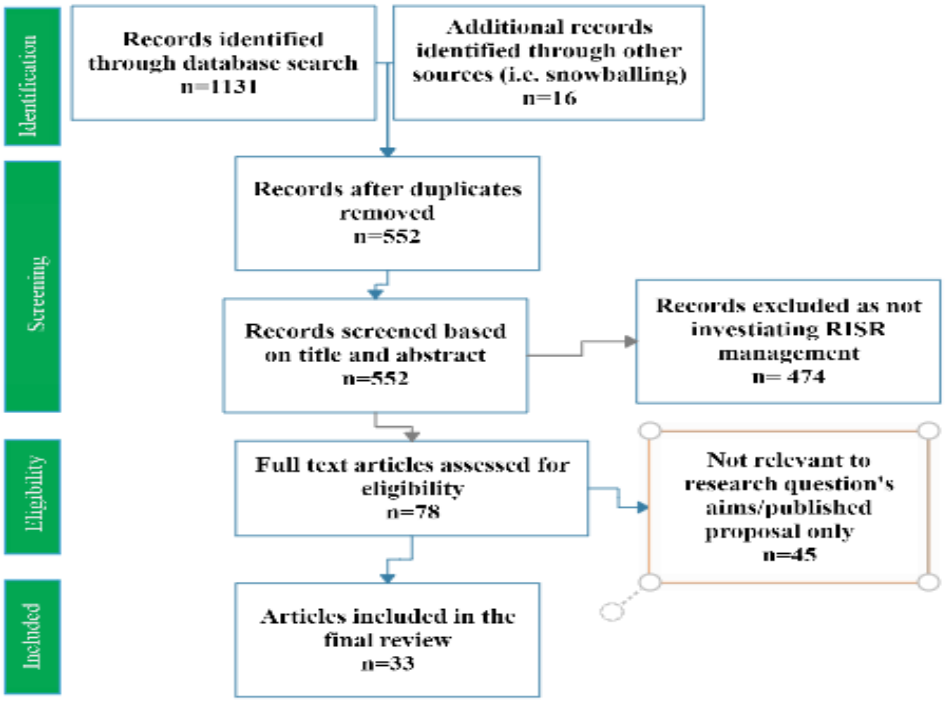
Quality assessment was completed by three academic researchers, who were part of the core group, assessing study quality independently; two independent reviews were completed on each article included in the review. The review has been reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group guidelines (PRISMA, 2009) to ensure transparency and improve the quality of the reporting process (Figure 1).

Initially articles were selected based upon their title relevance. Further selection was undertaken using the title and abstract and whether they matched the inclusion/exclusion criteria (Table 5).

Data extraction was undertaken using a verified extraction tool. Quality assessment used the appropriate method depending on whether the study involved randomisation or not (see above). Data from each article was recorded and saved electronically in a summary evidence table (***Appendices 7 and 8***). Narrative synthesis has been primarily used to report study findings using the Centre for Reviews and Dissemination (CRD) guidelines and strategy (CRD, 2008).

5.4 Results

Figure 1: PRISMA diagram



Quality assessment using the appropriate RoB, ROBINS-I or SIGN quality assessment tool (Scottish Intercollegiate Guidelines Network, 2019) was undertaken. A total of 33 articles were available for review: 21 RCTs, two feasibility studies, nine non-randomised trials and one pilot study.

Of the 33 studies included (n=33): 13/33 (39.4%) were assessed as having a high risk of bias; 6/33 (18.2%) were assessed as having a moderate risk of bias; and 13/33 (39.4%) were assessed as having a low risk of bias. There was one pilot study not assessed for bias (***Appendices 7 and 8***).

5.4.1 Ongoing trials

In order to ascertain current research being undertaken in this field, a search of clinical trials databases was undertaken. The following studies were identified (Table 6)**.**

Table 6: Ongoing trials

Study title	Author(s)	Trial registration number	Method	Anatomical areas	Country/ hospital(s)	Stage of study
Effects of Herbal Products on Reduction of Radiation-induced Dermatitis in Breast Cancer Patients	-----	NCT02922244	Randomised triple blinded	Breast cancer	Thailand	Completed July 2018
Laser Therapy for the Prevention of Radiodermatitis in Head and Neck Patients (DERMISHEAD)	Prof Dr Jeroen Mebis	NCT02738268	Double blinded RCT	Head and neck cancer	Belgium	Recruiting
Evaluating the Efficacy of Mepitel in Post-mastectomy Breast Cancer Patients, and Examining the Role of the Skin Microbiome in Radiation Dermatitis	Kimberly S Corbin	NCT03519438	Cohort study	Breast cancer	Mayo Clinic USA	Active, not recruiting
Photobiomodulation for Breast Cancer Radiodermatitis Prevention. A Randomized Controlled Trial	Francine Sgrott	NCT04059809	Randomised single blind controlled trial	Breast cancer	Brazil	Recruiting
StrataXRT vs Standard Clinical Practice for the Prevention of Acute Dermatitis in Patients Receiving Concurrent Chemoradiation for Head and Neck Cancers	David Chia	NCT03394417	Blinded RCT	Head and neck cancer	Singapore	Not yet recruiting
Prophylactic Interventions in the Management of Radiodermatitis in Patients With Breast or Head and Neck Cancer: a Randomized Clinical Trial	Elaine Barros Ferreira, RN	NCT02247830	Double blinded RCT	Breast cancer Head and neck cancer	Brazil	Active, not recruiting

Radiotherapy Related Skin Toxicity: Mepitel® Film vs. Standard Care in Patients With Locally Advanced Head-and-Neck Cancer	Prof Dr Dirk Rades	NCT03047174	Non-blinded RCT	Head and neck cancer	Germany	Completed, not published
Topical Doxepin for Prevention and Management of Radiation-induced Dermatitis	Golnaz Vaseghi	NCT02447211	Quadruple blinded RCT	Breast cancer	Iran	Recruiting
Urtica Comp. Gel for Prevention and Therapy of Radiation Dermatitis (An Interdisciplinary, Interprofessional Phase II Randomized Controlled Trial in Patients With Breast Cancer)	Gisa A Gerstenberg, MD PhD	NCT03494205	Non-blinded RCT	Breast cancer	Switzerland	Recruiting
Utilization of Low Level Laser Therapy for Radiation Induced Dermatitis in Patients With Head and Neck Squamous Cell Carcinoma	Karen Holeva	NCT02384434	Cohort study	Head and neck cancer	USA	Recruiting

5.5 Discussion

The results of the review are presented in four subsections. These subsections represent suitable groupings of research on the same or similar interventions for the prevention or treatment of RISRs as follows:

1. Steroid creams
2. Low-level laser (or photobiomodulation) therapy
3. Barrier films
4. Topical emollients

In each subsection, a summary table shows the studies reviewed on that topic, highlighting whether the research found statistically significant improvements in RISRs or patient reported measures of discomfort.

5.5.1 Steroid creams

Table 7: Steroid cream studies

References		Clinician Reported Outcomes									Patient Reported Outcomes							
Reduction in skin toxicity	Tumour type																	
		RTOG	CTCAE	RISRAS	CTC	EORTC	Digital Imaging	10 point Caterall	WHO Criteria	Other	SKINDEX 16 Overall	VAS	Symptom Inventory	McGill Pain Questionnaire	Likert Scales	Dermatology QoL Index	Skin Experience Diary(SED)	Other PROMS
Erridge et al 2016	H+N inc Brain, Breast, Pelvis, Other	+Ve																+Ve
Fenton-Kerimian 2015	Breast Cancer		NS														NS	
Ho 2018	Breast Cancer	+Ve									NS							
Sio 2016	Breast Cancer		NS															+Ve
Ulff 2017 (late toxicity)	Breast Cancer	NS																
Ulff 2017	Breast Cancer	+Ve										+Ve						
outcomes (+ve) significance P<0.05																		

(NS) not significant
Green= Low risk of bias, Orange= moderate risk of bias, Red=high risk of bias, White= not assessed as pilot study

In the 2014 systematic review undertaken as part of the SCoR's 2015 guidelines a number of studies investigated the use of topical steroids for the management of radiation dermatitis. Wong et al. (2013) made strong recommendations in their guidelines for the use of prophylactic topical steroids. In spite of this, some of the published research recommended exercising a degree of caution and a need for more work to be undertaken, particularly to determine any long-term implications of using steroids.

The rationale for using steroid creams is based on the known anti-inflammatory properties of steroids. Six studies included in this review reported equal or positive outcomes in relation to the use of topical steroid creams (Table 7). However, both the studies by Erridge et al. (2016) and Fenton-Kerimian et

al. (2015) were at high risk of bias due to a lack of reporting or controlling for many patient or treatment related confounding variables e.g. patient BMI, smoking status, breast size, or use of bolus. No information was provided in either of the papers as to any stratification and/or blinding of the assessors, and no information on assessment of inter- or intra-rater reliability of skin assessment. The control used in the study by Erridge et al. (2016) for cohort one was aqueous cream, which may affect the overall outcome, as the previous SCoR 2015 guidelines recommended it only be used as a soap substitute not a leave-on moisturiser due to its reclassification in the British National Formulary. In addition, Tsang and Guy (2010) and Patel et al. (2013) recommended using a moisturiser that is sodium lauryl sulphate free.

The studies by Ho et al. (2018), Sio et al. (2016) and Ulff et al. (2017a, 2017b) all reported statistically significant outcomes when using steroid creams and scored low for potential bias; all three were conducted on patients undergoing radiotherapy for breast cancer. The studies by Ho et al. (2018) and Sio et al. (2016) had a significantly lower rate of grade 2 or grade 3 (moist desquamation) using 0.1% mometasone furoate than the control arms. Ho et al. (2018) reported 43.8% vs 66.7% intervention vs control respectively (P=0.012) and a lower incidence of maximum grade radiation dermatitis, reporting 18.8% vs 33.3% (P=0.036) in their intervention arm. Yet lower rates of grade 2 dermatitis have been reported by others from just employing hypofractionated regimens. For example, Ahlawat et al. (2016) reported an incidence of 34% grade 2 radiation dermatitis and one patient with a grade 3 RISR (n=83) when a dose fractionation of 36.63Gy in eleven fractions (followed by a four-fraction boost) was given. Similarly, Deantonio et al. (2010) reported acute RISR toxicity of grade 2 and above in 24% of their sample of patients undergoing whole breast irradiation using a hypofractionated regimen.

There were no reported differences in patient reported outcome measures (PROMs) between the intervention and control arm for the study by Ho et al. (2018). However, longitudinal analysis by Sio et al. (2016) did show significant differences. There was good control of confounding variables in both studies, with assessors and patients blind to the intervention. However, the control arm in the study by Ho et al. (2018) used a cream containing ingredients that may have exacerbated skin reaction, including petroleum jelly and phenoxyethanol (which if used in large quantities can irritate the skin). Sio et al. (2016) did not use a control cream at all. The research reviewed from Ulff et al. (2017a, 2017b) considered two publications. One study reported acute toxicity following administration of betamethasone 17-valerate cream. The second reported long-term follow-up data (average follow-up was six years) to evaluate late toxicity. The cohorts in both the studies were patients diagnosed with breast cancer.

In the study of acute toxicity, Ulff et al. (2017a) aimed to test the hypothesis that preventative topical steroid treatment starting at the beginning of radiotherapy can ameliorate acute radiation dermatitis compared to a control moisturiser. Results from this study showed that the patients in the intervention (steroid cream) arm developed fewer skin reactions than those treated with a normal moisturiser (P<0.001) and this was regardless of the radiotherapy fractionation regimen used. However, the data clearly showed that patients treated with a hypofractionated (2.67Gy/fraction) course of radiotherapy had significantly lower acute toxicity than those treated with a conventional fractionation (2Gy/fraction). For those treated with hypofractionated regimens the incidence of grade 3 toxicity was 7% for those using the moisturiser vs 0% in the steroid cream arm. The sample size in the hypofractionated group is small (n=61) and it is possible that the differences seen are related to other factors, including radiation planning differences such as volume of tissue receiving 107% of the dose, or patient BMI status (slightly more patients had a BMI of 25 or more in the moisturiser arm compared with the steroid cream arm, 31% vs 26% respectively). All these variables are known to have an impact on RISRs. The differences observed between intervention and control for those treated with a hypofractionated regimen could be because the moisturiser used in the control arm,

Essex® cream (essentially aqueous cream), is an emollient no longer recommended for use as a leave-on topical cream because of the potential to cause irritation.

The long-term follow-up (average follow-up was six years) analysis by Ulff et al. (2017a) found no evidence of skin atrophy in any of the 60 patients included in the original analysis. There were also no significant differences between normal tissue and the tissue treated with steroids. Only ten patients (17%) had noticeable skin changes and three (5%) were reported as having altered skin pigmentation.

It is worth noting that not all studies assessing steroid creams included a PROM within their study design, and this is something the review team would strongly recommend. Although all clinical reporting tools were recognised and validated, a number of different combinations and review schedules were utilised, again making it difficult to draw comparisons across studies. Dose fractionation regimens across the studies that included breast cancer patients also varied. It is worth noting that Ho et al. (2018)[1] and Sio et al. (2016), and the studies by Ulff et al. (2017a, 2017b), all utilised up to and in excess of 50Gy for their radiotherapy schedules; we know that conventional fractionation schedules result in a higher incidence of acute RISRs compared with hypofractionated regimens (typically 40Gy in 15 fractions).

In summary, of the studies assessed as having a low or moderate risk of bias, all samples involved the assessment of steroid cream on patients undergoing radiotherapy for breast cancer. The positive outcomes identified are confounded by the use of conventional dose fractionations (e.g. 50Gy in 25 fractions) compared with the UK consensus guidelines recommendation of hypofractionated regimens (i.e. 40Gy in 15 fractions) where it is known that acute toxicity is lower in the hypofractionated schedules (Hickey et al., 2017), as well as other possible confounding variables such as BMI, volume of tissue receiving 107% (or 110%) of the prescribed dose or the use of a cream in the control arm that may exacerbate skin irritation (such as aqueous cream). For this reason, based on the studies reviewed these guidelines do not recommend the early use of steroid creams as a preventative intervention for women undergoing breast irradiation, given that most women undergoing breast or chest wall irradiation in the UK would be prescribed a hypofractionated regimen.

Instead it is recommended that steroids are reserved only for those patients identified as being at a high risk of developing a high-grade RISR i.e. moist desquamation (grade 3). There is likely to be a higher risk of an RISR when a bolus is used, the patient is a smoker (and is unable to give up smoking during radiotherapy), the total dose of radiation is >40Gy and the patient has a high BMI. There needs to be more high-quality research to identify the hazard ratios for these identified high-risk variables. The review team would particularly recommend more research to correlate planning parameters such as V107/V110, and acute skin toxicity, in order that an evidence-based risk stratification algorithm can be developed to support the appropriate preventative use of steroid creams.

It is important to note that primary care practitioners may be recommending the use of topical hydrocortisone in a related context for patients having radiotherapy with various comorbidities. This is however beyond the scope of this document.

5.5.2 Low-level laser or photobiomodulation therapy studies

Photobiomodulation therapy (PBMT) is the application of low-power infrared light to the skin to stimulate the natural healing process that may be interrupted by the impact of radiation interactions. The purpose of PBMT is to reduce inflammation and pain that is associated with the RISR, but researchers are also investigating whether PBMT can be used as a preventative tool to reduce or delay the development of acute radiation dermatitis.

Table 8: Low-level laser therapy studies

References		Clinician Reported Outcome Measures									Patient Reported Outcome Measures							
Reduction in skin toxicity	Tumour type																	
		RTOG	CTCAE	RISRAS	CTC	EORTC	Digital Imaging	10 point Caterall	WHO Criteria	Other	SKINDEX 16 Overall	VAS	Symptom Inventory	McGill Pain Questionnaire	Likert Scales	Dermatology QoL Index	Skin Experience Diary(SED)	Other PROMS
Robijns et al 2019	Breast Cancer	+Ve																
Strouthos et al 2016	Breast Cancer		+Ve				+Ve					+Ve						
outcomes (+ve)significance P<0.05																		

(NS)not significant
Green= Low risk of bias, Orange= moderate risk of bias, Red=high risk of bias, White= not assessed as pilot study.

Two studies investigated the use of photobiomodulation therapy (PBMT) to reduce or prevent the incidence of moist desquamation or radiation dermatitis; both studies involved samples of patients treated for breast cancer. Both Robijns et al. (2018) and Strouthos et al. (2017) demonstrated a statistically significant reduction in moist desquamation or radiation dermatitis when compared to either a placebo intervention (Robijns et al., 2018) or no intervention at all (Strouthos et al., 2017). The study by Robijns et al. (2018) demonstrated a significantly higher incidence of RISR in the control arm at the 66Gy time point compared to the intervention arm (P= 0.004).

Strouthos et al. (2017) also reported a lower incidence of radiation dermatitis in the PBMT group compared to control (P=0.0211). In addition, Strouthos et al. (2017) analysed pain level and intensity using a weekly patient reported visual analogue scale (VAS) and reported pain intensity in the PBMT group was significantly lower (P=0.003). Both studies were assessed as having a low risk of bias. However, PROMs were not studied by Robijns et al. (2018). The review team would strongly recommend the inclusion of PROMs in any future trials.

In summary, the use of PBMT is an emerging area, as noted by the two studies included in this review, with a number of ongoing trials that are currently recruiting (Table 6). There are some potential concerns about the long-term impact of PBMT and further research on this is needed. Both the studies included in this review involved samples of patients treated for breast cancer with total radiation doses of 50Gy and above, based on conventional dose fractionation schedules. As already indicated, there is sufficient evidence that hypofractionated regimens for breast cancer (compared with conventional fractionation) result in a lower incidence of grade 2 or 3 radiation dermatitis. It is not clear whether the benefits from PBMT presented from these two studies would be replicated in patients receiving whole breast radiotherapy with hypofractionated schedules. Therefore, these guidelines do not recommend the use of PBMT at this time. The work in this field is promising but future research needs to replicate these benefits reported with conventional dose fractionation in samples where modern dose fractionation schedules are employed, or demonstrate benefits in patients where there is likely to be a high risk of RISR, such as those treated with bolus or concomitant chemotherapy, or where there are skin folds.

5.5.3. Barrier films

A barrier film is a thin, often transparent, self-adhesive sheet. Barrier films may offer a protective layer to the surface layers of the skin that may be damaged by radiation treatment. By preventing further trauma or risk of infection, barrier films are proposed as a treatment or preventative measure for RISRs.

Table 9: Barrier film studies

Reference		Clinician Reported Outcome Measures								Patient Reported Outcome Measures							
Reduction in Skin Toxicity	Tumour type	RTOG	CTCAE	RISRAS	CTC	EORTC	10 point Caterall	WHO Criteria	Other	SKINDEX 16 Overall	VAS	Symptom Inventory	McGill Pain Questionnaire	Likert Scales	Dermatology QoL Index	Skin Experience Diary(SED)	Other PROMS
Arimura et al 2015	Prostate				+Ve												
Censabella et al 2016	Breast			+Ve						NS							
Chan et al 2019	Head and Neck		+Ve														
Lam et al 2019	Breast	NS															
Moller et al 2018	Breast				NS												+Ve
Rades et al 2019	Head and Neck		NS														
Shmeel et al	Breast	+Ve				+Ve											
outcomes (+ve) means significance P<0.05	Green= Low risk of bias, Orange= moderate risk of bias, Red=high risk of bias, White= not assessed as pilot study.																
(NS) not significant																	

Seven studies were identified that investigated the use of a barrier film or dressing to reduce skin reactions; five were conducted with patients diagnosed with a primary breast cancer, one with patients treated for a head and neck cancer, and one with patients treated for prostate cancer.

Rades et al. (2019) and Møller et al. (2018) investigated the use of Mepitel® film in patients with a head and neck cancer and breast cancer respectively. Rades et al. (2019) used their standard skin care protocol as the control while the control group in Møller et al. (2018) received 2–5% urea and fatty acid cream. These differences in the comparators may influence any differences observed between study groups. Neither study reported statistically significant improvements in reaction when using the Mepitel® film.

In the study by Rades et al. (2019), the study was halted at the point of the interim analysis (when some patients had received a total dose of 50Gy). The premature closure of the study was due to a high proportion of the sample being unable to tolerate the product (46.4% n=13).

Common toxicity criteria (CTC) scores in the Møller et al. (2018) study showed no significant difference between intervention and control in the incidence of grades 1 to 3 skin toxicity at the end of treatment or at 14 days post treatment. However, the PROMs showed significant differences in favour of the barrier film, with patients stating that the film was comfortable and that it made a difference. At 14 days, pain was reduced (P=0.001), and sensitivity of the skin, as well as itching, was also reduced (P<0.01).

The remaining five studies investigated a variety of different products. Schmeel et al. (2018) and Censabella et al. (2016) conducted studies into hydrofilm and hydroactive colloid gel respectively in patients undergoing radiotherapy for breast cancer. Schmeel et al. (2018) compared prophylactically

applied hydrofilm dressings with standard skin care (using moisturising 5% urea) and reported a statistically significant decrease in the severity of mean RTOG scores, with a mean of 0.35 compared with the control mean of 1.33 (P<0.001). Unfortunately, there was a high withdrawal rate in this study and intention-to-treat analysis does not appear to have been employed.

Censabella et al. (2016) conducted a non-randomised single centre study that used two historical control groups as comparators. Significant reductions in the onset of radiation induced moist desquamation using the hydroactive colloid gel were reported, an incidence of 6.9% in the intervention arm vs 35.1% and 12.6% in the historical control arms. However, this study was assessed as having a high risk of bias due to a lack of control of potentially confounding variables. The data was also censored at 50Gy because of differences in the use of electrons for the boost across the intervention and control arms, there was no blinding of assessors and no reporting of inter- or intra-rater reliability of skin assessments.

Chan et al. (2019) and Lam et al. (2019) both investigated the use of barrier film wound dressings (e.g. StrataXRT® or alternative product) in patients undergoing radiotherapy for head and neck cancer, lung cancer and breast cancer. In these two studies the control groups either had the standard local care, which included using Glaxal Base® cream, similar to aqueous cream (Chan et al., 2019), or sorbolene, a paraffin-based cream (Lam et al., 2019). Neither study included PROMs and both were assessed as having a moderate risk of bias. In the study by Chan et al. (2019), at the end of treatment grade 2 skin reactions were identified in 80% of patients in the StrataXRT® arm and grade 3 in 28%, compared with 91% and 45% respectively in the control arm. After controlling for the cancer drug cetuximab, the StrataXRT® arm had a 12% lower risk of experiencing grade 2 skin toxicity (RRR=0.876, 95% CI 0.778-0.987) and a 36% lower risk of developing a grade 3 reaction (RRR=0.648, 95% CI 0.442-0.947) P=0.025.

In the study by Lam et al. (2019), patients with breast cancer in the sample were treated with either a conventional fractionation (50Gy in 25 fractions) or a hypofractionated biologically equivalent dose. There was no statistically significant difference in PROMs for burning, pulling and tenderness for those where the barrier film was applied to the medial half of the chest, except for itching, where a significant improvement was seen (1.14 vs 2.06 barrier film vs control cream P=0.035). For cases where the barrier film was applied to the lateral half, only for burning was there a statistically significant difference in patient reported scores, 0.92 vs 1.83 (P=0.047, no confidence intervals presented). There was no significant difference seen between barrier film and standard local care for time taken to develop grade 2 radiation dermatitis. In those patients where the barrier film was applied to the lateral half of the chest, a grade 2 or more radiation dermatitis was reported in 17.3% of cases compared with 27.6% in the no film half (P=0.041). For those where the barrier film was applied to the medial half, a grade 2 dermatitis was reported in 17.2% of cases and 9.6% for no film (P=0.76). Post treatment, no difference was seen in grade 2, or above, scores for barrier film vs no film. Inter-rater reliability of skin assessments was poor. Intra-class correlation coefficient was r=0.45, indicating possible variability in the assessment of skin scores.

In summary, the review team acknowledge the difficulty of trying to implement a strong research design when using a barrier film as an intervention. For example, blinding assessors (or patients) to the intervention is difficult and there needs to be considerable care to ensure comparability in areas covered (or not covered) by the barrier film. Unfortunately, many of the studies reviewed in this section were considered to have some moderate or high risk of bias due to potentially confounding variables, lack of blinding of assessors, or use of a cream in the control arm that may have exacerbated skin irritation in those arms of the study. In addition, the high rate of intolerance of the barrier film in the study by Rades et al. (2019) leads to questions about the value of barrier films in patients having radiotherapy for head and neck cancer. Hence, the review team do not recommend use of barrier films for patients undergoing breast irradiation, particularly where hypofractionated dose schedules

are employed, or for patients receiving radiotherapy to the head and neck. Recommendations for improvements to study design for future research with barrier films are presented along with general recommendations for future research.

More evidence is also required on the potential practical implications of using barrier film in radiotherapy, to include potential dose inhomogeneity and inconsistency in applying and maintaining the film during treatment in the immobilised position.

5.5.4 Topical emollients

Topical emollients are used commonly to prevent RISRs or to provide comfort for patients once a reaction has occurred. As radiation damages the basal cell layer of the skin, the normal desquamation of cells and growth of replacement cells are both interrupted and dehydration of the skin occurs. Topical emollients are used to try to hydrate the skin and to ameliorate feelings of itching and soreness.

Table 10: Topical emollient studies

References		Clinician Reported Outcome Measures									Patient Reported Outcome Measures							
Reduction in Skin Toxicity	Tumour type																	
		RTOG	CTCAE	RISRAS	CTC	EORTC	Digital Imaging	10 point Caterall	WHO Criteria	Other	SKINDEX 16 Overall	VAS	Symptom Inventory	McGill Pain Questionnaire	Dermatology QoL Index	Likert Scales	Skin Experience Diary(SED)	Other PROMS
Aysan et al 2017	Breast	+Ve																NS
Ben-David et al 2016	Breast	+Ve																
Eda et al 2016	Breast	+Ve																
Halm 2014	Breast	NS																
Chan 2014	Breast, Lung, H&N		NS								NS							
Karbasforooshan et al 2018	Breast (Post Mast)	+Ve	+Ve															
Naff et al 2018	Breast				NS													
Ogita et al 2019	Breast									NS								
Sekiguchi 2015	Breast									NS	+Ve							
Sekiguchi 2018	Breast									NS	+Ve							
Togni et al 2015	Breast	NS																
Hoopfer 2015	Breast							NS								NS		
Rollman et al 2015	Breast		NS								NS						NS	
Cui et al 2015	Nasopharynx	+Ve																
Manas et al 2015	Breast and H&N				+Ve	+Ve												
Censebella 2016	Breast								+M4 Ve									

outcomes (+ve) significance P<0.05

(NS)not significant

Green= Low risk of bias, Orange= moderate risk of bias, Red=high risk of bias, White= not assessed as pilot study

A total of 15 studies investigated the use of a topical emollient. Across the studies 14 different products were investigated, including boron gel (Aysan at al., 2017), heparinoid (Sekiguchi et al. 2015 and 2018), emu oil (Rollman et al., 2015), high-quality aloe (Hoopfer et al., 2015), an emulsion containing melatonin (Ben-David et al., 2016), and an olive oil-based product (Cui et al., 2015).
Ten out of the 15 studies were assessed as having either a moderate or high risk of bias, with only four rated as low risk; one study was not assessed as it was a pilot study. Both Table 10 and the summary of evidence table (***Appendices 7 and 8***) demonstrate the breadth of choice and timing of outcome

measurements, the controls used and the person(s) assessing the skin reactions. Only seven of the studies used a PROM, and of those only two demonstrated statistically significant outcomes in either clinician reported or patient reported measures. Two studies were assessed as having a low risk of bias and statistically significant outcomes (Karbasforooshan et al., 2018; Ben-David et al., 2016). Karbasforooshan et al. (2018) studied the use of silymarin, a herbal medicine (dried extract of *Silybum marianum*, also known as milk thistle) given as a gel. At week 5 grade 1 radiation dermatitis was reported as 100% in the silymarin group, while in the control group grade 1 was reported as 55%, grade 2 as 40% and grade 3 as 5% (P=0.003). While these results look promising, a larger study is needed to replicate this data before the results and this product could be recommended for use in practice.

Ben-David et al. (2016) investigated a melatonin-containing emulsion in patients treated for breast cancer. The highest grade of radiation dermatitis was grade 2 (15% of cases). During treatment, no significant differences were observed between the two groups for clinician assessed skin toxicity in terms of dryness, erythema, tanning, swelling, rash, desquamation, bleeding, cellulitis and hyperpigmentation. For weeks 5-7 there was an interaction between time and group in favour of the melatonin emulsion group (P=0.049). At two weeks follow-up (week 7) the melatonin group were reported as having 59% grade 0, 41% grade 1 or 2, vs 11% grade 0 and 90% grade 1 or 2 in the placebo group (P=0.03). No differences in patient reported subjective measures were identified between the intervention or control groups. Patients in this study received a conventional fractionation (50Gy in 25 fractions) and further research is needed to identify whether the benefits reported in this study could be replicated in cases where a hypofractionated regimen is adopted.

In summary, there is no strong evidence to support or recommend any of the emollients reviewed. There are some promising interventions identified in the studies reviewed, but further research is required to replicate the results in wider populations or in samples using modern dose fractionation schedules before recommendations for use in practice can be made.

5.5.5 Other studies

Two further studies (***Appendix 9***) include one large multi-centre randomised placebo-controlled trial of oral *curcumin C3 complex* (n=283 intervention, n=295 placebo). This study was unable to identify any beneficial effects of using oral curcumin on levels of radiation dermatitis in the sample of patients with breast cancer studied (Ryan Wolf et al., 2018).

The second study (***Appendix 9***) is a dosimetry study on a phantom to test the dosimetric impact of aluminium based deodorant versus non-aluminium based deodorant. Surface dose was measured in tissue equivalent material using optically stimulated luminescent dosimeters (OSLDs). Two antiperspirants containing aluminium, both commercially available, were tested; one had 15% aluminium zirconium tetrachlorohydrex glycine and the other contained 25%. Eight roll on applications were applied to a 5x5 paper square to ensure a thick coating with a control of no coating. OSLDs were placed below the paper and 6MV photons were delivered using 200mu at 100cm SSD at angles 0, 30, 60 and 90 degrees using a Truebeam© linear accelerator. The OSLDs were replaced after each exposure fraction and the same process repeated with the extra strength antiperspirant. No difference in measured surface dose was seen between no antiperspirant and the two strengths of aluminium based antiperspirants tested (Baumann et al., 2017). These results provide further support to reassure patients that antiperspirant can be used safely during radiotherapy without concerns that it may increase the risk of radiation induced dermatitis.

6. Conclusions

Despite reviewing a significant amount of published evidence, still very few definitive recommendations can be made with respect to the optimal intervention for the management or prevention of radiation induced skin reactions.

The use of steroid-based creams is the one area where evidence shows consistent positive benefit across studies assessed as having a low risk of bias. Studies such as Ulff et al. (2017 (a) and (b)), which have reported no significant long-term impact, offer reassurance for their use in specific cases. However, it is important to note that even in cases where positive results were presented, those benefits may not be translated to cases where hypofractionated dose schedules are employed or where the comparator does not include a cream considered to potentially cause irritation. Therefore, the use of steroid-based cream is only recommended for RISR prevention in patients assessed as being at high risk of developing a high-grade radiation dermatitis.

Barrier films and dressings still seem to be widely used. However, the results of studies included in this review are not significant enough to recommend a change in practice. This is partly due to limitations in the design of some of the studies, as well as the variety of products investigated, the high drop-out rate in some cases (due to tolerability of the product), and the limited positive outcomes presented in some studies.

Photobiomodulation therapy (PBMT) is an emerging intervention to reduce RISRs. The use of PBMT has been recognised in other areas of radiotherapy toxicity, such as the treatment of oral mucositis and lymphoedema. Further research is needed on the long-term effects of the use of PBMT as a prophylactic intervention for RISRs before it could be recommended for widespread use, and future research should consider assessment on patients having modern dose fractionation schedules who are at higher risk of developing radiation induced skin reactions.

A significant amount of research is still being undertaken to investigate topical emollients, as shown by the number of such studies included in this review and trials currently recruiting participants. However, these are often single institution studies on one particular product, and as more enter the market the research base is spread across a number of small sample studies of different products. Hence, the review team are unable to draw confident conclusions as it is not possible to pool data in the form of a meta-analysis. Therefore, there is still not enough strong evidence to recommend or endorse any one specific product.

In addition, some of the issues highlighted by the review team with respect to study design and analysis only add to the uncertainty, with a lack of reporting or stratifying for many of the possible patient-related variables as well as variations in radiotherapy technique, planning and dose fractionation regimens.

There may be benefits to risk stratifying patients to allow those at high risk of developing severe (or high grade) radiation dermatitis to be treated with appropriate interventions. For example, there may be cases where it is appropriate for patients to use steroid cream, but currently there is limited data to confirm exactly which groups of patients with specific levels of risk would benefit. Choice of a control or placebo also requires careful consideration and justification within the research method. As identified in this review, some researchers adopted a cream for the comparator that may exacerbate skin irritation experienced by the control arm and thus may invalidate or limit the usability of the study results.

A wide variation in the timing of the assessment of skin reactions was observed, making it difficult to make comparisons across studies, and very few of the studies reviewed included assessment of inter- and intra-rater reliability of the clinician assessed reactions; where this was undertaken, poor reliability of the assessment process was evident. Furthermore, in the topical emollient studies reviewed, patient adherence to the intervention was rarely assessed; patient compliance is an important consideration when considering changes to practice, along with cost and resource use.

Many of the studies reviewed included patients treated for breast cancer prescribed 50Gy in 25 fractions in the adjuvant/post-operative setting. Evidence from good quality clinical trials has shown that hypofractionated regimens (e.g. 40Gy in 15 fractions), as recommended by the NHS England 2016 Clinical Commissioning Policy: Radiotherapy after primary cancer for breast cancer and the UK consensus guidelines for breast cancer radiotherapy, would reduce the incidence of acute skin toxicities compared with conventional (50Gy in 25 fractions) dose regimens.

In light of these concerns, the review team have therefore produced a set of recommendations for skin care research design, based on the assessment of the existing literature. In order to move the evidence base forward for interventions to prevent or treat RISRs we need high-quality research studies and we would recommend researchers in this field try to implement some of the recommendations when designing future studies (see section 9).

The review team recommend future research focuses on identifying the relationship between specific radiotherapy planning parameters (e.g. V107/V110) and acute skin toxicity as well as specific high-risk factors that can be attributed to a high-grade RISR in order that a risk stratification algorithm can be developed to support appropriate decision-making in practice.

The current methods used to evaluate skin toxicity (clinical examination, visual inspection and patient reported symptoms) are all objective. Therefore, collecting data about radiation dermatitis and comparability of studies is difficult. In their study, Saednia et al. (2020) focused on the physiological changes associated with radiation induced dermatitis in breast cancer patients, such as inflammation, which may increase body-surface temperature and can be detected by thermal imaging. They identified quantitative thermal imaging markers that were used in supervised machine learning to develop a predictive model for radiation dermatitis. Saednia et al. (2020) concluded that quantitative thermal imaging has the potential to reduce the biases in current grading systems. Such technologies require further research but may be used to predict those patients who require support and symptom management.

Faithfull et al. (2002) noted “a growing awareness of the need for evidence based practice in radiotherapy” but that there are “well documented disparities between clinical practice and research findings”, reflecting that supportive care is often based on no, little, or poor evidence. Comparing data across radiotherapy skin care studies is difficult as often the methods used are unclear, patient randomisations differ, different skin assessment scales are used, and follow-up data is inconsistent (Kedge, 2009). The findings from SCoR surveys and the survey by Nisbet et al. (2018, 2019) would support such a view.

The surveys highlighted that few departments are following updated national guidelines and undertaking baseline assessment of a patient’s current skin condition. Despite papers emphasising the potential risk factors (Russell et al., 1994; Porock and Kristjanson, 1999; McQuestion, 2011) that may exacerbate a skin reaction, 52% of departments (SCoR, 2014) stated they did not record this information. Without the collection of such data it is difficult to attain a complete picture of the extent of radiotherapy induced reactions, which will be essential for improved research and skin care studies.

Furthermore, 49% of departments (SCoR, 2014) failed to assess and record skin care products currently being used by patients.

Linking with other sectors of care, tissue viability nurses (TVNs) or their equivalent, and district nursing staff with an understanding of radiation induced skin reactions would strengthen improved communication. Understanding and consistency of radiotherapy skincare across the care pathway is needed to reduce patient and staff confusion (Harris, 1997; Cumming and Routsis, 2009).

A main area of variation across departments relates to washing instructions and the use of soap and deodorant (also confirmed by other studies by Barkham, 1993; Lavery, 1995; D'Haese et al., 2009). The traditional patient advice of 'not to wash' the affected area with soap and water, or even to use water alone and no soap, is still given, despite updated evidence that this is unnecessary and there should be no restriction to using a specific type of soap (Campbell and Illingworth, 1992; Burch et al., 1997; Westbury et al., 2000; Roy et al., 2001; Rudd and Dempsey, 2002; Aistars, 2006; Bolderston et al., 2006; Aistars and Vehlow, 2007; Butcher and Williamson, 2012). 74% of departments (SCoR, 2014) reported washing restrictions (i.e. either no soap or limited to specific brands such as Simple® and Dove®); this has the potential to control unnecessarily the choices and preferences that an individual may have.

Expecting patients to follow traditional practice advice of 'not to wash' and 'not to use deodorant', may affect their social wellbeing. For example, breast cancer patients who are advised not to use a deodorant often cite this as one less area of control they have in their life and they note concern regarding body odour (Komarnicki, 2010). In the past it was felt that the metallic compounds, particularly aluminium, within deodorants might cause a secondary radiation effect (Korinko and Yurick, 1997). However, more recent studies contradict this advice as unfounded and outdated (Bennett, 2009; Watson et al., 2012; Wong et al., 2013; Lewis et al., 2014). Currently, 55% of departments advise patients not to use a deodorant under the axilla of the affected side being treated for breast cancer (SCoR, 2014). Patient compliance with these requests has not been assessed (Gosselin, 2010).

There appears to be a propensity to continue with familiar traditional practice rather than an openness to test the effectiveness of products. With the introduction of more expensive skin care treatments to a potentially vulnerable patient group, health care professionals need to consider if such products are more effective than their cheaper comparators and why they choose one product over another (Fisher et al., 1999; Fisher et al., 2000; Pommier et al., 2004; Swamy et al., 2009).

An evaluation of treatment aftercare also requires review to ensure local continuity of care across the pathway; this is a general need highlighted by a Department of Health cancer patient experience survey (DH, 2013).

Radiation induced skin reactions can be uncomfortable and distressing, thereby affecting a patient's quality of life (Lawton and Twoomey, 1991). Skin care advice to patients undergoing external beam megavoltage radiotherapy in the UK is varied. Currently, some of the skin care provided may not alleviate the problem and indeed may even cause skin irritation. This area of patient care is time consuming and expensive, therefore it is important to understand what is being done and why (Harris, 2002b).

7. Guideline recommendations

Overall, the evidence base is not strong enough to either support or refute the use of any particular product for topical application. However, as Gosselin et al. (2010) noted, "patients prefer to take

action rather than do nothing", so the focus for skin care should be on alleviating symptoms and providing comfort.

Therefore, the following eight key principles of effective skin care management are recommended (***Appendices 10 and 11***):

1. Knowledge of intrinsic and extrinsic factors that may affect the development and severity of radiation dermatitis. Prior to the start of radiotherapy, patients should be identified as being at low, medium or high risk based on intrinsic and extrinsic factors.
2. Documentation of current skin care regimen and existing skin conditions, including sensitivities and allergies to certain products.
3. Use of a standardised tool for radiation dermatitis assessment for all patients undergoing a course of radiotherapy (RTOG is recommended; see Table 11). Using the agreed validated tool and scoring criteria, radiotherapy departments should standardise the initial assessment and continued regular monitoring of skin reactions, and ensure that these are recorded. (Cox et al., 1995; Campbell and Lane, 1996; Harris, 2002 (a) and (b); O'Shea et al., 2003).
4. Adherence to a standardised assessment process that includes a baseline assessment and weekly assessments during treatment using the standardised assessment tool.
5. Mandatory local training for all staff assessing skin toxicity, to ensure accurate reporting and maintenance of consistent management protocols.
6. Regular audit of skin reactions to collate accurate data on frequency and severity.
7. An emphasis on empowering patients to use products they are familiar with and to self-monitor their skin, being proactive to improve comfort and minimise the risk of developing severe skin reactions. Recording of patient acceptability/satisfaction and compliance with skin care advice is recommended as such information can be used to evaluate the appropriateness of skin care products for future patients (Harris, 1997; Noble-Adams, 1999; Gosselin, 2010).
8. Testing within a well-designed randomised controlled trial any new product or device designed to reduce radiation dermatitis, before its implementation.

Before radiotherapy begins (baseline assessment)

- Formally assess and document RTOG score (Table 11).
- Discuss and document the condition of the skin on and around the site of treatment.
- Ensure any pre-existing skin conditions, such as infection, sunburn, eczema and psoriasis, are recorded, even if they currently appear latent.
- Discuss and document patients' skin care routines, including any products that are already being used for a medicinal nature (e.g. creams for eczema, such as hydrocortisone).
- Assess, discuss and document intrinsic and extrinsic factors, providing appropriate support and information (e.g. smoking cessation, extra care if skin folds in the treatment area). Those patients with intrinsic or extrinsic influencing factors are at a higher risk of developing a significant skin reaction and should therefore be monitored frequently. Comorbidities, such as diabetes, cardiovascular disease and hypermobile Ehlers–Danlos syndrome (hEDS), may also increase the likelihood of a skin reaction during radiotherapy and should be recorded.
- Provide self-care advice. Education and health promotion strategies and interventions given to patients before treatment, such as nutritional advice and smoking cessation, would be beneficial and are advised (Wells et al., 2004; Kraus-Tiefenbacher, et al., 2012; Sharp, et al., 2013 (a) and (b)).
- Discuss the likelihood of radiation dermatitis developing and the possibility of permanent radiotherapy-related side effects to the skin, e.g. increased skin sensitivity, hyperpigmentation or hypopigmentation, and what precautions to take. For example, advise patients to reduce sun exposure to the treatment area and to use sunscreen with SPF50 (sun protection factor 50).

During radiotherapy

Throughout radiotherapy, the skin should be checked every day and patients should be asked if they have noticed any changes to their skin. The following assessments are recommended on (at least) a weekly basis (Fisher et al., 2000; Richardson et al., 2005; NHS Quality Improvement Scotland, 2010).

- Assess, discuss and document any changes to the patient's skin or skin care routines.
- Encourage self-monitoring of skin changes and support documentation and discussion of these with the radiotherapy team.
- Ask about any symptoms experienced, including pain, itching or sleep disturbance.
- Formally assess and document the RTOG score (see Table 11).
- Provide advice and support to promote comfort (see the summary information leaflet Radiotherapy Skin Reactions: Information for Patients in ***Appendices 12 and 13***).
- Consider over-the-counter or prescription medicines such as analgesics as appropriate.

At the end of radiotherapy

- Inform patients of the potential for skin reactions to worsen and 'peak' around 10–14 days after the last treatment session.
- If patients require ongoing wound management, ensure this is communicated to primary care teams.
- Encourage patients to contact the radiotherapy department or clinical nurse specialist if they have ongoing skin reactions that they are concerned about or that are not as expected.
- Establish effective, ongoing liaison with community care/GP services on post treatment skin (and other) care (Harris, 1997; Cumming and Routsis, 2009; SCoR, 2011a).
- Explain the possibility of permanent radiotherapy-related side effects to the skin, e.g. increased skin sensitivity, hyperpigmentation or hypopigmentation, and what precautions to take. For example, advise patients to reduce sun exposure to the treatment area and to use sunscreen with SPF50 (sun protection factor 50).

Late effects of radiotherapy

There is a small risk that patients may have a delayed skin reaction months or years after their treatment. There is an increased risk for patients who received systemic anti-cancer therapy (SACT) in addition to radiotherapy. Patients with long-term complications may be encountered at follow-up clinics, in the community, or when being seen for re-treatment. Examples of late effects include:

- fibrosis
- lymphoedema
- cellulitis
- telangiectasia.

These late effects can impact on the quality of patients' lives and may not resolve over time; therefore, they should be included in any local site-specific patient information where particularly relevant. Referral to a late effects clinic, dermatologist or appropriate lymphoedema management service may be required.

Table 11: Adapted Radiation Therapy Oncology Group (RTOG) acute radiation dermatitis grading criteria

Grade 0	Grade 1	Grade 2a	Grade 2b	Grade 3
No visible change to the skin	**Faint or dull erythema** Mild tightness of the skin and mild itching may occur.	**Tender or bright erythema** Skin may feel tighter, itchy and/or sore.	**Patchy moist desquamation** Areas where skin has broken down can be seen. Yellow/pale green exudate may be visible on the surface. Soreness and oedema are evident.	**Confluent moist desquamation** More pronounced areas of broken skin can be seen. Yellow/pale green exudate are visible. Soreness and oedema are evident.
ASSESSMENTS				
Weekly assessments and RTOG score			Daily assessments and RTOG score	
AIMS OF CARE				
To promote hydrated skin and maintain skin integrity To promote comfort			To reduce risk of complications of further trauma and infection To promote comfort	
GUIDANCE				
MOISTURISE: Advise the patient to continue moisturising with preferred products. If the patient is not already using a moisturiser, advise them to start. **ENCOURAGE SELF-CARE:** Discuss self-care guidelines and ensure that the patient has sources of information to refer to, including 'Radiotherapy skin reactions - Information for patients'. **STEROID OR CORTISONE CREAMS:** Steroid or cortisone creams should only be used following advice from an independent prescriber or from staff qualified to dispense medication under patient group directions (PGDs). Contraindications for using these creams are broken skin or signs of infection. **ANALGESIA:** Ensure adequate analgesia is prescribed for the patient if needed. **IF THE SKIN BREAKS:** Patients should be advised to discontinue using any cream and should be advised on, or provided with, appropriate dressings. If there are signs of infection, undertake screening. Increase skin assessments to daily frequency. Seek further advice, if required, from a practitioner trained in radiotherapy induced skin reactions and wound care or tissue viability.			**MOISTURISE:** Continue to apply moisturiser to skin within the treatment field that is still intact. **ENCOURAGE SELF-CARE:** Discuss self-care guidelines and ensure that the patient has sources of information to refer to. Follow skin care guidelines and ensure patient has information sources to refer to. including 'Radiotherapy skin reactions - Information for patients'. **DRESSINGS:** Use appropriate dressings/products on broken skin, e.g. non-adhesive, silicone low adhesion. **Do not use** paraffin/petroleum jelly-based products or gentian violet. **ANALGESIA:** Ensure adequate analgesia is prescribed for the patient if needed. **INFECTION SCREENING:** Take a swab if there are signs of infection and arrange antibiotic treatment if infection is indicated.	
If you are unsure, seek advice from the wound care team, tissue viability specialists or dermatology.				

Summary of skin care advice for patients and staff

To reduce friction to the treatment area, patients should be advised to:

- wash the skin gently with soap and water and gently pat dry (Aistars, 2006; Bolderston et al., 2006; Aistars and Vehlow, 2007; Butcher and Williamson, 2012; Wong et al., 2013)
- wash hair gently with usual shampoo (if the scalp is in the treatment field) but not to dry it with a hairdryer (Westbury et al., 2000; Bolderston et al., 2006).
- avoid rubbing, shaving (if possible), and using heat and cooling pads/ice, wax for hair removal and all hair removing creams/products, and adhesive tape (Harris, 2002 (a) and (b); Gosselin, 2010).

To reduce irritation in the treatment area, patients should be advised to:

- use a moisturiser that is preferably sodium lauryl sulphate free (Tsang and Guy, 2013; Patel et al., 2013) and avoid zinc oxide-based creams (Fackrell et al., 2013)
- avoid topical antibiotics unless there is a proven infection (Campbell and Lane, 1996; Korinko and Yurick, 1997)
- continue to use normal deodorant (unless this irritates the skin), but discontinue use if the skin is broken (Bennett, 2009; Butcher and Williamson, 2012; Watson et al., 2012; Wong et al., 2013; Lewis et al., 2014)
- avoid sun exposure, shield the area from direct sunlight and use a high SPF sunscreen or sunblock (Harris, 2002 (a) and (b)).

On broken skin, staff should:

- use an appropriate dressing/product to reduce further trauma and infection. Suitable products would be non-adhesive or silicone low adhesion.

Additional recommendations on training and use of skin assessment tools

The core and stakeholder groups also suggest the following are necessary to ensure consistent patient care:

- Standardised skin care education of all staff caring for patients receiving radiotherapy. All radiotherapy departments should implement pre-treatment skin assessment with baseline observations and pre-radiotherapy review and health promotion strategies. This should be followed with regular reviews (at least weekly, and more often depending on individual needs).
- The reviews can be undertaken by members of the radiotherapy team who have been trained to use the tools, and inter-observer variability between clinicians, radiographers, and radiotherapy nurses should be assessed periodically.
- Agreement on standardisation of assessment tools across departments in the United Kingdom would aid in gathering information nationally.
- Further investigations into the skin care reactions caused by superficial, orthovoltage, and proton beam radiotherapy are required.

8. Implementation strategies

8.1 Implementation and dissemination of learning resources

The core group has developed the following resources:

- A practice guideline for health professionals in Word and infographic format (***Appendices 10 and 11***).
- A patient information summary leaflet in Word and infographic format (***Appendices 12 and 13***).
- A presentation for use at conference and events in PowerPoint format (***Appendix 14***).

8.2 Impact measures and audit tools

- Departments will be encouraged and expected to use the RTOG scale to monitor rates of skin reaction and to share these in a national data collection.
- Departments will also be expected to undertake patient satisfaction audits.

8.3 Organisational or financial barriers to implementation

The majority of the recommendations have no financial implications. There is a requirement for additional training and some additional resources. The main blocks to implementation are likely to be organisational and cultural since the recommendations require changes to established working practices. However, many departments are working through the changes needed to embed person-centred care more fully into daily practice and this guideline's recommendations should be integral to this process.

9. Recommendations for future research

The following recommendations are made following assessment of the existing literature on products or interventions designed to reduce the development of radiation induced dermatitis.
There is a need for more research investigating the impact of dosimetry in modern radiotherapy planning on subsequent skin reactions. For example, more studies like Borm et al. (2018) need to be conducted to inform radiotherapy planning, particularly for patients who are already identified as being at a higher risk of developing significant radiation dermatitis.

Where centres want to consider implementing a new topical intervention or a new device to reduce radiation dermatitis, it is recommended that teams first test the new product/device within a well-designed randomised controlled trial (RCT) that includes the following features, to ensure the evidence is robust enough to inform practice:

a) There should be a clear scientific rationale for introduction of the new product or device.
b) Where possible, RCTs testing a topical agent or device should be placebo controlled.
c) Where barrier films are the focus of the investigation, researchers should use a within-subjects design, with the barrier film placed on half of the area of skin to be irradiated; standard skin care using simple moisturisers and standard washing instructions should be used on the other half of the treated area. The area that is covered by the barrier film should be randomly assigned at an individual level to ensure the impact of positioning does not affect the study outcomes. This is particularly relevant for breast irradiation where the lateral half of the breast is likely to contain more skin folds than the medial half.
d) Assessors should be blinded to the intervention, as should patients, if possible.
e) Skin should be measured/scored at baseline prior to radiotherapy.
f) A standard skin toxicity scoring system should be used, for example RTOG. Assessors should be trained to use the tool and an assessment of inter- and intra-rater reliability should be undertaken and presented along with the results.
g) RTOG scores are categorical (ordinal level) data and, as such, presentation of the data should be by percentage of each grade at each measurement interval during radiotherapy (i.e. week 1, week 2, week 3, etc.), at the end of radiotherapy, and at any measurement points post radiotherapy. Using a mean score to make judgements about the performance of an intervention can be misleading. For example, where a mean score of 2.1 vs 2.3 is presented for different interventions, can it be said that one intervention is better than the other when both are in the grade 2 category? Similarly, what difference in mean score would be considered a sufficient difference for one intervention to be considered better than the other? i.e. is a mean

score of 2.3 better than a mean score of 2.1? What about a mean score of 2.42 vs 2.40? It is understandable why researchers choose to calculate a mean score, but for this score to be relevant, percentages at the time points for each grade of radiation dermatitis (RD) at each measurement interval should also be stated.

h) Randomisation should be remote to the staff collecting and assessing data or providing care.

i) Stratification should be considered when using randomisation, to ensure that important confounding variables, such as breast volume (where appropriate), BMI, smoking status, or use of chemotherapy or targeted drugs (where relevant), are balanced between the study arms.

j) Where PROMs are used, it is useful to have patient reported outcomes in addition to clinician/practitioner reported assessments. The Skindex-16 is one example of a patient reported measure, or the RISRAS scoring system, which has a patient section for reporting factors such as itching and pain.

k) Researchers should employ multivariate analysis to control for confounding variables, and to identify the intervention's contribution to reducing (or preventing) radiation dermatitis in the context of contributions from other intrinsic or extrinsic factors.

l) Measurement and reporting of adherence to the intervention of new products or devices is important, as is reporting the reasons for withdrawal, e.g. whether patients were unable to tolerate it or found the intervention too uncomfortable to continue, which may not be recorded as adverse events.

m) Researchers should measure and document the following confounding factors:

- smoking status
- skin type, e.g. fair, medium, dark etc. or the Fitzpatrick skin type classification system
- use of bolus (size and frequency of use, i.e. daily, alternate days etc.)
- BMI
- use of immobilisation device that may cause attenuation, and therefore increase skin/surface dose
- breast size (volume preferable) where appropriate (not bra cup size)
- relevant treatment planning parameters, including V107%, V80% (skin), if possible, depth of maximum dose (dmax)
- radiotherapy dose and fractionation
- type of radiotherapy, i.e. IMRT, VMAT, 3D conformal etc.
- use of chemotherapy (whether sequential, concomitant, or neo-adjuvant)
- use of targeted drugs
- comorbid disease, such as diabetes
- current skin care regimen and any existing skin conditions, including sensitivities and allergies to certain products
- clear details of any co-interventions, e.g. if patients continue with existing skin care practices of moisturiser use, washing practices etc.

10. Date of publication, review and updating

The evidence available for the Society and College of Radiographers (SCoR) skin care guidelines must be reviewed at five yearly timelines, and revised if required, to ensure the evidence on which they are based is still valid.

An unplanned review may be required due to policy changes, published evidence or the emergence of new technologies and interventions. Identifying the need for unscheduled review is within the roles and responsibilities of the SCoR professional and educational (professional officer) team, under the direction of the Director for Professional Policy.

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Appendix 1

Group members

Appendix 1: Group members

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Appendix 2

Stakeholder consultation combined and outcomes

The Society & College of Radiographers (SCoR)

Template for Stakeholder Consultation Comments

(insert name of document...)

Order number	Commentator	Date	Comments	Actions(s)	Accept/decline
1					
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Appendix 3

External stakeholder comment form

The Society & College of Radiographers (SCoR)

Template for Stakeholder Consultation Comments

(insert name of document...)

Please detail below if you are commenting as an individual or on behalf of an organisation	
Stakeholder Organisation:	
Name of commentator:	

Order number	**Section Number**	**Page Number**	**Comments** **Please insert each new comment in a new row.**
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Please add extra rows as needed

Please email this form to: *(insert lead officer's name...)*

Closing date: *(insert date...)*

PLEASE NOTE: The Society & College of Radiographers reserves the right to summarise and edit comments received during consultations. SCoR may not publish all comments received, however, you can be reassured that every response will be recorded and will inform guideline development.

Appendix 4

2014 Systematic review

Appendix 4: Systematic review 2014

The aim of the 2014 systematic review was to determine if, since 2010, there has been any additional evidence which could further inform or improve current clinical practice and if so what the impact of this additional evidence would be.

Method

The same search criteria were used as in the 2010 review. Initially a search question was formulated using the; Population, Intervention, Control, Outcome (PICO) method **(Table 1)**.

Table1: PICO method

Population	Adult patients undergoing external beam radiotherapy: radiation therapy, irradiation
Intervention	Preventative measures e.g. washing practices, topical applications, deodorant guidance **and/or** management measures - dressings, topical and medical applications
Control	Standard intervention
Outcome	Skin reactions, radiation effect, adverse effect, radiation dermatitis, erythema, moist desquamation, skin care, skin reactions

The review was based on a systematic search of Medline, Pub Med, CINAHL, EBSCO, Science Direct, ISI Web of Science and Index to Thesis.

Hand searches of the *Journal of Radiotherapy in Practice* (JRP), *The European Journal of Cancer* (EJC), *Radiography, Journal of Medical imaging and Radiation Science* (JMIR), *the International Journal of Radiation, Oncology, Biology, Physics* (IJROB) and *Radiotherapy and Oncology* were also undertaken.

In addition, a secondary evaluation of the clinical trials' databases was examined for any ongoing research as well as a search of the grey literature, including index to theses and conference papers. Finally a broad search of *Google Scholar* was used as a 'mop up' technique to ensure no additional relevant research had been missed.

Owing to the fact that a wealth of evidence had been reviewed in the primary audit and this is a continuation of that work it was deemed appropriate to map out and replicate the initial search strategy and then where appropriate include any additional resources.

The traditional pearl growing method begins with a single document relevant to the topic under review and utilizes key words for this key or seminal text, but pearl growing until more recent years has often been overlooked as a strategy for literature searching (Schlosser et al., 2006). The Comprehensive Pearl Growing (CPG) method has developed from this and uses multiple key

documents rather than just one. It is considered to be more systematic in its approach and deemed an appropriate method to be used for yielding results in a systematic review (Schlosser et al., 2006). For the purpose of this review, Comprehensive Pearl Growing is an appropriate and important method to use in the initial stages of the strategy as this is following on directly from a seminal piece of previous published work and one other key document.

Table 2 indicates the key terms used within the search strategy, drawn from the seminal articles.

Table 2: Key terms

Aspect	**Key term**
Radiotherapy	Radiotherapy, radiation therapy, irradiation
Outcome	Skin reactions, radiation effect, adverse effect, radiation dermatitis, erythema, moist desquamation, skin care, skin reactions, evidence-based practice

Those studies included initially had to fulfil the following criteria:

- All literature from November 2010;
- All papers that have an English abstract;
- Papers that assess the use of a topical agent;
- Papers where the primary focus is skin reaction to radiotherapy.

Studies excluded were either owing to not meeting the above criteria or for the following reasons:

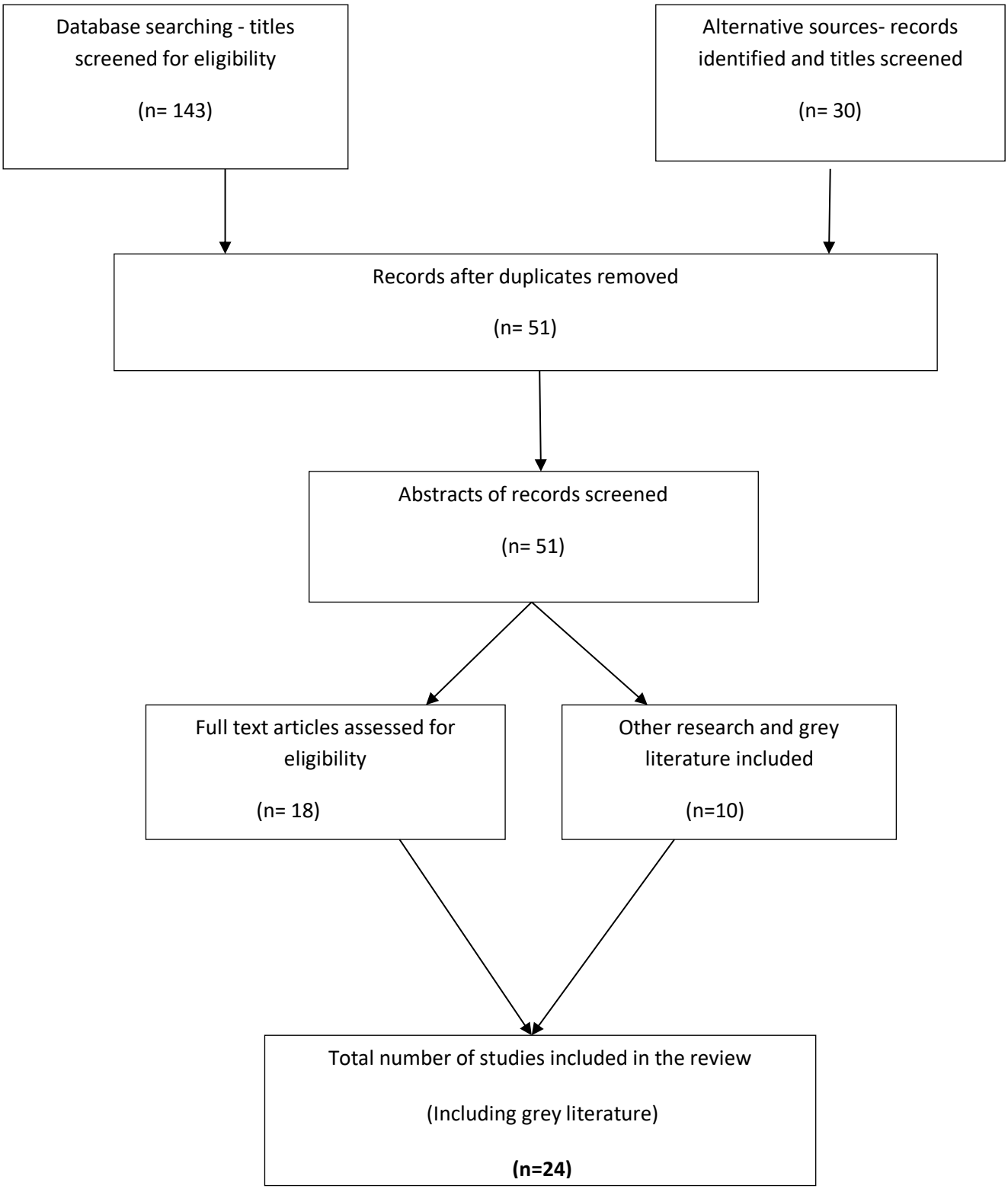
- Reactions caused by a pre-existing genetic or medical disposition;
- Case studies;
- Rare skin reactions caused by topical agents or chemotherapy drugs;
- Papers where the primary focus is the impact of the immobilization device or radiotherapy planning technique on the skin reaction.

All appropriate full text articles underwent quality assessment using the Scottish Intercollegiate Guidelines Network (*SIGN)* quality assessment tool. Initially the Grading of Recommendation, Assessment, Development and Evaluation (*GRADE)* system was proposed, however upon further investigation the *SIGN* tool was deemed more appropriate and relevant for this particular study. To ensure the correct assessment questionnaire was used, all studies were mapped against the *SIGN*: 'Algorithm for classifying study design for questions of effectiveness' (www.sign.ac.uk, 2013)

Results of Review

A flowchart including the number of hits obtained in the database searches, those abstracts screened for relevance, down to the final number of articles are included in the review.

Diagram 1: Flowchart of literature review



Research is continually emerging within this area, possibly due to the lack of conclusive evidence and the disparity between the published research as highlighted earlier, therefore it was deemed appropriate to include within the results any relevant 'grey literature' such as research protocols, conference presentations, symposiums and ongoing research trials.

Randomised Control Trials (RCTs) and Systematic Reviews (SR)

- Quality assessment using the appropriate *SIGN* checklist was undertaken, a total of 17 articles were available for review: 2 Systematic reviews, 14 RCTs, I case control.
- Of the RCTs and systematic reviews (n=16): 5/15 (33%) were classed as high quality evidence; 8/15 (53%) classed as acceptable evidence; 3/15 (20%) rejected as unacceptable quality. (See ***Appendix 5*** for summary of articles table.)
- The final number of studies included in the review: 2 systematic reviews, 11 RCTs and I case control.

Of the RCTs (n=11)included in the final review, nine were studying a different topical emollient or product (Jensen et al., 2011; Kirova et al., 2011; Miller et al., 2011; Abbas and Bensadoun, 2012; Niazi et al., 2012; Graham et al., 2013; Sharp et al., 2013; Ulff et al., 2013; Herst et al., 2014,) and two studies were reporting the use of non-metallic antiperspirants (Watson et al., 2012; Lewis et al. 2014). *(*see ***Appendix 6*** for full systematic review report.*)*

The RCTs

Jensen et al. (2011) reported results of an RCT assessing an oil in water emulsion on 68 breast cancer patients experiencing radiation dermatitis following completion of radiotherapy treatment. Patients were randomised to either a treatment group where the emulsion was applied for 6-8 weeks or a control in which they were not treated at all. It was considered that the emulsion would increase skin hydration, especially to the stratum corneum (as measured by a corneometer) and this would reduce clinical symptoms of radiation dermatitis. Results showed no pronounced differences between the two groups.

Kirova et al. (2011) conducted a phase III RCT comparing Hyaluronic acid to an unspecified emollient placebo arm. Two hundred breast cancer patients receiving external beam radiotherapy were recruited with 1:1 randomization. Evaluations were undertaken weekly using the RTOG scale and patient pain and quality of life (QoL) were also completed on alternate weeks. The results found no significant difference between the 2 arms however a lower level of pain and colorimerty was seen in the treatment arm (P=0.46), although not statistically significant.

Miller et al. (2011) also investigated the effect of a steroidal treatment, 0.1% Mometasone Furoate (MMF) using a double blind RCT, on 176 patients receiving external beam radiotherapy for breast cancer. Patients were randomised to either 0.1% MMF or to an identical appearing placebo. Patients underwent baseline evaluation and then at weekly intervals using the *Common Terminology Criteria for Adverse Events (CTCAE)* and patients also reported QoL and symptoms on an assessment form, as recommend by Schnur et al. (2013). No baseline demographic characteristics were reported in this study such as BMI, breast size, patient age and skin colour. The primary endpoint of the study was radiation dermatitis. No significant difference was found in the mean results of the assessment for dermatitis as most patients only encountered grade 1 or 2 toxicity. This limited the assessment of

how effective MMF might be on radiation induced dermatitis. The secondary endpoints of patient itching, irritation and annoyance, were reported as reduced in the treatment group (P=0.07), however this was not statistically significant. The authors concluded that further research is required with respect to the use of MMF.

Abbas and Bensadoun (2012) conducted a non-blinded RCT on the use of an oil based emulsion, Trolamine®, with washing instructions versus a control group of washing only. The washing instructions were complex and compliance with these instructions was not assessed or evaluated. Patients in the treatment arm were to apply Trolamine® from day 1 of treatment and for 2 weeks post radiotherapy completion. Assessment of radiation dermatitis was undertaken using the RTOG scale. The results of the study indicated that Trolamine® can reduce the acute dermatitis particularly at higher grades, citing a significant difference between the treatment and control arms with 20% of participants in the treatment group and 53.4% in the control group developing RTOG grade III reaction ($P<0.01$). The study does however report conflicting results from previous research undertaken by Elliot et al. (2006) who found no advantages to using Trolamine®.

Niazi et al. (2012) phase III study investigated the use of a silver clear nylon dressing (SLND) as a prophylactic and interventional skin treatment for patients receiving external beam radiotherapy for lower gastrointestinal cancer. Patients with both rectal and anal cancers were included in the study and were randomised to either receive the dressing or the normal standard of care which was sulfadiazine cream at the point grade 1 dermatitis became present. It was not possible to blind the study due to the visible nature of the dressing, however adequate concealment was addressed. Forty patients' results were reported in the trial on a 1:1 ratio and compliance in dressing application was evaluated on a weekly basis. There were some differences between the histological diagnosis of the patients and then subsequently the concurrent chemo/ radiotherapy regimes. Radiotherapy doses were presented as a range rather than as discreet values which may be worth noting. The primary endpoint was skin toxicity on the final day of treatment and high resolution photographs were taken 2 weeks prior, on the last day and 2 weeks after radiation completion. To reduce bias due to the fact blinding could not occur, evaluation of the data was undertaken by 10 oncologists from multiple centres who were blinded to the intervention. The study reports mean scores in favour of the SLND arm ($p =0.01$) so that SLND reduced the severity of radiation induced dermatitis in the included patient cohort and that it is a cheap, simple effective method to use and these results also further validate their results from a Phase II trial. Further discussion with the manufacture resulted in modification to the dressing to be integrated into a boxer short style which they report resulted in improved patient compliance. No further recommendations were made by the authors to repeat the study using the shorts or with a larger cohort.

Graham et al. (2013) undertook a randomised double blind RCT to test the impact on radiation induced skin reactions of a barrier cream containing acrylate terpolymer (ATP) vs a 10% glycerine cream (Sorbolene) on women undergoing post-mastectomy radiotherapy. The primary outcome investigated peak and overall skin reactions using the Common Terminology Criteria for Adverse Events (CTCAE) scoring tool (version 3.0); frequency of grade 3 or greater reactions and mean area under the curve was used to assess differences between the products; levels of moist desquamation was also recorded. The authors also used a photographic audit of skin scores to confirm reactions scored by clinicians. The majority of patients had bolus, which will have increased the overall

severity of the skin symptoms. Eleven percent of the sample had concurrent chemotherapy, 65% were on hormone therapy, and radiation doses ranged from 38Gy to 56Gy in a range of 19-28 fractions. These variable confounders were not individually or collectively assessed within the analysis to identify the impact on skin reactions post treatment.

Randomisation was undertaken for 333 patients using a within-subjects design. Medial and lateral compartments of the chest wall were allocated to one of the two cream products; 94% completed RT and 96% had complete skin assessment scores (actual sample for analysis n=318). Skin reactions were worse in the lateral compartment than the medial compartment, with moist desquamation rates higher laterally than medially. No significant difference was identified between the two skin creams for grade 3 or higher skin reactions.

Interestingly only 2/3 of participants fully adhered to the guidelines on cream use. This was primarily related to patients either applying more cream than required or applying the cream more frequently. Non-adherence appeared even between medial and lateral applications and across products. When medial/lateral was compared, in the proportion of cases with ≥ grade 3 skin reaction, there was a significant difference between skin reaction rate for medial applied creams (Sorbolene vs barrier cream) - 18% (Sorbolene) - vs. 28% (ATP moisturizing double barrier cream) respectively (p=0.047); no significant differences between products could be identified for creams applied to the lateral portion of the chest wall (45% Sorbolene vs 37% barrier cream p=0.13). The authors consider this a chance finding (type I error). This is a well-conducted study that shows no difference between cream products on the extent of acute radiation induced skin reactions. A number of limitations of the study are of note as follows:

- The publication lacks a flow diagram of study participants entered and those completing RT and skin assessments. It is unclear how many patients were approached to be randomised and refused or how much missing data there is for each assessment time period.
- There is a distinct lack of information and detail on the RT techniques employed across the 12 participating centres. It is possible that different levels of quality assurance are achievable across so many centres and may have gone undetected with unknown effects on overall skin reactions.
- The centres employed a range of dose and fractionation schedules, which may influence skin reactions. We know nothing about whether simple tangential fields were employed or 3D conformal techniques or field in field techniques.
- The addition of bolus in the majority of cases will have increased the severity of skin reactions seen, as well as concurrent chemotherapy in some cases (chemotherapy regimens were not documented).

Sharp et al. (2013) conducted a randomised blinded study comparing two topical agents, Calendula Weleda® cream vs. Essex® (Aqueous) cream (n=411) in patients undergoing radiotherapy for breast cancer. The primary endpoint was the difference in the proportion of patients with acute radiation induced skin reactions (ARSR) assessed using the RTOG skin scoring system. The authors also measured quality of life using the EORTC (European Organisation for research and Treatment of Cancer) QLQ C30 scale, sleep disturbance and symptoms from the irradiated area using a visual analogue scale as well as patient experience and adherence. The incidence of severe ARSR (RTOG

grade ≥2) was 23% in the Calendula group and 19% in the Aqueous cream group at the follow up time point (p=0.55). Similarly no difference was found between the groups for patient reported symptoms of pain, burning, itching, pulling or tenderness. No difference was found between the groups when comparing QoL or sleep disturbances at the follow up visit. There were adherence rates of 86-87%.

There was no difference between the groups in "no" or "mild" acute radiation induced skin reactions at any of the assessment points, and no grade 4 toxicity was reported. Overall moist desquamation rates are modest (3% and 2% Calendula vs. aqueous cream respectively). This high quality study demonstrated no benefit from using Calendula Weleda® cream over Aqueous cream BP although some study limitations are worth noting:

- There are relatively few data collection points during the course of radiotherapy ie not weekly, and the follow up data time point varied.
- Information about the radiotherapy technique employed is sparse; we only know that IMRT was not used in any cases.
- While the researchers were given training on use of RTOG and the RTOG has previously been tested for inter and intra-rater variability, it was not assessed in this study.
- A substantial number of patients declined to participate in the study (n=250). It is postulated that this may be due to the participants being aware they were going to be assessed for smoking status. However, similar (in fact slightly higher) proportions of smokers were included in this study compared with other similar studies.

Ulff et al. (2013) undertook a double blinded RCT investigating the use of Betamethasone® (a steroid cream) versus two alternative moisturising creams. The study concentrated on patients with breast cancer and a total of 104 patients were randomised into 3 arms:

- 1. Betamethasone® combined with Essex® cream
- 2. Essex® cream (moisturiser)
- 3. Canoderm® cream (moisturiser)

Patients started application of the cream to the whole of the irradiated area during week one of treatment and continued until two weeks post radiotherapy completion. The authors state that the contra-lateral breast was used as control which sounds a little misleading as it isn't being irradiated but it could be interpreted that they were using it as a way of measuring increases in skin redness. Assessments of dermatitis were made using the RTOG scale and skin redness was measured with a colorimeter. All patients received adjuvant chemotherapy and baseline demographics for each patient were recorded such as bra size, age, and BMI. Patients were also measured on the degree of itching, burning and discomfort using the *Visual Analogue Scale* (VAS) and *Dermatology Life Questionnaire Index* (DLQI).

Patient-related measures have been highlighted as an area often neglected by the research and that patients are very rarely asked about their experiences (Schnur et al. 2013)**.** It is suggested this is potentially due to a lack of agreement on the best scale to use but recommended that all future research should include at least "one patient-rated measure" (Schnur et al. 2013).

Results of the study found a statistically significant difference in the RTOG scored skin reaction at week 4 between those treated with Betamethasone® combined with Essex® cream (P= 0.003) versus stand-alone moisturisers. Some patients developed a mild reaction but this was reported as less in the treatment group than the control. Although patient demographics were recorded within the study no reference was made to these with respect to the efficacy of the treatments. The final assessment was undertaken as a telephone follow-up two weeks post radiotherapy completion. The results may be open to a greater bias as this was patient perception led rather than researcher led evaluation. The authors concluded that there may be contraindications to the long term use of steroids, such as loss of skin integrity.

Herst et al. (2014) conducted a within-subject RCT into the prophylactic use of Mepitel® film for breast cancer patients receiving radical external beam radiotherapy. A total of 78 patients were included in the study and were randomised to have the medial or lateral half of their breast/chest wall to receive either Mepitel® or a control of aqueous cream. It was not possible to blind the study due to the nature of the film being visible but patients doubled as their own control. The primary endpoint of the study was to evaluate extent of moist desquamation. The study reported 0% moist desquamation rates for the Mepitel® covered areas and 26% for the control areas ($p<0.0001$) and subsequently determined that within the Mepitel® film cohort moist desquamation was completely prevented.

Separations in this study ranged from 16.1cm up to 31.2 cm, and BMI mean was 27.06 (range 16.12-42.72). The mean BMI is quite high ie >25 suggesting most of the sample were overweight although no association between BMI and skin toxicity was seen. It could be that the following factors led to the unusually high moist desquamation rates reported in the control arm of this study:

- larger patients, combined with 3D conformal (rather than IMRT)
- 37% of the sample had a boost treatment,
- Moist desquamation rates were taken at 4 weeks post treatment
- Aqueous cream used in the control arm and
- Approximately 47% had 50Gy in 25# (rather than 40Gy in 15# or equivalent).

The authors also reported that even within their control that their rates were still lower than had been previously presented in the literature. No further recommendations by the authors were made to sample a larger cohort or to undertake a multicentre RCT to further strengthen their results. It is also interesting to note that the control was aqueous cream which has itself recently undergone scrutiny and is not widely recommended as a standard of care

Compared with the Cambridge breast trial [(1)] where rates of moist desquamation of 0-2% were reported the MD rates in this study seem high. Given the study design it would be sensible for Mepitel film to be tested in other centres where techniques other than 3D conformal techniques are used (ie simplified IMRT or field in field techniques where it has been shown that outcomes such as skin toxicity is better) and where the control arm does not use aqueous cream but is a comparator of the patients normal skin care regime under national guideline advise and where the now accepted regimen of 40Gy in 15# (or equivalent) is used and detailed assessment of patient weight/size is

given in the analysis as this has also been shown to be a significant predictor in other studies of acute skin toxicity.

1.Barnett GC, Wilkinson JS, Moody AM, Wilson CB, Twyman N, Wishart GC, et al. The Cambridge Breast Intensity-modulated Radiotherapy Trial: patient- and treatment-related factors that influence late toxicity. Clinical oncology. 2011;23(10):662-73.

Watson et al. (2012) performed a single centre non blinded RCT evaluating the use of aluminium based antiperspirants for 198 patients receiving external beam radiotherapy for stage I and II breast cancer. The authors highlight the negative impact on patients' quality of life that can arise due to the restrictions on deodorant usage. Patients were randomised into either a control group of standard skin care instruction which included no antiperspirant usage or the experimental group where patients were provided with a specific deodorant containing a "moderate amount" (21%) of aluminium. Both groups underwent weekly skin assessment reviews and were measured using the CTCAE throughout treatment and two weeks post completion. There was no measurement of compliance within the control arm to ensure patients were not using a deodorant. Results demonstrated no statistical difference between the groups with respect to skin reaction or QoL. The authors report that two independent RCTs were also being undertaken but with non-aluminium based antiperspirant and they also found no significance between the control and the experimental groups. The authors therefore conclude that the use of a non-metallic deodorant/antiperspirant does not increase the risk of a skin reaction; however they acknowledge that more research needs to be undertaken with respect to metallic deodorants. Watson et al (2012) are cited in the MASCC (Wong et al., 2013) clinical practice guidelines which make "strong recommendations to allow the use of antiperspirants during breast radiotherapy".

Lewis et al. (2014) conducted a randomised double blind study (n =285) assessing effects of aluminium based deodorants. The study consisted of three arms, 1, Aluminium –containing deodorant plus soap, 2, Non aluminium containing deodorant plus soap and 3, soap only. Soap was low irritant pH6, free from fragrance, colour and lanolin and propylene glycol. Outcome measures: RTOG, sweating assessed by the Hyperhidrosis Disease Severity Scale (HDSS) plus weekly assessment of itching, pain and burning using a visual scale measured at 4 weeks.

There was no association between deodorant use and RTOG score. The change in itching, pain or burning in the axilla was 0.02cm higher in the aluminium deodorant group compared with the control but this was not significant, patients in the aluminium deodorant group experienced significantly less sweating than the control group.

Conclusion: use of aluminium deodorant did not adversely affect skin reaction.

<u>Self controlled clinical trial</u>

Haddad et al. (2013) undertook a within-subjects trial on the use of an Aloe Vera product on 60 patients receiving external beam radiotherapy for treatment sites within the head and neck, pelvic and breast regions. The anatomical treatment area was divided into two symmetrical halves and patients were instructed to apply the Aloe Vera product on one half of the area. Grading of dermatitis was via the RTOG scale. Results of this study indicated no significant difference between the control and the treatment halves at lower doses but indicated a positive effect on the Aloe Vera

side at higher doses and reported statistically significant differences in support of Aloe Vera from week four until the end of radiotherapy. The steering group for The College of Radiographers feels that the study by Haddad et al. (2013) is not methodologically strong enough to refute or support previous published evidence in the use of Aloe Vera products.

The systematic reviews

Butcher and Williamson (2012) undertook a systematic review of the literature on the management of erythema and skin preservation for patients receiving external beam radiotherapy to the breast. All literature was assessed for quality and in total 10 studies were included in the final analysis. They concluded that no one product was considered superior to another. The review advocates the safe use of non-metallic deodorants. The review also highlights the wide variety of methods and assessment scales used to report study findings thus making meaningful comparisons very difficult.

Chan et al. (2014) undertook a systematic review and meta-analysis which included 47 RCTs from 1962-2012. This large date range is a slight limitation as studies conducted during the 1960s are likely to include orthovoltage energies and Cobalt treatments with subsequent associated skin reactions that are not relevant to the skin sparing effects achieved with modern linear accelerators. Studies examined a range of practices:

- 6 trials investigated oral systemic therapies
- 2 investigated washing practices
- 4 examined deodorant use
- 5 investigate topical steroidal therapies
- 23 examined non-steroidal topical therapies
- 6 investigated dressings
- 1 investigated light emitting diode photo-modulation

Thirty-six of the included studies were considered at high risk of bias, 10 rated at unclear risk and one as low risk; confirming our own experience of quality assessment of studies in this field. Allocation concealment was only reported in 22 of the 47 studies reviewed. Blinding of assessors was only adequately described in 21 of the 47 studies. Similarly, only 21 of the 47 studies adequately reported how attrition was handled in the analysis.

A small meta-analysis of two studies investigating oral systemic therapy (oral Wobe-Mugos E vs. no medication) indicated the odds of developing a radiation induced skin reaction was 87% lower for people receiving Wobe-Mugos E (although heterogeneity for the studies was high I^2=70%). A meta-analysis of 226 participants from two un-blinded studies found no difference in radiation induced skin reactions when comparing deodorant use to no deodorant use. Four trials investigated the role of topical steroidal agents on radiation induced skin reaction. Three of these studies identified no benefit while one small study (n=20) found a statistically significant benefit for using prednisolone with neomycin compared with no treatment. However, some of the topical steroid trials had small sample sizes and wide confidence intervals hence the results should be viewed with caution.

Overall the review concludes that the evidence for any intervention is 'thin' i.e. no strong evidence of effect for any of the included trial products to reduce radiation induced skin reactions. The study concludes that patients should be advised to wash gently and using non-metallic deodorant is not contraindicated. Recommendations for future studies include a focus on an area of promise such as oral Wobe-Mugos E and oral zinc. Future studies should also attempt to clarify which patients would benefit from corticosteroid cream, and appropriately powered RCTs comparing different dressings for those that develop moist desquamation.

Other published Literature

Chan et al. (2012) compared the effectiveness of a natural oil-based emulsion (Moogoo Udder® cream) to a control of aqueous cream. The double blind randomized study included patients undergoing radical radiotherapy to variety of treatment sites, including breast, chest, and head and neck regions. The primary end points of the study were to assess the incidence of grade 2 and 3 dermatitis, with secondary end points to assess QoL, pain and itching, throughout a course of treatment and up to four weeks post radiotherapy completion. Standard departmental skin care advice was given to both groups and measurements undertaken using the CTCAE as well as a survey to assess quality of life. Results from this study have not yet been presented.

Uzaraga et al.* (*2012) conducted a 16 patient single arm pilot study into the use of a topical gel mix of Amitriptyline, Ketamine.and Lidocaine (AKL) especially for the treatment of neuropathic pain caused by radiation induced skin reactions. The authors noted that neuropathic pain is often experienced by patients and there is a lack of evidence investigating how this could be managed. The pilot study reported that AKL gel may be effective in alleviating this type of pain particularly in those patients for whom standard opioids are not effective. They concluded that following the results of the pilot there was a need for a Phase III multi centre RCT.

Zenda et al. (2013) undertook a prospective phase II study investigating the possible reduction in the incidence of severe radiation dermatitis in 113 patients undergoing head and neck radiotherapy. They proposed the implementation of a "Dermatitis Control Program" which contains 3 well defined steps:

> *Step 1* - a watchful wait approach where patients are only advised to undertake gentle washing;
> *Step 2* - consists of supportive treatment for Grade 2 dermatitis which involves the use of Vaseline® and gauze;
> *Step 3* - consists of supportive treatment for grade 3-4 radiation dermatitis plus the use of topical applications to reduce the risk of infection.

This study did not advocate the use of corticosteroids or antibiotics unless an infection was present. The results showed that no patients developed Grade 4 Dermatitis, grade 2 and 3 were seen in 56% and 9.7% respectively. The authors could not report the prevention of radiation dermatitis or the effectiveness of corticosteroids. They acknowledge the need for further research into the use of corticosteroids.

Robertson and Brown (2011) surveyed 237 members of the UK public in two cities to identify which brands of soap were considered as "mild". Interestingly the authors undertook PH tests of the 8 leading brands reported by the general public and found that all of them were actually acidic. The authors reported that patient instructions on using a "mild soap" can often be quite vague and open to misinterpretation and also found that 83.1% of the sampled population preferred to shower rather than bath and used liquid soaps rather than solid soaps and therefore highlighted possible implications when recommending "soaps" to patients. They also noted that when recommending a particular brand there are often a wide variety of options within that particular brand, so for example within the brand Dove® there are 10 different types of body wash.

Within the inclusion dates of this review there have been publications to the *Journal of Community Nursing* which raise some interesting points. Firstly, ***Trueman (2013)*** investigated the ability of healthcare practitioners to manage radiation induced skin reactions within the community and also highlighted the recent evidence base which shows that aqueous cream containing sodium lauryl sulphate can be a skin irritant. Secondly, ***Scott (2013)*** reported on an ongoing study evaluating the use of polymeric (PolyMem®) dressings for patients with an RTOG score of 1-2.5 over a 4 week period. Scott (2013) reports that the use of the PolyMem® reduced skin reactions within the first week of treatment when measured with clinical observations and that by week four 75% of patients' skin reactions had healed. The authors report one of the most significant findings being the decline in pain scores between weeks 1 and 3 when using the 'Wong and Baker grades' (Wong and Baker, 1988) and a numerical rating description. This work is part of a multi centre study which is currently ongoing.

Grey literature

During the inclusion period of this review there have been a number of abstracts and short publications published, as well as conference presentations, which are of note.

Hardefeldt et al. **(2012)** submitted a letter to the editor of *Radiotherapy and Oncology* for publication regarding a meta-analysis of deodorant use and the risk of skin toxicity in patients undergoing radiotherapy. Their aim was to analyse all published RCTs which investigated the adverse effect of using deodorant. In total they found four RCTs, three of which favoured the use of deodorant. They concluded that no evidence had been found that deodorant increases adverse events but recommended the need for more "high quality" studies to be undertaken to fully exclude a link.

Lopez et al. (2013) submitted an abstract to the Journal *Reports of Practical Oncology and Radiotherapy* which outlined their study into the use of a hydrofibre dressing to prevent the progression of radiation dermatitis. They concluded that the dressings were effective in reducing dermatitis and could be safely used even over long periods of time.

Bennett et al. (2013) published an abstract in the *Journal of Medical Imaging and Radiation Sciences* outlining a RCT into the use of Mepilex® dressing versus a control of aqueous cream in managing

radiation skin reactions in post mastectomy patients receiving external beam radiotherapy. They concluded that Mepilex®Lite dressings reduce all aspects of radiation induced skin reactions.

At the 2013 *RTi3 Conference, Canada,* ***Lock and Rempel*** (2013) presented a webinar of their research on the use of 3M Cavilon®, no sting barrier cream. The study method involved dividing the affected breast of those patients receiving external beam radiotherapy into 4 quadrants with randomisation to apply the cream in 2 of the quadrants. Measurements were taken using the Skin Toxicity Assessment tool (STAT) and photographs were also taken on day one of treatment and during the 7-10 day post radiotherapy follow up appointment. This is an ongoing trial so no final analysis is available at this time.

At both the *UKRO* and *ASTRO* 2013 conferences, ***Hindley and Dunn (2013)*** presented the results of a trial on the effectiveness of Mometasone Furoate (MMF). One hundred and twenty patients were randomized to receive either MMF or the emollient Diprobase®. They concluded that: *"Mometasone Furoate cream significantly reduces radiation skin reactions when used from the start of radiation".* They also reported a 60% reduction in the appearance of moist desquamation. They recommended: *"where skin reaction cannot be prevented, then Mometasone should be prescribed from the start of radiation until the reaction begins to subside".* However at the *UKRO* presentation the authors did highlight the need for further work to ascertain the impact of the chronic use of steroid creams.

Literature rejected *(following Quality assessment using the SIGN checklist)*

Studies from this review were excluded for a number of reasons including methodical qualities. Two examples of these studies have been included below.

Zhong et al. (2013) undertook a single centre study RCT comparing Mepilex® Lite dressing vs. normal skin care (cleaning with salted water) in a sample of patients undergoing radiotherapy following a diagnosis of nasopharyngeal carcinoma (n=88). Patients were invited to participate if they developed moist dermatitis post radiotherapy. The primary outcome measure was time to wound healing; defined as time from recruitment to the study and observation of complete re-epithelealisation and absence of moist desquamation. In the intervention group the median time to wound healing was 16 days (95% CI 12-19 for Mepilex®) and 23 days for the control arm (95%CI 19-27) p=0.009. Although on multivariate analysis initial tumour stage, n-status, radiotherapy technique and initial wound size were the only independent factors that determined prolonged time to wound healing, dressing type was no longer significant. The average increase in RISRAS scores demonstrated less increase in scores with the Mepilex® Lite dressings than the control arm (p=0.009). However, it is unclear as to why the researchers chose to present the average increase scores rather than the total average RISRAS scores. If patients start with a high score (ie 3 for pain and discomfort) and continue to get no resolution in the pain, their score will remain at 3 so will not increase. Thus the endpoint may give misleading results. It is also interesting to note that the patient reported RISRAS scores between the control and intervention arm differ by less than 0.5 (ie less than 1 category score on the grading scheme).

While there may be some patient comfort to be gained by using the Mepilex® Lite dressings, the lack of blinding and lack of assessment of scoring reliability by researchers makes establishing the true

benefit of the dressing difficult. Owing to this unreliability, the study was rejected by the reviewers on quality grounds.

Paterson, et al. (2012) undertook a within subjects RCT (with no blinding) comparing Mepilex® Lite dressings with aqueous cream. All women undergoing post-mastectomy RT across four RT centres were screened for recruitment and inclusion into the study. Eighty patients were randomised and 74 complete data sets were available for analysis. Radiotherapy was delivered via tangential beams in almost all cases, however at one centre some patients were treated with skin apposition electrons based on clinician preference (9.5% of total sample), most had bolus although this varied between 3-5mm (44.6% and 21.6% respectively), but bolus was less common in one of the centres. Dose fractionation varied but for 68% of the sample was 50Gy in 25 fractions, 52% of cases had pre treatment chemotherapy, and 12.2% had concurrent chemotherapy. Almost a third of the sample was current or ex smokers. Radiotherapy technique employed tangentials with field in field in some cases to reduce hot spots, although it is not known for how many cases this was employed. Interventions were only introduced once erythema had started and then the focus of the treated area remained that site despite other sites of erythema or worse skin reactions appearing later. As radiotherapy progressed, the area that developed moist desquamation either continued to be covered by the Mepilex® Lite (if already in the intervention area) or, if it was in a control area, was covered with dressings standard to that department ie in two centres this was Mepilex® Lite, in one centre it was hydrogel covered with a non adherent wound contact layer and an absorbent pad and in the fourth centre a cotton gauze with Sivadene cream 1% was used.

Results showed improved average RISRAS scores for Mepilex® Lite compared with aqueous cream ($p<0.001$) although no significant difference was identified for moist desquamation (MD) rates. The Mepliex lite did not reduce the likelihood of the erythematous area developing into MD and this was primarily a function of the use of bolus across most of the centres. As the comparator arm employed aqueous cream, it is not clear whether Mepilex® Lite is any better than no intervention for reducing erythema. The patient reported RISRAS scores do point to improvements in patient related symptoms that maybe of note.

However, again it is difficult to be clear whether the Mepilex® Lite would perform better than no intervention. In addition, the greater use of higher dose fractionations (50Gy in 25 fractions and the use of bolus are likely to contribute to the erythema experienced and with different dose fractionation schedules, use of IMRT and avoidance of bolus, the skin reactions experienced by patients may be significantly less. Therefore this study was rejected primarily based on lack of Radiotherapy QA, no inter-rater reliability assessments and a lack of blinding.

Diggelmann, et al. (2010) undertook a systematic inpatient controlled trial into the use of Mepilex lite dressings on 24 breast cancer patients. Patients were randomised, however blinding was not undertaken as this was a within subjects design. Areas of erythema were divided in half and randomly assigned to have either the Mepilex lite dressing or aqueous cream. Outcome measures included severity of skin reaction, dose build up and skin surface temperature. The primary trial outcome was dry desquamation, so if erythema developed into dry desquamation then Mepilex lite dressing was used regardless if it was assigned to aqueous cream or Mepilex lite. RISRAS scoring was used, however there was no assessment of inter or intra-rater reliability.

Patients received 50Gy in 25# and of the 28 patients recruited of these 2 patients were excluded because aqueous cream not used and Mepilex was not replaced correctly and it could be argued that they should have still been included and used as an intention to treat analysis.

A further 2 patients were not included because erythema not reported. No power calculation for sample size and confounding variables such as skin type, chemo status, and hormone status not controlled for in the analysis. Randomisation was not concealed but undertaken based on order of recruitment into the trial. There was also no blinding of assessors. The study was rejected by reviews based on a lack of methods to minimise bias.

Appendix 5

2014 On-going trials table (1)

Appendix 5: Ongoing trials in 2014

In order to ascertain current research being undertaken in this field, a search of the clinical trials database was undertaken **(www.clinicaltrials.gov).**

The following studies were found and have been outlined in the table below.

Study Title	Authors	Method	Anatomical areas	Stage	Country	Hospital(s)
A phase III double blind study on the efficacy of topical Aloe Vera Gel on irradiated Breast tissue	Johnson JS	Double blind phase III RCT into topical Aloe Vera comparing 2 over the counter aloe Vera products	Breast	Recruiting	USA	Lewis Hall Singletary Oncology Center at John D. Archbold Memorial Hospital, Thomasville Georgia, USA
A Phase II Study Designed to Evaluate the Value of NeoVIDERM Skin Emulsion in the Prevention of Radiation Dermatitis for Patients Undergoing External Radiation Therapy	Vuong T, Davis MB.	Patients are randomized to receive either the Control- standard care with Aveeno® cream until they get dry desquamation then Flamazine® vs Treatment standard care with NeoVIDERM	Head and Neck, Breast	Trial Terminated	Canada	Jewish General Hospital, Quebec, Montreal, Canada
Mometasone Furoate 0.1% Versus Eucerin on Moderate to Severe Skin Toxicities in Breast Cancer Patients Receiving Post mastectomy Radiation: A Randomized, Double Blind Trial	Memorial Sloan-Kettering Cancer Center	A double blind RCT where patients are randomized to receive either Control – Eucerin® (a placebo comparison) or Experimental- Mometasone Furoate 0.1%	Breast	Recruiting	USA	**Multi center** 1-memorial Sloan-Kettering cancer center in New Jersey 4 x Sloan-Kettering cancer centers in New York, USA

A Phase II Study Designed to Evaluate the Value of Alkagin Paste in the Prevention of Radiation Dermatitis - for Patients Undergoing External Beam Radiotherapy	Vuong T.	Standard care vs Aveeno cream (Alkagin paste)	Anus, Rectum, Urogenital system	Trial terminated	Canada	Jewish General Hospital, Quebec, Montreal, Canada

Appendix 6

2014 On-going trials table (2)

Appendix 6: Summary of Evidence: RCT/Systematic reviews in 2014

++ = high quality study

+ = acceptable quality

0 = rejected, unacceptable quality

Author and Year	Description	Scale or other measuring tool	n	Intervention and control	Category of patients	Category (primary endpoint)	Results	P-value	QA
Butcher et al 2012	Systematic review		10	N/A	Breast	All			+
Chan et al 2014	Systematic Review		47 RCTs from 1962-2012	Trials of oral systemic therapies (n=6) Washing practices (n=2) Deodorant use (n=4) Topical steroids (n=5) Non-steroidal topical therapies (n=23) Dressings (n=6) Light emitting	All included	Radiation Induced skin reaction	36/47 of included articles considered at high risk of bias 10/47 rated at unclear risk Allocation concealment only reported in 22/47 studies Blinding and attrition only adequately described 21/47		++

				diode photo-modulation (n=1)					
Abbas 2012	Non blinded RCT single centre	RTOG	30	Trolamine® vs. standard of care	Head and Neck	Grade 1-2 Grade 3	80% (12/15) treatment group 46.6% (7/15) control group 20%(3/15) treatment group 53.4%(8/15) control group	P<0.01	+
Watson et al 2012	Non blinded RCT single centre	CTCAE FACT-B QoL questionnaire	198	Aluminium based antiperspirant vs. standard of care	Breast	Grade 3	4/99 treatment and 3/99 control developed toxicity No statistical difference between intervention and control for QoL		+
Haddad et al 2013	Non RCT - Self-controlled study	RTOG	60	Aloe Vera self-controlled. Half treatment	Head and Neck, Pelvis, Breast	Grade 1-3 by week 5	treatment half Grade 1 n=42 Grade 2 n=3		+ (omitted Q2, 3,and

				field control, other half intervention			Grade 3 n=1 Control half Grade1 n= 32 Grade2 n=17 Grade3 n=1		4 on RCT SIGN)
Herst et al 2014	Intra- patient RCT - blinding not possible	RTOG and Modified RISRAS	78	Mepitel® /film vs. aqueous cream	Breast	Moist desquamation	0% intervention 26% control	P<0.001	+
Jensen et al 2011	Single Centre RCT	ONS	66	WO1932 (oil in water emulsion) vs. no treatment	Breast	ONS 0-3	visit 3 (day 47 +/- 7) normalised skin higher in treatment group n=14 vs. control n=6	P=0.059	+
Kirova et al 2011	Phase III RCT	RTOG VAS EORTC	200	Hyaluronic Acid vs. control emollient	Breast	Disappearance of erythema based Colormetric values failure = interruption of treatment	20.4% in intervention arm 13% in control arm n=23 (24.2%) in intervention arm n=32 (33.7%) in control arm	P=0.46 p=0.15	+

Paterson et al 2012	Within subjects RCT, no blinding	RISRAS	74	Mepilex®lite dressings vs. aqueous cream	Breast (post mastectomy)	RISRAS score	Results showed improved average RISRAS scores for Mepilex ®lite compared with aqueous cream although no significant difference was identified for MD rates.	(p<0.001)	0
Miller et al 2011	Double blind RCT	CTCAE version 3 Skindex-16	176	Mometasone Furoate (MMF) vs. placebo cream	Breast	CTCAE mean maximal grade and SD (range 0.0-3.0)	1.2 ± .85 intervention 1.3 ± 0.8 control	P=0.18	+
Niazi et al 2012	Phase III RCT - blinding not possible	CTCAE version 4	44	Sliver Clear Nylon Dressing (SCND) vs. standard skin care	Lower GI	Skin toxicity on final fraction of radiotherapy. Mean dermatitis and SD scores	1.67 (1.2 SD) intervention group 2.53 (1.17 SD) control group	P= 0.1	++

Graham et al 2013	Double blind RCT	CTCAE version 3 Photographic audit	318	barrier cream containing acrylate terpolymer (ATP) vs. a 10% glycerine cream (Sorbolene)	Breast (post mastectomy)	peak and overall skin reactions using the CTCAE scoring tool (version 3.0) plus a photographic audit of skin scores to confirm reactions scored by clinicians	medial/lateral applications were compared for the two products. In the proportion of cases with ≥ grade 3 skin reaction, there was a significant difference for medial applied creams 18% (Sorbolene) vs. 28% (moisturizing double barrier cream)	p=0.047.	+
Sharp et al 2013	Blinded RCT	RTOG EORTC QLQ C30, a visual analogue scale patient experience and adherence	411	Calendula Weleda® cream vs. Essex® (Aqueous) cream	Breast	Follow up	ARSR (RTOG grade ≥2) was 23% in the Calendula group and 19% in the Aqueous cream group at follow up	p=0.55.	++
Ulff et al 2013	Double Blinded RCT 3 arm	RTOG Colorimeter VAS	125	Betsmethasone (steroid) +Essex® cream	Breast	RTOG 0-1	22/53 B+E 7/49 moisturisers	P=0.001	++

		DLQI		(B+E) vs. Essex® cream vs. Canoderm® cream		RTOG 3	7/53 B+E 15/49 moisturisers		
Zhong et al 2013	Single centre RCT	RISRASS	88	Mepilex® lite dressing vs. normal skin care (cleaning with salted water)	Nasopharynx	Time to wound healing	Mepilex® median time to wound healing 16 days (95% CI 12-19) Control median time to wound healing 23days (95% CI 19-27)	p=0.009.	0
Lewis et al 2014	Single centre RCT remote randomisation double blinded	RTOG, HDSS plus visual scale	285	Three arms, aluminium – containing deodorant plus soap; non-containing aluminium deodorant plus soap and soap only. Soap was low irritant pH6 free from fragrance, colour and	Breast	RTOG grade ≥2 score	There was no association between deodorant use and RTOG score. The change in itching, pain or burning in the axilla was 0.02cm higher in the aluminium deo		++

				lanolin and propylene glycol.			group compared with the control but this was not significant; pts in the aluminum deo group experienced significantly less sweating than the control group. Conclusion: use of aluminium deodorant did not adversely affect skin reaction.		
Diggelmann et al 2010	systematic inpatient controlled trial	RISRAS	N=24	Areas of erythema were divided in half and randomly assigned to have either the Mepilex lite dressing or aqueous cream	Breast	Included severity of skin reaction, dose build up and skin surface temperature. The primary trial outcome was dry desquamation,	Mepilex lite significantly decreased the extent or radiation induced skin reactions	p <0.001	0

Appendix 7

2019 Summary of evidence table

Author and year	Description	Scale or other measuring tool (RTOG etc.)	Sample size n=	Intervention and control	Category of patients	Primary endpoint	Results	P-value	QA (risk of bias)
Robijns et al. 2018	A single centre prospective placebo controlled RCT	RTOG measured at baseline, 40Gy and 66Gy time points, objective measures of skin hydration, transdermal water loss and pigmentation	139, n=120 included in the analysis	Photobiomodulation therapy vs placebo (control)	Breast cancer	Incidence of moist desquamation	Incidence significantly higher in control arm at 66Gy time point OR=6 95% CI 1.881-19.82	0.004	Low
Aysan et al. 2017	A single centre double blind placebo controlled RCT	RTOG measured at baseline and at 5th week of RT	Number analysed =47	Boron gel, vs placebo (Vaseline®, petroleum jelly)	Breast cancer	RTOG score at week 5	Statistically significantly higher proportion of patients in the control arm had grade 2 (or above) RTOG score although patient satisfaction higher in control arm	0.03	Moderate
Arimura et al. 2015	A single centre trial – patient preference, non-randomised	CTC version 4 measured on alternate days during treatment, then after treatment once a week for a month then every three months for two years	271 enrolled in the study (n=145 chose film dressing) (n=126 chose standard care)	Film dressing (Airwall®) vs standard skin care	Prostate cancer	Highest grade of RD	Time to grade 1 or 2 same for both groups, 14% in film dressing group developed grade 2 or higher RD, vs 48% in control group	p<0.001	High
Baumann et al. 2017	Single centre phantom dosimetry study	Assessment of surface dose with and without aluminium containing antiperspirants using optically stimulated	Tested on a 5x5 paper with eight rolls of antiperspirant	Compared two strengths of aluminium antiperspirant 15% and 25%	n/a	Surface dose in cGy	No difference seen between no antiperspirant and both perspirant strengths, at a range of gantry angles	No significant difference	Low (non-human study)

		luminescent dosimeters (OSLDs)							
Ben-David et al. 2016	Phase II prospective randomised placebo controlled double blind trial	RTOG CTC version 3 measured at baseline weekly during five weeks of treatment and two weeks post treatment	n=47, 26 in the melatonin cream group, 21 in the placebo group	Melatonin-containing emulsion intervention vs placebo cream control. Physician and patient blind to allocated arm. Asked to apply the cream twice daily over the treated breast (but not less than two hours before treatment). Patients advised not to use any other marketed or natural product during the radiation period	Breast cancer	RTOG scores during RT and at two weeks follow-up.	No difference in RTOG scores during RT, but at week 7 (two weeks post RT) melatonin group 59% grade 0, 41% grade ½ vs 11% grade 0 and 90% grade ½ in the placebo group (p=0.03). No difference in patient reported subjective reports between the groups	p=0.03 only at FU	Low
Censabella et al. 2016	Single centre non-randomised trial	RTOG and RISRAS , Skindex-16 (QoL) measured before the start of laser therapy (LT) and at the end of radiotherapy (RT)	n=87, n=45 control arm (n=41 analysed) n=42 LT (n=38 analysed)	Control had standard skin care: hydrocolloid gel, self-adhesive silicone foam dressing (Mepilex®) for painful skin reactions. Intervention – standard skin care plus six sessions of LT, given twice a week starting from fraction 20	Breast cancer patients	Severity of RD (RTOG and RISRAS) and QoL (Skindex-16)	At fraction 20 RD levels were comparable between groups (baseline score). In the control arm there was a significant increase in RTOG score grade 2 to 29.3% at end of RT compared with 4.9% at #20 (p=0.01). In the LT group RD remained stable (p=0.22) with only one patient with an RTOG grade 2 at the end of RT. There were significant differences between the control and LT RISRAS scores for both patient reported and clinician reported scores in favour of the LT	RISRAS scores total p=0.003	Moderate

Chan et al. 2019	A single blind randomised controlled superiority trial	CTCAE version 4.0 end of treatment	n=197. Intervention arm n=89 analysed (n=11 lost to FU or exited the trial). Control arm n=83 analysed (n=13 lost to FU or exited the trial)	Intervention StrataXRT® vs control sorbolene	Head and neck cancer	Severity of RD at the end of RT	Age, total dose, skin dose verification, number of fractions prescribed and PTV size were comparable between groups. The StrataXRT® group had higher mean BMI than the control arm. The control arm had greater proportion of patients with tomotherapy and greater number having 6FFF energy. All other characteristics were comparable between groups. Authors state that after adjustment BMI and technique (VMAT or tomotherapy) had no effect on outcome, At the end of treatment: StrataXRT® arm – grade 2 (80%) and grade 3 (28%); control arm – grade 2 (91%) and grade 3 (45%). Unclear why these add up to more than 100%. After controlling for cetuximab, the StrataXRT® arm had 12% lower risk of experiencing grade 2 skin toxicity (RRR=0.876, 95% CI 0.778-0.987) and a 36% lower risk of developing a grade 3 reaction (RRR=0.648 95%CI 0.442-0.947) p=0.025	p=0.025	Moderate

Eda et al. 2016	A double blind randomised controlled trial	RTOG – not clear at what time point the RTOG was measured	Number enrolled=40, number analysed =38, Intervention=18, control=20	Intervention= glutamine 15g per day in three doses, started one week prior to RT continued until one week post treatment. Control received a placebo	Breast cancer	RTOG	Intervention: grade 1= 88.9%, grade 2= 11.1%. Control: grade 1=0, grade 2=80%, grade 3=20%	p<0.001	High
Erridge et al. 2016	Audit of new skin care policy using steroid cream (betamethasone valerate 0.1%)	RTOG and PROM via a questionnaire at the end of RT and two weeks post treatment	Total sample size =219, cohort 1=112, cohort 2=107	Patients identified as high risk applied steroid cream (betamethasone valerate 0.1%) from day 1 of RT and up to two weeks post treatment (once a day). Medium and high risk patients were also given Diprobase® as an emollient. Control was a cohort of patients treated prior to the implementation of the policy	Head and neck, including brain, n=27 Breast n= 170 Pelvis n=17 Other n=4	Severity of RD at the end of RT and two weeks post treatment	Patient assessment at end of treatment: cohort 2 scored lower for itch and discomfort (mean 1.3 C2 vs 3.0 C1) discomfort (2.2 vs 3.3) respectively. Radiographer scored: RTOG C1 Grade 0=8% Grade 1=49% Grade 2=34% Grade 3= 9% C2 Grade 0=26% Grade 1=53% Grade 2=16% Grade 3=5% P<0.001 When they compared those using steroid creams vs those not using steroid creams at the end of RT there was a significant reduction in patient reported redness, itch, discomfort and pain and less use of analgesia and lower sleep disturbance in the steroid use group	p<0.001	High

Fenton-Kerimian et al. 2015	Pilot randomised feasibility study comparing three topical interventions	CTCAE at baseline, each week during RT, one week post RT, one month post RT and three months post RT, also used the Dermatology Life Quality Index at the same time points	n=30, n=10 per intervention	Intervention 1= homeopathic cream calendula applied twice daily to the treated breast Int 2= hydrogel cream (RadiaPlex®) applied twice daily Int 3= medium potency steroid cream (0.1% mometasone furoate) twice per week in weeks 1 and 2 then once daily in week 3 and an emollient Aquaphor® used daily throughout treatment.	Breast cancer	Severity of RD reported	Little data reported. All patients reported a grade 1 reaction and highest skin reaction was grade 2 reported in all three groups (interventions 1, 2 and 3) and this was at one week post RT. No statistical difference reported in DLQI scores (to be expected given the small numbers per group)	NS	High
Halm et al. 2014	Randomised feasibility trial	RTOG at three weeks, and six weeks	n=24, control n=11, intervention n=13	Control = RadiaPlexRx® ointment (hyaluronic acid and mannan polysaccharides) 3x per day during RT and up to one month post treatment. Intervention = four essential oils, Helichrysum angustifolium, (helichrysum 2.5%) Boswellia cateri (frankincense 5%) Lavandula angustifolia (lavender 5%) and Pelargonium graveolens (geranium 5%) total concentration of 17.5%. This mixture also had a carrier composition that	Breast cancer	Reported mean RTOG scores at three weeks and six weeks	No difference in mean RTOG scores at 3 weeks or 6 weeks. Rash rating were higher in the control subjects at 6 and 10 weeks compared with the experimental group, pain scores were higher in control subjects at week 6 but ulcer ratings were higher in the experimental group at week 6 and 10, none of the differences were statistically significant (given the small sample this is not unexpected). Adherence was good but the authors indicate participants also used other creams and topical	NS	High

				included jojoba, aloe vera, tamanu and evening primrose. This was applied 3x daily until one month FU			agents during the study as time went on- which is likely to confound the results.		
Ho et al. 2018	Phase III double blind RCT	CTCAE scores of acute radiation dermatitis	n=143, intervention analysed n=64, control analysed n=60	Intervention= 0.1% mometasone furoate vs control= Eucerin® original cream. Eucerin® contains the following ingredients: • water • petrolatum • mineral oil • ceresin • lanolin alcohol • phenoxyethanol • piroctone olamine	Breast cancer	Grade 2 or above CTCAE version 4 radiation dermatitis with moist desquamation or any grade 3 or above dermatitis. Secondary endpoints were time to occurrence of maximum grade dermatitis and patient reported skin symptoms using Skindex-16 assessments were by provider	The intervention arm had a significantly lower rate of grade 2 or grade 3 with moist desquamation than the control arm (43.8% vs 66.7% respectively p=0.012). The intervention arm had a lower incidence of maximum grade RD 18.8% vs 33.3% p=0.036. Time to development of grade 2 RD was similar between the two groups but time to development of grade 3 dermatitis was shorter in the control arm, 35.5 days vs 46 days (control arm) p<0.001. Univariate analysis identified only V110 as the only significant predictor of moist desquamation p=0.0021 with reconstruction close to sig P=0.072. Multivariate analysis indicated that a BMI>30 HR 1.04 p=0.02 and use of the control cream HR 2.34 p<0.001 were predictive of moist	p=0.012	Low

							desquamation. A second multivariate analysis showed that V110 was predictive of moist desquamation HR 1.03 p=0.0021. Patient reported outcome measures showed no difference between groups		
Chan et al. 2014	Double blind single centre RCT	CTCAE version 4 measured at baseline, and weekly through treatment up to week 11, also measured patient reported outcomes through pain measure and Skindex-16	n=174 randomised, n=89 allocated to cream 1 (oil-based emulsion), n=85 allocated to cream 2, n=88 analysed cream 1 and n=85 analysed cream 2	Oil-based emulsion containing allantoin vs aqueous cream (control). Creams applied at start of RT twice daily or more if needed until reaction subsided	Breast cancer, lung cancer, and head and neck cancer		Cream 1 (oil base emulsion) showed significantly lower average skin toxicity scores at week 3, approx 0.8 vs approx 1.0 p<0.05. However, patients in group 1 had significantly worse average skin toxicity scores in weeks 7,8 and 9 p<0.001. There was a significantly higher proportion of patients with a skin toxicity grade higher than grade 2 in the cream 1 group in weeks 6 (72% vs 58% p=0.045), 7 (71.6% vs 41.7% p<0.001), 8 (40% vs 24% p=0.02) and 9 (24.7% vs 6.6% p=0.001). No significant difference in time to event data for grade 2 and above toxicity. Univariate analysis identified age and treatment site (lung	p<0.05	Low

							vs breast) as significant factors influencing skin toxicity. In the multivariate analysis, lung treatment site was identified as a significant predictive factor for skin toxicity P<0.001		
Karbasforooshan et al. 2018	Double blind single centre randomised placebo controlled trial	RTOG and CTCAE measured at baseline and then weekly during radiotherapy (weeks 1 to 5)	n=40, n=24 allocated to silymarin group, n=21 randomised to placebo, intervention n=20 analysed, control n=20 analysed	Intervention-silymarin (herbal medicine, dry extract of Silybum marianum, also known as milk thistle) given as a gel 1% containing 80% active ingredient based on silymarin flavonolignans. Used once daily or placebo (matched in consistency and colour to the intervention gel). Used from the start of RT, used consecutively for five weeks	Breast cancer (post mastectomy)		In weeks 1 and 2 both groups are comparable in terms of RTOG scores (20% grade 1 at week 2 for both groups). By week 3 the silymarin group demonstrates a non-significant lower toxicity rate: grade 1 80%, grade 2 20% (silymarin) vs grade 1 45%, grade 2 50%, grade 3 5%. By weeks 4 and 5 the reduced toxicity is marked and significant. Week 5 grade 1 100% silymarin group, placebo grade 1 55%, grade 2 40%, grade 3 5% p=0.003	p=0.003 (for week 5 data)	Low
Lam et al. 2019	Within subject's experimental design single centre	RTOG measured at baseline, and baseline photographs were taken on day 1 of treatment. Of the weekly RTOG scores, the highest was recorded for score during	n=56 randomised (over two years) n=27 randomised to lateral and n=29 randomised to medial for barrier film (BF). For lateral applied BF, data available for analysis of blinded photographs was n=24. For medial applied BF, data available	Barrier film (alcohol-free film formulated from two polymers. For the half of the breast not covered with film, standard care was used that included using Glaxal Base® cream, which is similar to aqueous cream. BF started on first day of treatment. Applied twice per	Breast cancer		Patient reported outcomes, no significant difference in reported scores seen for burning, pulling and tenderness for those with BF applied to medial, one significant improvement in score for itching 1.14 vs 2.06 p=0.035. In cases where the BF	p=0.041 for laterally placed BF	Moderate

		treatment. The photographs taken at baseline and FU were assessed blind	for analysis of blinded photographs was n=29	week, not applied between last RT session and FU appointment			was applied to the lateral only, for burning was there seen a significant difference in patient reported scores, 0.92 vs 1.83 (p=0.047), no confidence interval presented. No significant difference seen between BF and standard care for time to development of grade 2 RD. RTOG during treatment – some errors in results presented for calculated numbers with grade 2 or more RTOG (numbers presented not added correctly). In those with lateral BF grade 2 or more RD 17.3% vs 27.6% for no film p=0.041. For medial cases 17.2% for the BF cases and 9.6% for no film p=0.76. Post treatment no difference seen in grade 2 or above scores for BF vs no film. There was no significant difference seen in the RTOG obtained from photographs		

Møller et al. 2018	RCT patient own control	CTC scored by RTT blinded to randomisation. Patient reported outcome surveys (PROs)	101 n=79 analysed	Intervention: Mepitel® applied to lateral or medial breast. Control: opposite side treated as per guidelines i.e. using moisturiser and for itch/steroids	Breast cancer	To investigate patient reported symptoms related to radiotherapy dermatitis and to examine patient preferences using Mepitel® film compared to standard skin care. Secondary, compare to general population	CTC scores: no significant difference in grades 1 to 3 at end of treatment or at 14 days. Patient reported outcomes were that the film was comfortable, and patients felt it made a difference. At 14 days pain was reduced (p.0.001) and sensitivity of the skin ($p<0.01$) as well as itching	Pain reduced p.0.001	Low
Näf et al. 2018	Pilot study	CTC scored by nurse and doctor, grade 2 s2,4,6 and 8 weeks	20 int in analysis. 100 controls	Intervention: administration of the Camellia sinensis nonfermentatum (CSNF) 0.4% lotion seven days prior to RT, preventative gel CSNF 2.5% administered 1-2 hours prior to radiotherapy. Control: comparative group had treatment related to care guidelines i.e. Excipial® or Bepanthol® or Ialugen® cream	Breast cancer	To assess effectiveness of NPE® of CNSF extract in prevention and recovery of acute radiation induced skin reactions	CTC scores not significantly different. Showed trend, significant delay in grade 2	NS	High

Rades et al. 2019	RCT	CTCAE v4	57 (n=28 Mepitel® n=29 standard care	Intervention: Mepitel® film started on first day continued until grade 2 moist desquamation. Film changed twice weekly. Control: 2-5% urea and fatty acid cream	Head and neck cancer stratified between groups	Comparison of Mepitel® film to standard skin care for prevention of grade 2 radiation dermatitis	46.4 % of patients had sensitivity to Mepitel® (13 of 28) so study stopped at interim analysis. At 50Gy 8/23 (34.8%) in the intervention group had grade 2 and 10/28 (35.7%) in control group (NS). At 60Gy grade 2 rates were 65.2% (15/23) and 59.3% (16/27) in the control (NS)	See results column	Low
Ogita et al. 2019	RCT	Sebum content and composition. Sebumeter at four time points 2,4 weeks and 3 months	81 (80 randomised), n=74 analysed (intervention=16) (control=64), then from this group post whole breast radiotherapy (WBRT), intervention n=32 and control n=32	Intervention: prophylaxis used heparinoid 2x daily from first txt until 2 weeks after WBRT. Control: no moisturiser but reassigned at 2 weeks after WBRT to receive moisturiser or not	Breast cancer	Explore time course and water content of stratum corneum to assess skin damage with heparinoid cream	Intervention significantly reduced sebum content overall. No differences seen between groups but confusing analysis	See results column	High
Schmeel et al. 2018	RCT patient own control	RTOG and EORTC recorded weekly, RISRAS but not reported	62 (56 analysed)	Intervention: hydrofilm. Control: 5% urea	Breast cancer	Compare prophylactically applied hydrofilm dressings with standard skin care using moisturising 5% urea	Significantly reduced severity of RTOG mean 0.35 and 1.33 in the control with p<0.001. RTOG/EORTC end of treatment severity: grade 0 48% film vs control 12.5%, grade 1 39.3% vs 46.4%, grade 2 12.5%.vs 30.4%, moist desquamation 0% vs 10.7%	p<0.001	High

Sekiguchi et al. 2015	RCT	Sebum content and composition. Sebumeter at four time points 2,4 weeks and 3 months. Diary for compliance (acute radiation dermatitis ARD) scores i.e. clinician rated score	749 women assessed: intervention 14 and control 32	Intervention: prophylaxis used heparinoid 2x daily from first txt until two weeks after WBRT. Control: no moisturiser	Breast cancer	Efficacy of heparinoid moisturiser as prophylactic agent	Skin dryness was significantly higher in the control group at 2 and 4 weeks. Itching and pain VAS scores generally higher at last day, No significant differences at 3 months	See results column	High
Sekiguchi et al. 2018	RCT	Water content, and severity scoring none to very severe 2 to 4 weeks after RXT	749 women assessed: intervention 32 and control 32	Intervention: prophylaxis used heparinoid 2x daily from first txt until two weeks after WBRT. Control: no moisturiser	Breast cancer	Efficacy of heparinoid moisturiser as prophylactic agent	Skin dryness significant difference between groups between moisturiser and no moisturiser (p=0.01). No significant clinician rated skin toxicity or patient reported except pain scores at last day of RT	p=0.01	High
Sio et al. 2016	RCT	CTCAE v3 4 PROS (LASA) assessed at baseline and weekly	167 women	Intervention: topical 0.1% mometasone. Control: no moisturiser	Breast cancer	Dermatitis evolution of mometasone furoate	Radiation symptoms started between weeks 4-7 and subsided after week 8. CTCAE showed no significant differences. Significant differences in PROs over time between arms (p=0.001)	P=0.001	Low

Togni et al. 2015	RCT	Camera visual intensity and colour analysis. RTOG	114 n=55 Boswellia cream, n=59 base cream	Intervention: Boswellia cream, control base cream	Breast cancer	Safety and efficacy of boswellia-based cream for prevention of adjuvant skin damage	RTOG grade 2 toxicity 71.2% for control and 54.6% boswellia cream. Not significant. Claims in abstract it is able to reduce erythema, no regression for risk factors. Skin colour intensity less in intervention but not significant	p=0.066	High
Ulff et al. 2017	Long-term follow-up from trial comparing normal breast tissue	RTOG. Skin thickness using ultrasound. Dryness measured. Cosmetic results. Six years after treatment	60 (intervention=28, control=32)	Intervention: betamethasone 0.1%. Control: moisturiser	Breast cancer	Evaluate whether treatment with potent steroid during adjuvant ExBRT is associated with late toxicity	Skin atrophy not noted in any of the 60 patients. No significant differences between normal tissue and treated with steroids. Ten (17%) had noticeable skin changes. Three (5%) had altered skin pigmentation	NS	Low
Ulff et al. 2017	RCT	RTOG. VAS of itching, skin irritation	686	Intervention: betamethasone 17-valerate cream, Applied seven days per week until two weeks after RT. Control: moisturiser	Breast cancer	Test hypothesis that preventative topical steroid treatment instituted at start of radiotherapy can ameliorate acute radiation dermatitis	Patients receiving hypofractionated RT developed less skin reactions than those treated with control Those on steroid cream had significantly less skin reactions regardless of RT schedule	p<0.001	Low

Ryan Wolf et al. 2018	Phase 2 multi-site, randomised, double blind, placebo controlled trial	Baseline, weekly after every fifth RT session, at the end of RT (end RT), and 1 week after RT completion. RDS scale, digital imaging, completion of three self-report questionnaires, McGill Pain Questionnaire, Skindex-29, Symptom Inventory	578 total: intervention=283 and control=295	Intervention: curcumin capsule, four capsules 3x daily for full course of RT and one week post RT with food. Control: placebo capsule, four capsules 3x daily for full course of RT and one week post RT with food	Breast cancer	To determine the efficacy of oral curcumin, one of the biologically active components in turmeric, at reducing radiation dermatitis severity (RDS) at the end of RT, using the RDS scale, compared to placebo	No significant difference in mean RDS score at end RT between curcumin and placebo. No beneficial effect reported from using curcumin	p=0.565 end of RT	Moderate
Strouthos et al. 2017	Non-randomised single centre study	Weekly CTCAE and physical assessment, weekly VAS, weekly photographs	70 total: intervention=25, control (no intervention)=45	Photobiomodulation (PBM) LED therapy	Breast cancer	To evaluate the beneficial role of photobiomodulation therapy in preventing/reducing radiation dermatitis during radiotherapy for breast cancer. Primary endpoint RD grade and pain	8% of PBM group experienced grade 1 RD and 12% grade 3 RD. 55.6% of control group experienced grade 1 RD, 40% grade 2 and 4.4% grade 3 (resulting in RT pause). 48% of matched group grade 1, 44% grade 2 and 4% grade 3	RD lower in PBM group compared to control p=0.0211	Low

Hoopfer et al. 2015	Phase III RCT	10-point Catterall skin scoring profile (CSSP) scoring, six-point Likert scale for severity and changes in burning, itchiness, pain and dryness. Maximum CSPP scores for erythema, dry and moist desquamation < 50% and > 50% of field	248 in total : 81 aloe cream, 77 placebo,79 powder	1. aloe cream 2. placebo cream: composed of Aquatrix II™. Both creams subjected to bioassay testing. 3. dry powder: non-metallic baby powder or cornstarch to intact skin followed by one month of Glaxal Base® cream post RT	Breast cancer	Phase III RCT to test hypothesis that the use of aloe would lead to a one point reduction in RISR severity and a decrease in symptom severity compared with a traditional dry powder skin care regime	Mean of max CSSP value: 6.27 for the powder, 6.96 for the aloe (p=0.227 and 6.99 for the placebo (p=0.845). These did not meet the one point difference that was deemed to infer clinical significance. Symptom severity (pain) reported significant changes with 9/67 powder arm rating pain as high, 21 /72 aloe cream and 25/74 for the placebo when reported one week post RT	Intervention p=0.227, placebo p=0.845	Low
Rollman et al. 2015	Double blind randomised pilot study	CTCAE v3.0 scale, Skindex-16, skin experience diary (SED). Baseline, weekly intervals during RT, six weeks post treatment completion	42 in total: intervention=28, control=14	Emu oil, placebo (cottonseed oil). Applied 1.5ml 2x daily for duration of RT and up to six weeks post RT. Not applied sooner than four hours before delivery of RT. Had to have used before 3rd fraction. No other creams or oils. Discretion by provider as to other supportive treatments for symptom relief. Any Skin treatments were documented	Breast cancer	Demonstrate the feasibility and safety of using an oil-based product during breast cancer radiotherapy	PROM from Skindex: average scores 7.4 vs 10.4 for the intervention and control respectively. Lower mean scores for all areas: emotional, symptoms and functional. Peak CTC toxicity occurred at week 6 of intervention group, appeared slightly worse but "not statistically significant" (not reported statistically, just narrative)	p=0.29	Pilot study

Cui et al. 2015	Single institution, prospective study	RTOG and VAS also used	94 in total, 47 in each group	Intervention: administration of olive oil 3 x daily from #1 and for two weeks post RT completion. Control: placebo (water) during RT (not specified if same as above) and for two weeks post treatment completion	Nasopharynx	Evaluate the effect of olive oil on radiation dermatitis	Grade 1 and 2 reactions in 93.6% intervention and 72.3% of control grade 3 in 6.4% of intervention and 27.7% of control	p<0.001	Moderate
Censabella et al. 2017	Single institution, non-randomised with historical controls	WHO criteria for grading acute cutaneous toxicities	222 in cohort plus two matched historical groups from two previous studies, 136 and 100 respectively, but half of each of these were excluded due to a change in RT technique Numbers analysed N= 202 (hydrogel gp) n=131 (Dexpanthenol group) n=87 (dexpanthenol and hydrogel group).	Hydroactive colloid gel to the irradiated area	Breast cancer	The efficacy of this same hydroactive colloid gel in the prevention of RIMD, with the hypothesis that using this agent preventively would be even more beneficial with respect to incidence and onset time of RIMD.	Incidence of RIMD 6.9% in intervention arm v's 35.1% and 12,6% in the historical control arms The difference in moist desquamation was significant when looking at medium and larger breasted patients P<0.0001 In univariate analysis breast size and use of the hydrogel as a preventative measure were the only significant factors that contributed to the incidence of moist desquamation.	p<0.0001	High

Manas et al. 2015	Randomised clinical trial	CTCAE and EORTC QLQ with breast and head and neck modules	n=102, number analysed n=98 (four excluded as did not meet inclusion criteria)	Topical R1 was applied once per day within two hours of RT, R2 applied four times a day (three times during the day and last application just before bedtime). R1 and R2 applied from first day of RT until two weeks post treatment. Control= use of a urea-containing ointment 5% wt/wt urea. Applied from day 1 until two weeks post treatment	Breast cancer and head and neck cancer	Primary end point was progression to grade 3 or 4 CTC RD. Secondary were overall response rate and effects on quality of life (EORTC QLQ)	Significant differences seen in grade of toxicity between intervention and control arm at each time point. At end of RT 57% of patients in the R1 R2 group had RD compared with 100% in the control arm p<0.0001.Two weeks post RT, 33.3% of the R1 R2 patients and 66% of the control had RD p=0.0003. QoL score showed benefits for the R1 R2 patients in terms of skin dryness, stinging and desquamation for patients with breast cancer and reduced use of medication for pain for those with head and neck cancer. No actual data is presented to confirm the extent of the differences stated	p<0.0001	High

OR = Odds ration common statistical abbreviation

CI = Confidence interval

HR= Hazard ratio

NS= None significant

Appendix 8

2019 Review summary of evidence table

Author and Year	Description	Scale or other measuring tool (RTOG etc.)	Sample size n=	Intervention and control	Category of patients	primary endpoint	Results	P-value	QA (Risk of bias)
Robijns et al 2019	A single centre prospective placebo controlled RCT	RTOG measured at baseline, 40Gy and 66Gy time points, objective measures of skin hydration, transdermal water loss and pigmentation	139, n=120 included in the analysis	Photobiomodulation therapy, placebo (control)	Breast cancer	Incidence of moist desquamation	Incidence sig higher in control arm at 66Gy time point OR=6 95%CI 1.881-19.82	0.004	Low
Aysan et al 2017	A single centre double blind placebo controlled RCT	RTOG measured at baseline and at 5th week of RT	number analysed =47	Boron gel, placebo (Vaseline, petroleum jelly)	Breast cancer	RTOG score at week 5	Statistically sig higher proportion of patients in the control arm had grade 2 (or above) RTOG score p=0.03) although patient satisfaction higher in control arm).		Moderate
Arimura et al 2015	A single centre trial- patient preference non randomised.	CTC version 4 measured an alternate days during treatment, then after treatment once a week for a month then every 3 months for 2 years.	271 enrolled in the study (n=145 chose FD) (n=126 chose standard care).	FD- Airwall, vs standard skin care	Prostate cancer	Highest grade of RD	Time to grade 1 or 2 same for both groups, 14% in FD group developed grade 2 or higher RD, vs 48% in control group.	p<0.001	High
Baumann et al 2017	Single centre phantom dosimetry study	Assessment of surface dose with and without aluminium containing anti-perspirants using optically stimulated luminescent dosimeters (OSLDs)	tested on a 5x5 paper with 8 rolls of antiperspirant	Compared two strengths of aluminium antiperspirant 15% and 25%	n/a	Surface dose in cGy	No difference seen between no antipersp and both perspirant strengths, at a range of gantry angles,	no sig diff	Low (non human study)
Ben-David et al 2016	Phase II prospective Randomised placebo controlled double-blind Trial.	RTOG CTC version 3 measured at Baseline Weekly during 5 weeks of treatment and 2 weeks post treatment	n=47, 26 in the melatonin-cream group, 21 in the placebo group	Melatonin-containing emulsion intervention placebo cream control, physician and patient blind to allocated arm asked to apply the cream 2x daily over the treated breast (but not less than 2 hours before treatment). Pts advised not to use any other marketed or natural product during the radiation period.	Breast Cancer	RTOG scores during RT and at 2 weeks follow up.	No difference in RTOG scores during RT, but at week 7 (2 weeks post RT)Melatonin group, 59% grade 0, 41% grade ½ vs 11% grade 0 and 90% grade ½ in the placebo group (p=0.03). No difference in patient reported subjective reports between the groups.	p=0.03 only at FU	Low
Censabella et al 2016	Single centre non-randomised trial	RTOG and RISRAS , Skindex-16 (QoL) measured before the start of laser therapy and at the end of radiotherapy	n=87, n=45 control arm (n=41 analysed) n=42 LT (n=38 analysed)	Control had standard skin care-hydrocolloid gel, self-adhesive silicone foam dressing (Mepilex) for painful skin reactions Intervention-standard skin care plus 6 sessions of LT-give 2x per week starting from fraction 20	Breast Cancer patients	Severity of RD (STOG and RISRAS) and QoL (Skindex-16)	At fraction 20 RD levels were comparable between groups (baseline score) In the control arm there was a significant increase in RTOG score grade 2 to 29.3% at end of RT compared with 4.9% at #20(p=0.01). In the LT group RD remained stable (p=0.22) with only 1 patient with an RTOG grade 2 at the end of RT. There was significant differences between the control and LT RISRAS scores for both patient reported and clinician reported scores in favour of the LT.	RISRAS scores total p=0.003	Moderate
Chan et al 2019	A single blind Randomised controlled superiority trial.	CTCAE version 4.0 end of treatment	n=197, Intervention arm n=89 analysed (n=11 lost to FU or exited the trial) Control arm n=83 analysed (n=13 lost to FU or exited the trial)	Intervention StrataXRT, control Sorbolene	Head and Neck cancer	Severity of RD at the end of RT	Age, Total dose, skin dose verification, number of fractions prescribed and PTV size were comparable between groups. The StrataXRT group had higher mean BMI than the control arm. The control arm had greater proportion of patients with tomotherapy and greater number having 6FFF energy. All other characteristics were comparable between groups Authors state after adjustment BMI and technique (VMAT or tomotherapy had no effect on outcome) but it is not clear if they controlled for FFF or FB- FFF beams show a modest increase in surface dose compared with flattened beams so if not controlled for this could have an impact on outcomes in the control arm. At the end of treatment StrataXRT arm- grade 2 (80%) grade 3 (28%), control arm grade 2 (91%) and grade 3 (45%)- I'm not sure why these add up to more than 100%? After controlling for Cetuximab the StrataXRT arm had 12% lower risk of experiencing grade 2 skin toxicity (RRR=0.876, 95% CI 0.778-0.987) and a 36% lower risk of	p=0.025	moderate
Eda et al 2016	A double-blind Randomised controlled trial	RTOG - not clear at what time point the RTOG was measured	number enrolled=40 number analysed =38, I=18, Control=20	Intervention= Glutamine 15g per day in 3 doses started 1 week prior to RT continued until 1 week post trt, control received a placebo	Breast cancer	none given	Intervention grade 1= 88.9%, grade 2= 11.1%, Control grade 1=0, grade 2=80%, grade 3=20% sig p<0.001	p<0.001	High
Erridge et al 2016	Audit of new skin care policy using steroid cream (Betamethasone valerate 0.1%.)	RTOG and PROM via a questionnaire at the end of RT and 2 weeks post treatment.	Total sample size =219 cohort 1= 112, cohort 2 = 107	"Patients identified as high risk, applied steroid cream from day 1 of RT and up to 2 weeks post trt (once a day) Betamethasone valerate 0.1%. Medium and high risk patients were also given Diprobase as an emollient. Control was a cohort of patients treated prior to the implementation of the policy."	H+N including brain n=27 Breast n= 170 Pelvis n=17 Other n=4	Severity of RD at the end of RT and 2 weeks post treatment	Patient assessment at end of treatment Cohort 2 scored lower for itch and discomfort (mean 1.3 C2 vs 3.0 C1) (2.2 vs 3.3) respectively. Radiographer scored RTOG C1 Grade 0=8% Grade 1= 49% Grade 2= 34% Grade 3= 9% C2 Grade 0=26% Grade 1= 53% Grade 2= 16% Grade 3= 5% P<0.001 When they compared those using steroid creams vs those not using steroid creams at the end of RT there was a significant reduction in patient reported redness, itch,	p<0.001	High
Fenton-Kerimian 2015	Pilot randomised feasibility study comparing three topical interventions	CTCAE at baseline, each week during RT, one week post RT, one month post RT and three months post RT, also used the Dermatology Life Quality Index at the same time points	N=30, n=10 per intervention	Int 1= homeopathic cream calendula applied twice daily to the treated breast Int 2= Hydrogel cream (RadiaPlex) applied twice daily Int 3= medium potency steroid cream (0.1% mometasone fuorate) twice per	Breast Cancer	Severity of RD reported		NS	High
Halm 2014	Randomised feasibility trial	RTOG at 3 weeks, and 6 weeks	n=24, control n=11, Int n=13	Control = RadiaPlexRx ointment (hyaluronic acid and mannan polysaccharides) 3x per day during RT and up to one month post treatment. I= 4 essential oils, Helichrysum angustifolium, (Helichrysum 2.5%) Boswellia cateri (Frankincense 5%) Lavandula angustifolia (Lavenda 5%) and Pelargonium graveolens (Geranium 5%) total concentration of 17.5% this	Breast cancer	Reported mean RTOG scores at 3 weeks and 6 weeks	Little data reported. All patients reported a grade 1 reaction and highest skin reaction was grade 2 reported in all three groups (Interventions 1, 2 and 3) and this was at one week post RT. No statistical difference reported in DLQI scores (to be expected given the small numbers per group).	NS	High
Ho 2018	Phase III double blind RCT	CTCAE scores of acute radiation dermatitis	N=143, I analysed n=64, Control analysed n=60	Intervention= 0.1% mometasone furoate vs Control= Eucerin original cream.Eucerin contains the following ingredients:• Water • Petrolatum • Mineral Oil • Ceresin • Lanolin Alcohol • Phenoxyethanol • Piroctone Olamine	Breast cancer	grade 2 or above CTCAE version 4 radiation dermatitis with moist desquamation or any grade 3 or above dermatitis. Secondary endpoints were time to occurrence of maximum grade dermatitis and patient reported skin symptoms using Skindex-16 Assessments were by	The intervention arm had a significantly lower rate of grade 2 or grade 3 with moist desquamation than the control arm (43.8% vs 66.7% respectively P=0.012). The Intervention arm had a lower incidence of maximum grade RD 18.8% vs 33.3% P=0.036. Time to development of grade 2 RD was similar between the two groups but time to development of grade 3 dermatitis was shorter in the control arm 35.5 days vs 46 days (control arm) P<0.001. Univariate analysis identified only V110 as the only significant predictor of moist desquamation P=0.0021 with reconstruction close to sig P=0.072. Multi variate analysis indicated that a BMI>30 HR 1.04 P=0.02 and use of the control cream HR 2.34 P<0.001 were predictive of moist desquamation. A second Multivariate analysis showed that V110 was predictive of moist desquamation HR 1.03 P=0.0021	P=0.012	Low
Chan 2014 (ref 75)	Double-blind single centre RCT	CTCAE version 4 measured at baseline, and weekly through treatment up to week 11, also measured patient reported outcomes through pain measure and Skindex-16	N=174 randomised, n=89 allocated to cream 1 (oil based emulsion), n=85 allocated to cream 2, n=88 analysed cream 1 and n=85 analysed cream 2	oil-based emulsion containing allantoin vs aqueous cream (control) Creams applied at start of RT twice daily or more if needed until reaction subsided.	Breast cancer, Lung cancer and head and neck cancer		Cream 1 (oil base emulsion) showed significantly lower average skin toxicity scores at week 3 approx. 0.8 vs approx. 1.0 p<0.05, however, patients in group 1 had significantly worse average skin toxicity scores in weeks 7,8 and 9 P<0.001 There was a significantly higher proportion of patients with a skin toxicity grade higher than grade 2 in the cream 1 group in weeks 6 (72% vs 58% P=0.045), 7 (71.6% vs 41.7% P<0.001) 8 (40% vs 24% P=0.02)and 9 (24.7% vs 6.6% P=0.001) No significant difference in time to event data for grade 2 and above toxicity. Univariate analysis identified age and treatment site (lung vs breast)as significant factors influencing skin toxicity, in the multivariate analysis lung treatment site was	P<0.05	Low
Karbasforooshan et al 2018	Double-blind single centre randomised placebo controlled trial	RTOG and CTCAE measured at baseline and then weekly during radiotherapy (weeks 1 to 5).	N=40 N=24 allocated to Silymarin group n=21 randomised to placebo, intervention n=20 analysed, control n=20 analysed	Intervention- Silymarin (herbal medicine, dry extract of S. marianum, also known as milk thistle) given as a gel 1% containing 80% active ingredient based on silymarin flavonolignans used once daily, or placebo (matched in consistency and colour to the intervention gel) Used from the start of RT used consecutively for 5 weeks.	Breast Cancer (post mastectomy)		In weeks 1 and 2 both groups are comparable in terms of RTOG scores (20% grade 1 at week 2 for both groups). By week 3 the Silymarin group demonstrates a non-significant lower toxicity rate Grade 1 80% grade 2 20% (Silymarin) vs Grade 1 45%, grade 2 50%, grade 3 5%. By weeks 4 and 5 the reduced toxicity is marked and significant. Week 5 Grade 1 100% Silymarin group, (almost unbelievable) placebo grade 1 55%,	P=0.003 (for week 5 data)	Low
Lam et al 2019	Within subjects experimental design-single centre	RTOG measured at baseline and baseline photographs were taken on day 1 of treatment, of the weekly RTOG scores the highest was recorded for score during treatment. The photographs taken at baseline and FU were assessed blind.	N=56 randomised (over 2 years) n=27 randomised to lateral and n=29 randomised to medial for BF. For lateral applied BF data available for analysis of blinded photographs was n=24 For medial applied BF data available for analysis of blinded photographs was n=29	Barrier Film (alcohol-free film formulated from two polymers, the half of the breast not covered with BF standard care was used, that included using Glaxal based cream which is similar to aqueous cream. BF started on first day of treatment. Applied twice per week, not applied between last RT session and FU appointment.	Breast Cancer		Patient reported outcomes, no sig difference in reported scores seen for burning, pulling and tenderness for those with BF applied to medial, one sig improvement in score for itching 1.14 vs 2.06 P=0.035. For cases where the BF was applied to the lateral only for burning was there seen a sig difference in patient reported scores, 0.92 vs 1.83 (P=0.047) no CI presented. No significant difference seen between BF and standard care for time to development of grade 2 RD. RTOG during treatment – some errors in results presented for calculated numbers with grade 2 or more RTOG. In those with lateral BF Grade 2 or more RD 17.3% vs 27.6% for no film P=0.041. For medial cases 17.2% for the BF cases and 9.6% for no film P=0.76 Post treatment no difference seen in grade 2 or above scores for BF vs no film. There	P=0.041 for laterally placed BF	moderate
Moller et al 2018	RCT pt. own control	CTC scored by RTT blinded to randomisation. PROS	101 N=79	Intervention: Mepitel applied to lateral or medial breast. Control: Opposite side treated as per guidelines i.e. using moisturiser and for itch/steroids	Breast	To investigate PR symptoms related to radio dermatitis and to examine patient preferences using mepitel film compared to standard skin care. Secondary compare to general population	CTC scores: no significant difference in grades 1 to 3at end of treatment or at 14 days. Patient reported outcomes were that the film was comfortable and patients felt made a difference, at 14 days pain was reduced (p.0.001) and sensitivity of the skin (p<0.01) as well as itching	pain reduced p.0.001	Low
Naff et al 2018	Pilot study	CTC (ARSM) scored by nurse and doctor G2 s2,4,6 & 8 weeks	20 int in analysis. 100 controls	Intervention: Administration of the CSNF 0.4% lotion 7 days prior to RT, • Preventative gel CSNF 2.5% administer 1-2 hours prior to radiotherapy. Control: Comparative group had treatment related to care guidelines i.e. Excipal or nepanthol or lalugen cream	Breast	To assess effectiveness of NPE of CNSF extract in prevention and recovery of acute radiation induced skin reactions	CTC scores not significantly different showed trend. Significant delay in grade 2	P =0.014	High
Rades et al 2019	RCT	CTCAE v4	57 (28 MEP/ 29STD)	Intervention: Mepitel film started on first day continued until Grade 2 moist desquamation MEP changed 2x weekly. Control: 2-5% urea and fatty acid cream	Head and neck stratified between groups	Comparison of Mepitel film to standard skin care for prevention of grade 2 radiation dermatitis	46.4 % of patients had sensitivity to MEP (13 of 28) so study stopped at interim analysis at 50Gy 8/23 (34.8%) in the mEP group had Grade 2 and 10/28 (35.7%) in STD group (NS). At 60Gy grade 2 rates were 65.2% (15/23) and 59.3% (16/27) in the STD NS	see results column	Low
Ogita et al 2019	RCT	Sebum content and composition Sebumeter at 4 time points 2,4,weeks and 3 months	81 (80 rand) 74 analysed (I=16) (C=64) then from this group post WBRT I n=32 and control n=32	Intervention: prophylaxis used heparinoid 2x daily from first txt until 2 weeks after wbrt. Control: No moisturiser but reassigned at 2 weeks after WBRT to receive moisturiser or not	Breast	explore time course and water content of strateum Corneum to assess skin damage with heparinoid cream	Rxt significantly reduced sebum content overall. No differences seen between groups but confusing analysis	see results column	High
Schmeel et al 2018	RCT pt. own control	RTOG and EORTC recorded weekly, RISRAS but not reported	62 (56 analysed)	Intervention: hydrofilm. Control: 5% urea	Breast	compare prophylactically applied hydrofilm dressings with standard skin care using moisturising 5% urea	Significantly reduced severity of RTOG mean 0.35 and 1.33 in the control with p<0.001 RTOG/EORTC end of treatment severity Grade 0 48% film control 12.5%, Grade 1. 39.3%--46.4%, Grade 2 12.5%...30.4%, Moist desquamation 0% 10.7%	p<0.001	High
Sekiguchi et al 2015	RCT	Sebum content and composition Sebumeter at 4 time points 2,4,weeks and 3 months. Diary for compliance ARD scores i.e. clinicians rated score	749 women assessed I 14 and C 32	Intervention: prophylaxis used heparinoid 2x daily from first txt until 2 weeks after wbrt. Control: No moisturiser	Breast	Efficacy of heparinoid moisturizer as prophylactic agent	Skin dryness was significantly higher in the control group 2 and 4 weeks . Itching and pain VAS scores generally higher at last day, No significant differences at 3 months	see results column	High
Seliguchi et al 2018	RCT	Water content, and severity scoring none to very severe 2 to 4 weeks after RXT	749 women assessed I 32 and C 32	Intervention: prophylaxis used heparinoid 2x daily from first txt until 2 weeks after wbrt. Control: No moisturiser	Breast	Efficacy of heparinoid moisturizer as prophylactic agent	Skin dryness significant difference between groups between moisturiser and no moisturiser (p0.01). No significant clinicians rated skin toxicity or patient reported except pain scores at last day of RT	p<0.001	High
Sio et al 2016	RCT	CTCAE v3 4 PROS (LASA) assessed at baseline and weekly	167 women	Intervention: topical 0.1% mometasone. Control: No moisturiser	Breast	Dermatitis evolution of mometasone furoate	Radiation symptoms started between week 4-7 and subsided after week 8 . CTCAE showed no significant differences. Significant differences in PROS over time between arms(p0.001)	p<0.001	Low
Togni et al 2015	RCT	camera visual intensity and colour analysis. RTOG		Intervention: base cream. No control reported	Breast	Saftey and efficacy of Boswellia based cream for prevention of adjuvant skin damage	RTOG grade 2 toxicity 71.2% for control and 54.6% boswelellua cream. Not significant. Claims in abstract it is able to reduce erythema, no regression for risk factors. Skin colour intensity less in intervention but not significant	p=0.009	High
Ulff et al 2017	Long term follow up from trial comparing normal breast tissue	RTOG. Skin thickness using ultrasound. Dryness measured. Cosmetic results. 6 years after treatment	60(I=28, C=32)	Intervention: betamethasone 0.1%. Control: Moisturiser	Breast	evaluate whether treatment with potent steroid during adjuvant EXBRT is associated with late toxicity	Skin atrophy not noted in any of the 60 patients. No significant differences between normal tissue and treated with steroids. 10 (17%) had noticeable skin changes. 3 (5%) had altered skin pigmentation.	P<.0.001	Low
Ulff et al 2017	RCT	RTOG.VAS of itching, skin irritation	686	Intervention: betamethasone-17 valeroate cream, Applied 7 days per week until 2 weeks after RT. Control Moisturiser	Breast	Test hypothesis that preventative topical steroid treatment instituted at start of radiotherapy can ameliorate acute radiation dermatitis	Patients receiving hypofractionated RT developed less skin reactions than those treated with CTR. Steroids had significantly less skin reactions -.0.001 regardless of RT schedule	P<.0.001	Low
Wolf et al 2018	phase 2 multi-site, randomized, double-blinded, placebo-controlled trial	baseline, weekly after every fifth RT session, at the end of RT (End RT), and 1 week after RT completion RDS scale , digital imaging , completion of three self-report questionnaires, McGill Pain Questionnaire, Skindex-29, Symptom inventory	578 total Intervention= 283 and Control =295 .	Intervention: curcumin capsule- 4 capsules 3x daily for full course of RT and 1 week post RT with food Control: Placebo capsule - 4 capsules 3x daily for full course of RT and 1 week post RT with food	Breast	To determine the efficacy of oral curcumin, one of the biologically active components in turmeric, at reducing radiation dermatitis severity (RDS) at the end of RT, using the RDS scale, compared to	no significant difference in mean RDS score at End RT between curcumin and placebo. No beneficial effect reported from using Curcumin	p=0.565 end of RT	Moderate
Strouthos et al 2016	non-randomised single centre study	weekly CTCAE and physical assessment. weekly VAS, Weekly photographs	70 total Intervention=25 control (no intervention)= 45	photobiomodulation LED therapy	Breast	To evaluate the beneficial role of Photo-biomodulation therapy in preventing/reducing	8% of PBM group experienced grade 1 RD and 12% grade 3 RD. 55.6% of control group experienced Grade 1 RD 40% grade 2 and 4.4% grade 3 (resulting in RT pause) 48% of matched group grade 1 , 44% grade 2 and 4% grade 3	RD lower in PBM group compared to control P=0.0211	Low
Hoopfer et al 2015	Phase III RCT	10 point Catterall skin scoring, 6 point Likert tool for severity and changes in burning, itchiness, pain and dryness , Maximum CSPP scores for erythema, dry and moist desquamation < 50% and > 50% of field	248 in total : 81 to Aloe cream /77to placebo/79 to powder	1. Aloe cream 2. placebo cream: composed of Aquatrix II Both creams subjected to bioassay testing 3. Dry powder: non-metallic baby powder or corn-starch to intact skin followed by one month of Glaxal based cream post RT.	Breast	Phase III RCT to test hypothesis that the use of Aloe would lead to a 1 point reduction in RSR severity and a decrease in symptom severity compared with a traditional dry powder skin care regime	Mean of Max CSSP value: 6.27 for the powder, 6.96 for the aloe (P=0.227 and 6.99 for the placebo (P=0.845) These did not meet the 1 point difference that was deemed to infer clinical significance Symptom Severity (pain) reported significant changes with 9/67 powder arm rating pain as high, 21 /72 aloe cream and 25/74 for the placebo when reported 1 week post RT	Intervention: P=0.227 placebo P=0.845	Low
Rollman et al 2015	double -blinded randomised pilot study	CTCAE v3.0 scale - Skindex 16 SED (Skin experience Diary) baseline, weekly intervals during RT 6 weeks post treatment completion	42 in total intervention=28 Control = 14	EMU oil/ placebo (cottonseed oil) Applied 1.5Ml 2x daily for duration of RT and up to 6 weeks post RT Not applied sooner than 4hrs before delivery Had to have used before 3rd Fraction No other creams or oils Discretion by provider as to other supportive treatments for symptom	Breast	Demonstrate the feasibility and safety of using an oil based product during breast cancer radiotherapy	PROM from Skindex : average scores 7.4 V's 10.4 for the intervention and control respectively Lower mean scores for all areas: emotional, Symptoms and functional Peak CTC toxicity occurred at week 6 of intervention group appeared slightly worse but "not statistically significant" (not reported statistically just narrative)	P=0.29	pilot study
Cui et al 2015	single institution, prospective study	RTOG and VAS also used	94 in total 47 in each group	Intervention: administration of olive oil 3 X daily from #1 and for 2 weeks post RT completion. Control: placebo (water)during RT (not specified if same as above) and for 2 weeks post treatment completion	Nasopharynx	evaluate the effect of olive oil on radiation dermatitis	Grade I and II reactions in 93.6% intervention and 72.3% of control Grade III in 6.4% of intervention and 27.7% of control	p<0.001	Moderate
Censebella et al 2016	single institution, non randomised with historical controls	WHO criteria for grading acute cutaneous toxicities	222 in cohort plus 2 matched historical groups from 2 previous studies 136 and 100 respectively but ½ of each of these were excluded due to a change in RT technique	Hydroactive colloid gel to the irradiated area	Breast	the efficacy of this same hydroactive colloid gel in the prevention of RIMD, with the hypothesis that using this agent preventively would be even more beneficial with respect to incidence and onset time of RIMD.	Incidence of RIMD 6.9% in intervention arm v's 35.1% and 12,6% in the historical control arms	p<0.001	High
Manas et al 2015	Randomised clinical trial	CTCAE and EORTC QLQ with breast and head and neck modules	n=102, number analysed n=98 (4 excluded as didnt meet inclusion criteria)	Topical R1 was applied once per day within 2 hours of RT, R2 applied 4 times a day, 3 times during the day and last application just before bedtime. R1 and R2 applied from first day of RT until 2 weeks post trt. Control= use of a urea-containing ointment 5% wt/wt urea. Applied from day 1 until 2 weeks post treatment.	Breast cancer and head and neck cancer	Primary end point was progression to grade 3 or 4 CTC RD Secondary were overall response rate, and effects on QoL (EORTC QLQ)	Significant differences seen in grade of toxicity between intervention and control arm at each time point. At end of RT 57% of patients in the R1 R2 group had RD compared with 100% in the control arm P<0.0001 2 weeks post RT 33.3% of the R1 R2 patients and 66% of the control had RD P=0.0003 QoL score showed benefits for the R1 R2 patients in terms of skin dryness, stinging and desquamation for patients with breast cancer and reduced use of medication for pain for those with H+N cancer no actual data is presented to confirm the extent of the differences stated.	P<0.0001	High

Appendix 9

Other interventions

Appendix 9 Other Interventions including oral interventions

References		Clinician Reported Outcome Measures									Patient reported outcome measures							
Reduction in toxicity	**Tumour type**																	
		RTOG	CTCAE	RISRAS	CTC	EORTC	Digital Imaging	10 point Caterall	WHO Criteria	Other	SKINDEX 16 Overall	VAS	Symptom Inventory	McGill Pain Questionnaire	Likert Scales	Dermatology QoL Index	Skin Experience Diary(SED)	Other PROMS
Ryan Wolf et al 2018	Breast	NS					NS				NS		NS	NS				
Baumann et al 2017	Dosimetry study									NS								

outcomes (+ve)
significance P<0.05
(NS)not significant

Green= Low risk of bias, Orange= moderate risk of bias, Red=high risk of bias, White= not assessed as pilot study.

Appendix 10

Staff infosheet skin care

Radiation Dermatitis Information Sheet for Radiotherapy Healthcare Professionals

This information has been written to support radiotherapy healthcare professionals in providing advice to patients about skin care and includes guidance on assessing and managing skin toxicity.

Key principles of effective skin-care management

1. Knowledge of intrinsic and extrinsic factors that may affect the development and severity of radiation dermatitis.
2. Documentation of current skin care regimen and existing skin conditions, including sensitivities and allergies to certain products.
3. Use of a standardised tool for radiation dermatitis assessment for all patients undergoing a course of radiotherapy (RTOG is recommended. See Table 2).
4. Adherence to a standardised assessment process that includes a baseline assessment and weekly assessments during treatment using the standardised assessment tool.
5. Mandatory local training for all staff assessing skin toxicity, to ensure accurate reporting and maintenance of consistent management protocols.
6. Regular audit of skin reactions to collate accurate data on frequency and severity.
7. An emphasis on empowering patients to use products they are familiar with and to self-monitor their skin, being proactive to improve comfort and minimise the risk of developing severe skin reactions.
8. Testing within a well-designed randomised controlled trial any new product or device designed to reduce radiation dermatitis, before its implementation.

Incidence

- Radiation dermatitis can appear at any time but is more likely in treatment schedules over 10 fractions.
- Reactions peak towards the end of treatment and may worsen for 10–14 days after treatment completion.
- Most patients find their skin has improved around 4 weeks after treatment finishes.
- If skin has blistered or broken, healing may take longer.

Influencing factors

It is important to be aware of factors that can influence the severity of skin reactions.

Prior to the start of radiotherapy, patients should be identified as being at low, medium or high risk based on intrinsic and extrinsic factors.

Table 1: Intrinsic and extrinsic factors that influence the severity of skin reactions.

Intrinsic factors	Extrinsic factors
Demographic or disease-related characteristics	Treatment-related characteristics
Age, ethnic origin, smoking, obesity, breast size, hormonal status, presence of infection, co-existing diseases (such as diabetes, cardiovascular disease hypermobile Ehlers–Danlos syndrome), skin type.	Technique, dose, volume, fractionation, beam energy, use of bolus, immobilisation devices, addition of systemic anti-cancer therapies (SACTs). Clinical site of treatment, e.g. areas containing skin folds, such as the head and neck, breast, and axilla.

Assessments and management

Before radiotherapy begins (baseline assessment)

Before radiotherapy begins, the following assessments are recommended:

- Formally assess and document RTOG score (see Table 2).
- Discuss and document the condition of the skin on and around the site of treatment.
- Ensure any pre-existing skin conditions, such as infection, sun burn, eczema, etc. are recorded.
- Discuss and document patients' skin care routines, including any products that are already being used for a medicinal nature (e.g. creams for eczema – such as hydrocortisone).
- Assess, discuss and document intrinsic and extrinsic factors, providing appropriate support and information (e.g. smoking cessation, extra care if skin folds in the treatment area). Those patients with intrinsic or extrinsic influencing factors are at a higher risk of developing a significant skin reaction and should therefore be monitored frequently.
- Provide self-care advice (see *Radiotherapy Skin Reactions: Information for Patients*).
- Discuss the likelihood of radiation dermatitis developing and the possibility of permanent radiotherapy-related side effects to the skin, e.g. increased skin sensitivity, hyper- or hypo-pigmentation, and what precautions to take. For example, advise patients to reduce sun exposure to the treatment area and to use sunscreen with SPF 50 (sun protection factor 50).

During radiotherapy

Throughout radiotherapy, the skin should be checked every day and patients should be asked if they have noticed any changes to their skin. The following assessments are recommended on (at least) a weekly basis:

- Assess, discuss and document any changes to the patients' skin or skin care routines.
- Encourage self-monitoring of skin changes and support documentation and discussion of these with the radiotherapy team.
- Ask about any symptoms experienced including pain, itching or sleep disturbance.
- Formally assess and document the RTOG score (see Table 2).
- Provide advice and support to promote comfort (see *Radiotherapy Skin Reactions: Information for Patients*).
- Consider over-the-counter or prescription medicines such as analgesics as appropriate.

At the end of radiotherapy

- Inform patients of the potential for skin reactions to worsen and 'peak' around 10–14 days after the last treatment session.
- If patients require ongoing wound management, ensure this is communicated to primary care teams.
- Encourage patients to contact the radiotherapy department or clinical nurse specialist if they have ongoing skin reactions that they are concerned about or that are not as expected.

Late effects of radiotherapy

There is a small risk that patients may have a delayed skin reaction months or years after their treatment. There is an increased risk for patients that received SACT in addition to radiotherapy. You may encounter patients with long-term complications at follow-up clinics, in the community, or when seeing a patient for a re-treatment. Examples of late effects include:

- Fibrosis
- Lymphoedema
- Cellulitis
- Telangiectasia

These late effects can impact on the quality of patients' lives and may not resolve over time; therefore, they should be included in any local site-specific patient information where particularly relevant. Referral to a dermatologist or appropriate lymphoedema management service may be required. There are also local community and charity support groups able to offer support in managing these conditions.

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Table 2: Radiation Therapy Oncology Group (RTOG) acute radiation dermatitis grading criteria.

Grade 0	Grade 1	Grade 2a	Grade 2b	Grade 3
No visible change to the skin	**Faint or dull erythema** Mild tightness of the skin and mild itching may occur.	**Tender or bright erythema** Skin may feel tighter, itchy and/or sore.	**Patchy moist desquamation** Areas where skin has broken down can be seen. Yellow/pale green exudate may be visible on the surface. Soreness and oedema are evident.	**Confluent moist desquamation** More pronounced areas of broken skin can be seen. Yellow/pale green exudate are visible. Soreness and oedema are evident.
ASSESSMENTS				
Weekly assessments and RTOG score			Daily assessments and RTOG score	
AIMS OF CARE				
• To promote hydrated skin and maintain skin integrity. • To promote comfort.			• To reduce risk of complications of further trauma and infection. • To promote comfort.	
GUIDANCE				
MOISTURISE: Advise the patient to continue moisturising with preferred products. If the patient is not already using a moisturiser, advise them to start. ENCOURAGE SELF-CARE: Discuss self-care guidelines and ensure that the patient has sources of information to refer to. STEROID OR CORTISONE CREAMS: Steroid or cortisone creams should only be used following advice from an independent prescriber or from staff qualified to dispense medication on Patient Group Directives. Contraindications for using these creams are broken skin or signs of infection. ANALGESIA: Ensure adequate analgesia is prescribed for the patient if needed. IF THE SKIN BREAKS: Patients should be advised to discontinue using any cream and should be advised on, or provided with, appropriate dressings. If there are signs of infection, undertake screening. Increase skin assessments to daily frequency. Seek further advice, if required, from a practitioner trained in radiotherapy-induced skin reactions and wound care or tissue viability.			MOISTURISE: Continue to apply moisturiser to skin within the treatment field that is still intact. ENCOURAGE SELF-CARE: Discuss self-care guidelines and ensure that the patient has sources of information to refer to. Follow skin care guidelines and ensure patient has information sources to refer to. DRESSINGS: Use appropriate dressings/products on broken skin, e.g. non-adhesive, silicone low adhesion. **Do not use** paraffin/petroleum jelly-based products or gentian violet. ANALGESIA: Ensure adequate analgesia is prescribed for the patient if needed. INFECTION SCREENING: Take a swab if there are signs of infection and arrange antibiotic treatment if infection is indicated.	
If you are unsure, seek advice from the wound care team, tissue viability specialists or dermatology.				

Appendix 11

Staff infosheet skin care
A5 leaflet

Radiotherapy
Skin Reactions

Radiation Dermatitis Information Sheet for Radiotherapy Healthcare Professionals

SCoR
THE SOCIETY & COLLEGE OF RADIOGRAPHERS

Introduction

This information has been written to support radiotherapy healthcare professionals in providing advice to patients about skin care and includes guidance on assessing and managing skin toxicity

Key principles of effective skin care management

01 Knowledge of intrinsic and extrinsic factors that may affect the development and severity of radiation dermatitis

02 Documentation of current skin care regimen and existing skin conditions, including sensitivities and allergies to certain products

03 Use of a standardised tool for radiation dermatitis assessment for all patients undergoing a course of radiotherapy (RTOG is recommended. See Table 2)

04 Adherence to a standardised assessment process that includes a baseline assessment and weekly assessments during treatment using the standardised assessment tool

05 Mandatory local training for all staff assessing skin toxicity, to ensure accurate reporting and maintenance of consistent management protocols

06 Regular audit of skin reactions to collate accurate data on frequency and severity

07 An emphasis on empowering patients to use products they are familiar with and to self-monitor their skin, being proactive to improve comfort and minimise the risk of developing severe skin reactions

08 Testing within a well-designed randomised controlled trial any new product or device designed to reduce radiation dermatitis, before its implementation

Incidence

Radiation dermatitis can appear at any time
but is more likely in treatment schedules over 10 fractions

Reactions peak at the end of treatment and may worsen

10–14 days
after treatment completion

Most patients find their skin has improved by about

4 weeks after treatment finishes

If the skin is blistered/broken, healing may

take longer than this

Influencing factors

It is important to be aware of factors that can influence the severity of skin reactions

Prior to the start of radiotherapy,
patients should be identified as being at

low, medium or high risk
based on intrinsic and extrinsic factors

Table 1: Intrinsic and extrinsic factors that influence the severity of skin reactions

Intrinsic factors	Extrinsic factors
Demographic or disease-related characteristics Age, ethnic origin, smoking, obesity, breast size, hormonal status, presence of infection, co-existing diseases, such as diabetes or cardiovascular disease. Skin type	**Treatment-related characteristics** Technique, dose, volume, fractionation, beam energy, use of bolus, immobilisation devices, addition of systemic anti-cancer therapies (SACTs). Clinical site of treatment, e.g. areas containing skin folds, such as the head and neck, breast, and axilla

Assessments and management

Before radiotherapy begins, the following baseline assessments are recommended:

RTOG score

Formally assess and document RTOG score (see Table 2)

Any pre-existing skin conditions

Ensure any pre-existing skin conditions, such as infection, sun burn, eczema, etc. are recorded

Condition of the treated area

Discuss and document the condition of the skin on and around the site of treatment

Self-care advice

Provide self-care advice (see Radiotherapy Skin Reactions: Information for Patients)

Skin care routine

Discuss and document patients' skin care routines (including any routinely used products on or near the site of treatment)

Intrinsic and extrinsic factors

Assess, discuss and document intrinsic and extrinsic factors providing appropriate support and information (e.g. smoking cessation, extra care if skin folds in the treatment area). Those patients with intrinsic or extrinsic influencing factors are at a higher risk of developing a significant skin reaction and should therefore be monitored frequently

Radiation dermatitis

Discuss the likelihood of radiation dermatitis developing and the possibility of permanent radiotherapy-related side effects to the skin, e.g. increased skin sensitivity, hyper- or hypo-pigmentation, and what precautions to take. For example, advise patients to reduce sun exposure to the treatment area and to use sunscreen with SPF 50 (sun protection factor 50)

During radiotherapy

Throughout radiotherapy, the skin should be checked every day and patients should be asked if they have noticed any changes to their skin. The following assessments are recommended on (at least) a weekly basis:

Assess, discuss and document

any changes to the patients' skin or skin care routines

Consider over-the-counter

or prescription medicines such as analgesics as appropriate

Ask about any symptoms

experienced including pain, itching or sleep disturbance

Formally assess and document

the RTOG score (see Table 2)

Encourage self-monitoring

of skin changes and support documentation and discussion of these with the radiotherapy team

Provide advice and support

to promote comfort (see Radiotherapy Skin Reactions: Information for Patients)

At the end of radiotherapy

Inform patients of the potential for skin reactions to worsen and 'peak' around

10–14 days

after the last treatment session

If patients require

ongoing wound management

ensure this is communicated to primary care teams

Encourage patients to contact the

radiotherapy department or clinical nurse specialist

if they have ongoing skin reactions that they are concerned about or that are not as expected

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Late effects of radiotherapy

There is a small risk that patients may have a delayed skin reaction months or years after their treatment. There is an increased risk for patients that received SACT in addition to radiotherapy. You may encounter patients with long-term complications at follow-up clinics, in the community, or when seeing a patient for a re-treatment

Examples of late effects include:

01 **Fibrosis**

02 **Lymphoedema**

03 **Cellulitis**
(an infection which requires antibiotic treatment)

04 **Telangiectasia**

This can impact on

patients' lives

and may not resolve over time; therefore, these late effects should be included in any local site-specific patient information where particularly relevant

Referral to a

dermatologist

or appropriate lymphoedema management service may be required. There are also local community and charity support groups able to offer support in managing these conditions

Table 2: Radiation Therapy Oncology Group (RTOG) acute radiation dermatitis grading criteria

Grade 0	Grade 1	Grade 2a	Grade 2b	Grade 3
No visible change to the skin	**Faint or dull erythema** Mild tightness of the skin and mild itching may occur	**Tender or bright erythema** Skin may feel tighter, itchy and/or sore	**Patchy moist desquamation** Areas where skin has broken down can be seen. Yellow/pale green exudate may be visible on the surface. Soreness and oedema are evident	**Confluent moist desquamation** More pronounced areas of broken skin can be seen. Yellow/pale green exudate are visible. Soreness and oedema are evident
Assessments				
Weekly assessments and RTOG score			Daily assessments and RTOG score	
Aims of care				
• To promote hydrated skin and maintain skin integrity • To promote comfort			• To reduce risk of complications of further trauma and infection • To promote comfort	
Guidance				
Moisturise: Advise the patient to continue moisturising with preferred products. If the patient is not already using a moisturiser, advise them to start **Encourage self-care:** Discuss self-care guidelines and ensure that the patient has sources of information to refer to **Steroid or cortisone creams:** Steroid or cortisone creams should only be used following advice from an independent prescriber or from staff qualified to dispense medication on Patient Group Directives. Contraindications for using these creams are broken skin or signs of infection **Analgesia:** Ensure adequate analgesia is prescribed for the patient if needed **If the skin breaks:** Patients should be advised to discontinue using any cream and should be advised on, or provided with, appropriate dressings. If there are signs of infection, undertake screening. Increase skin assessments to daily frequency. Seek further advice, if required, from a practitioner trained in radiotherapy-induced skin reactions and wound care or tissue viability			**Moisturise:** Continue to apply moisturiser to skin within the treatment field that is still intact **Encourage self-care:** Discuss self-care guidelines and ensure that the patient has sources of information to refer to. Follow skin care guidelines and ensure patient has information sources to refer to **Dressings:** Use appropriate dressings/products on broken skin, e.g. non-adhesive, silicone low adhesion. Do not use paraffin/petroleum jelly-based products or gentian violet **Analgesia:** Ensure adequate analgesia is prescribed for the patient if needed. **Infection screening:** Take a swab if there are signs of infection and arrange antibiotic treatment if infection is indicated	
If you are unsure, seek advice from the wound care team, tissue viability specialists or dermatology				

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Appendix 11

Staff infosheet skin care
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Radiotherapy
Skin Reactions

Radiation Dermatitis Information Sheet for Radiotherapy Healthcare Professionals

SCoR
THE SOCIETY & COLLEGE OF RADIOGRAPHERS

Introduction

This information has been written to support radiotherapy healthcare professionals in providing advice to patients about skin care and includes guidance on assessing and managing skin toxicity

Key principles of effective skin care management

01 Knowledge of intrinsic and extrinsic factors that may affect the development and severity of radiation dermatitis

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08 Testing within a well-designed randomised controlled trial any new product or device designed to reduce radiation dermatitis, before its implementation

Incidence

Radiation dermatitis can appear at any time
but is more likely in treatment schedules over 10 fractions

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after treatment completion

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Assessments and management

Before radiotherapy begins, the following baseline assessments are recommended:

RTOG score

Formally assess and document RTOG score (see Table 2)

Any pre-existing skin conditions

Ensure any pre-existing skin conditions, such as infection, sun burn, eczema, etc. are recorded

Condition of the treated area

Discuss and document the condition of the skin on and around the site of treatment

Self-care advice

Provide self-care advice (see Radiotherapy Skin Reactions: Information for Patients)

Skin care routine

Discuss and document patients' skin care routines (including any routinely used products on or near the site of treatment)

Intrinsic and extrinsic factors

Assess, discuss and document intrinsic and extrinsic factors providing appropriate support and information (e.g. smoking cessation, extra care if skin folds in the treatment area). Those patients with intrinsic or extrinsic influencing factors are at a higher risk of developing a significant skin reaction and should therefore be monitored frequently

Radiation dermatitis

Discuss the likelihood of radiation dermatitis developing and the possibility of permanent radiotherapy-related side effects to the skin, e.g. increased skin sensitivity, hyper- or hypo-pigmentation, and what precautions to take. For example, advise patients to reduce sun exposure to the treatment area and to use sunscreen with SPF 50 (sun protection factor 50)

During radiotherapy

Throughout radiotherapy, the skin should be checked every day and patients should be asked if they have noticed any changes to their skin. The following assessments are recommended on (at least) a weekly basis:

Assess, discuss and document

any changes to the patients' skin or skin care routines

Consider over-the-counter

or prescription medicines such as analgesics as appropriate

Ask about any symptoms

experienced including pain, itching or sleep disturbance

Formally assess and document

the RTOG score (see Table 2)

Encourage self-monitoring

of skin changes and support documentation and discussion of these with the radiotherapy team

Provide advice and support

to promote comfort (see Radiotherapy Skin Reactions: Information for Patients)

At the end of radiotherapy

Inform patients of the potential for skin reactions to worsen and 'peak' around

10–14 days

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If patients require

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ensure this is communicated to primary care teams

Encourage patients to contact the

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Late effects of radiotherapy

There is a small risk that patients may have a delayed skin reaction months or years after their treatment. There is an increased risk for patients that received SACT in addition to radiotherapy. You may encounter patients with long-term complications at follow-up clinics, in the community, or when seeing a patient for a re-treatment

Examples of late effects include:

01 **Fibrosis**

02 **Lymphoedema**

03 **Cellulitis**
(an infection which requires antibiotic treatment)

04 **Telangiectasia**

This can impact on

patients' lives

and may not resolve over time; therefore, these late effects should be included in any local site-specific patient information where particularly relevant

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Aims of care				
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If you are unsure, seek advice from the wound care team, tissue viability specialists or dermatology				

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Appendix 12

Patient information sheet

Radiotherapy Skin Reactions: Information for Patients

Introduction

This information describes the skin reactions you may develop during and after your radiotherapy. It also provides advice on how you can look after your skin.

A skin reaction will only occur in the area being treated. Ask your radiographers and clinical nurse specialist where this is if you are not sure. If you have any questions that are not answered by this document, please talk to your radiographers and clinical nurse specialist.

How might my skin react to treatment?

A radiotherapy skin reaction is likely for most patients. It will not happen straight away but tends to develop gradually throughout treatment, and usually starts to settle 2–4 weeks after treatment finishes.

During the course of your radiotherapy, you may develop a skin reaction in the area being treated. You may notice one or more of the following:

- Your skin may become gradually pinker or darker, depending on your skin colour.
- Your skin may feel dry or tight, and sore.
- A rash may appear and feel itchy and this may feel worse when you get warm or hot.
- Sometimes the skin may blister or peel. If this happens, tell your radiographers and clinical nurse specialist; they will be able to give you further advice and provide any gel or dressings that might be needed.
- You may get an 'exit rash' (this is where the radiotherapy beam causes a reaction in the area opposite to where it goes in). This will depend on how and where you are being treated. Tell your radiographers and clinical nurse specialist if you see or feel anything on your skin that concerns you.

What can make my skin reaction worse?

If you develop a skin reaction during the course of your radiotherapy, a number of factors that may affect the reaction include:

- If you are prescribed a higher dose of radiation for your type of cancer.
- If you receive treatment to areas where your skin folds, such as the groin, breast, buttocks or armpit; these areas can be warm, moist and rub together, making the skin more sensitive.
- If you receive treatment to the head and neck area (due to the sensitive nature of the skin and the tendency for this area to be exposed to the sun). If you are receiving treatment on your neck, you can help by covering this area with a cotton or silk scarf when you go outside.
- If you are prescribed chemotherapy and/or immunotherapy alongside radiotherapy (due to their combined effects).
- If you smoke (as this can affect the oxygen levels in your skin). Please ask for advice if you need help to stop or to cut down on smoking.
- If you have other conditions such as diabetes and heart disease (as these may affect the overall well-being of your skin). Please tell your radiographers and clinical nurse specialist if you have any other health conditions so that it can be noted in your records.

Skin care advice

Tell your radiographers and clinical nurse specialist about your usual daily skin care routine. They will let you know if any changes are advised.

Please keep notes of any differences to your skin so that you can share these with your radiographers and clinical nurse specialist. Please also tell them if your skin reaction is painful, so that they can recommend pain relief. Talk to your radiographers and clinical nurse specialist about any worries you have.

Reactions to your skin cannot be prevented, however, there are things you can do to help yourself feel more comfortable.

Health and well-being

- It will help your overall health if you keep up an intake of at least 6–8 glasses of water a day and eat a nutritionally well-balanced diet that includes fruit, vegetables, whole grains and lean protein. You can ask your radiographers and clinical nurse specialist to provide examples and to explain the importance of staying hydrated and eating a healthy diet in more detail. If you are receiving treatment to your abdominal area they may recommend a different diet.
- If your skin is **not** blistered or peeling, you may go swimming. It is best to shower immediately afterwards to wash off the chlorine and then apply moisturiser. Please stop swimming if it irritates your skin.
- Avoid sun exposure and protect the treated area from direct sunlight. You can wear a brimmed hat and/or cover up with clothing. Continue to protect the treated area from the sun for at least one year after you have finished treatment. Because your skin will be more sensitive, use sunscreen with SPF 50 (sun protection factor 50).
- You may find it more comfortable to wear loose-fitting clothing made of natural fibres, such as cotton or silk.

Hygiene and moisturising

- When washing and bathing, make sure the water is not too hot; wash the skin gently with products you would normally use and gently pat dry.
- Please continue to use the moisturiser you prefer and like to use. No specific moisturiser can be recommend for use during and after treatment as there is not sufficient evidence to support the use of one product over another.
- Use moisturiser frequently; gently smooth it onto your skin until it is absorbed. The aim is to help keep your skin supple.
- If you do not currently use a moisturiser, speak with your radiographers and clinical nurse specialist and they will be able to suggest a few options for you.
- You do not need to wipe your moisturiser off before receiving treatment, but please do not apply moisturiser immediately before your treatment.
- Please stop using moisturiser if it irritates your skin and talk to your radiographers and clinical nurse specialist.
- If your skin blisters or peels, stop using moisturiser in that particular area and ask your radiographers and clinical nurse specialist for more advice.
- Please continue to use the deodorant you normally use, unless it irritates your skin; stop if your skin blisters or peels.

‘DON’Ts’ for the treatment area

- Avoid rubbing the area.
- Avoid or reduce shaving, if possible, unless advised differently by your radiographers and clinical nurse specialist.
- Do not use wax, creams or lasers for hair removal on or close to the treated area during your treatment.
- Do not use sticky tape on the area (such as Elastoplast™ or Micropore™).
- Avoid using make up, hair dye, perfumes and aftershave on or close to the treated area.

After treatment

- When you finish receiving treatment, your skin reaction may worsen for the following 10–14 days before starting to improve.
- If your skin has blistered or peeled it may take longer to heal.
- About 4 weeks after treatment finishes, most patients find that their skin has improved.
- The treated area will continue to be more sensitive than the rest of your skin, even once you have completed your radiotherapy, especially to heat and sunlight.

Do you have any questions?

Please talk to your radiographers and clinical nurse specialist. They are here to help you during and after your treatment.

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Appendix 13

Patient infosheet skin care
A5 leaflet

Radiotherapy
Skin Reactions

Information for Patients

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Introduction

This information describes the skin reactions you may develop during and after your radiotherapy. It also provides advice on how you can look after your skin

A skin reaction will only occur in the area being treated. Ask your radiographers and clinical nurse specialist where this is if you are not sure. If you have any questions that are not answered by this document, please talk to your radiographers and clinical nurse specialist

How might my skin react to treatment?

A radiotherapy skin reaction is likely for most patients. It will not happen straight away but tends to develop gradually throughout treatment, and usually starts to settle 2–4 weeks after treatment finishes

During the course of your radiotherapy, you may develop a skin reaction and notice your skin...

gradually become pinker or darker

depending on your skin colour

feel dry or tight, and sore

develop a rash and feel itchy

This may feel worse when you get warm or hot

blister or peel

If this happens seek further advice as you may need dressings or gel

You may develop an **exit rash**

This is where the radiotherapy beam causes a reaction in the area opposite to where it goes in

This will depend on how and where you are being treated. Tell your radiographers and clinical nurse specialist if you see or feel anything on your skin that concerns you

What can make my skin reaction worse?

If you develop a skin reaction during the course of your radiotherapy, a number of factors that may affect the reaction include:

01

If you are prescribed a higher dose of radiation for your type of cancer

02

If you receive treatment to areas where your skin folds

This includes the groin, breast, buttocks or armpit; these areas can be warm, moist and rub together, making the skin more sensitive

03

If you receive treatment to the head and neck area

This is due to the sensitive nature of the skin and the tendency for this area to be exposed to the sun. If you are receiving treatment on your neck, you can help by covering this area with a cotton or silk scarf when you go outside

04

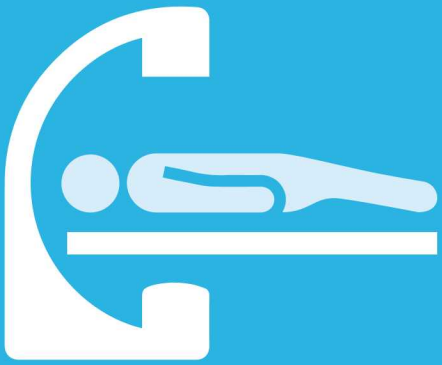
If you smoke (this can affect the oxygen levels in your skin)

Please ask for advice if you need help to stop or to cut down on smoking

05

If you have other conditions such as diabetes or heart disease

Please tell your radiographers and clinical nurse specialist if you have any other health conditions so that it can be noted in your records



Skin care advice

Reactions to your skin cannot be prevented, however, there are things you can do to help yourself feel more comfortable

Tell your
radiographers and clinical nurse specialist
about your usual daily skin care routine. They will let you know if any changes are advised

Keep notes of any differences
to your skin so you can share these with your radiographers and clinical nurse specialist. Please tell them if your skin reaction is painful, so they can recommend pain relief. Talk to them about any worries you have

Health and well-being

It will help your overall health if you...

keep up an intake of
6–8 glasses of water a day

eat a
nutritionally well-balanced diet

A diet that includes fruit, vegetables, whole grains and lean protein. You can ask your radiographers and clinical nurse specialist to provide examples and to explain the importance of staying hydrated and eating a healthy diet in more detail

If you are receiving treatment to your abdominal area they may recommend a different diet

you may

go swimming if your skin is NOT blistered or peeling

It is best to shower immediately afterwards to wash off the chlorine and then apply moisturiser. Please stop swimming if it irritates your skin

you may

find it more comfortable to wear loose-fitting clothing

made of natural fibres, such as cotton or silk

please avoid

sun exposure and protect the area from direct sunlight

You can wear a brimmed hat and/or cover up with clothing. Continue to protect the treated area from the sun for at least one year after you have finished treatment. Because your skin will be more sensitive, use sunscreen with SPF 50 (sun protection factor 50)

Hygiene and moisturising

Moisturisers

01 **Please continue to use the moisturiser you prefer and like to use.** No specific moisturiser can be recommended for use during and after treatment as there is not sufficient evidence to support the use of one product over another

02 **Use moisturiser frequently; gently smooth it onto your skin until it is absorbed.** The aim is to help keep your skin supple

03 If you do not currently use a moisturiser, **speak with your radiographers and clinical nurse specialist** and they will be able to suggest a few options for you

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washing and bathing

Make sure the water is not too hot; wash the skin gently with products you would normally use and gently pat dry

deodorants/sprays

Please continue to use the deodorant you normally use, unless it irritates your skin; stop if your skin blisters or peels

'DON'Ts' for the treatment area

Please avoid...

rubbing the area

using sticky tape
on the area (such as Elastoplast™ or Micropore™)

shaving
reduce shaving if possible, unless advised differently by your radiographers and clinical nurse specialist

using wax, cream or lasers
for hair removal on or close to the treated area

using make-up
hair dye, perfumes and aftershave on or close to the treated area

After your treatment has finished...

Your reaction may worsen for the next **10–14 days** before starting to improve

Most patients find that their skin has improved around **4** weeks after treatment

If skin has blistered or peeled it may **take longer** to heal

The treated area will continue to be **more sensitive** than the rest of your skin, even once you have completed your radiotherapy, especially to heat and sunlight

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Appendix 13

Patient infosheet skin care
A5 leaflet - PRINT READY

Radiotherapy
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Information for Patients

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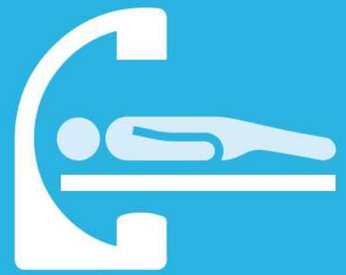

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Appendix 14

Skin care presentation

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Radiation Dermatitis Information for Radiotherapy Healthcare Professionals

What current evidence is there to give the optimal skin care advice to patients undergoing radiotherapy?

Introduction

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- Turesson et al. (1996) demonstrated that the number of basal cells in the epidermis declines during fractionated RT due to increased cell cycle arrest and reduced mitosis. This causes a thinning of the epidermis and an inflammatory reaction and the variation in the reaction appears to be a **genetic predisposition** related to individual DNA repair capacity. *(Chang-Claude et al., 2005; Pinar et al., 2007; Andreassen and Alsner, 2009)*

- Certain **clinical factors can aid in the prediction** of which patients are more likely to experience a significant radiation reaction. *(Russell et al., 1994; Russell 2010)*

Influencing factors

- It is important to be aware of factors that can influence the severity of skin reactions.

- Prior to the start of radiotherapy, patients should be identified as being at **low, medium or high risk** based on intrinsic and extrinsic factors.

Extrinsic factors	Intrinsic factors
Radiotherapy Technique, dose, fractionation, beam energy, and modality of radiotherapy.	Age. Ethnic origin. Skin type
Site of treatment e.g. skin folds	Breast size. Hormonal status
Bolus, immobilisation devices	Nutrition
Radiosensitisers Some Cytotoxic agents can increase the severity of reaction e.g. Cisplatin, 5-Flurouracil, Mitomycin C.	Smoking. Alcohol
Chemicals/ thermals/ mechanical irritants	Co-morbidities e.g. diabetes, cardiovascular disease
Addition of systemic anti-cancer therapies (SACTs).	Previous damage
	Trauma
	Obesity
	Infection
	UV exposure

Incidence

- Radiation dermatitis can appear at any time but is more likely in treatment schedules over 10 fractions.
- Reactions peak towards the end of treatment and may worsen for 10–14 days after treatment completion.
- Most patients find their skin has improved around 4 weeks after treatment finishes.
- If skin has blistered or broken, healing may take longer.

The extent of the problem? 2014 data

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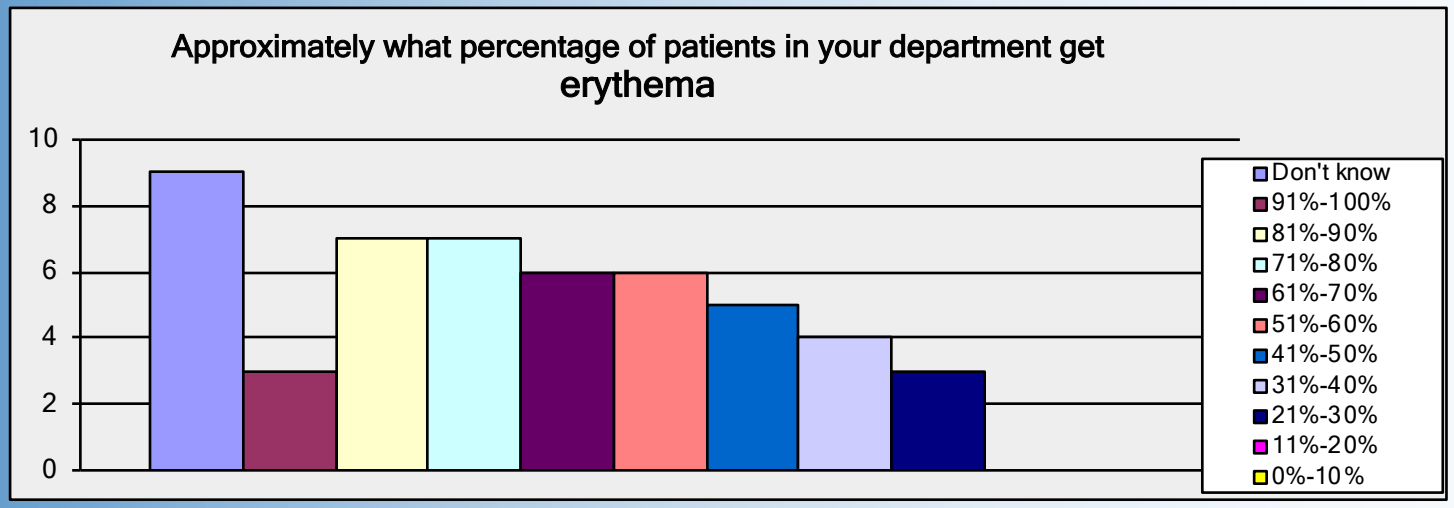
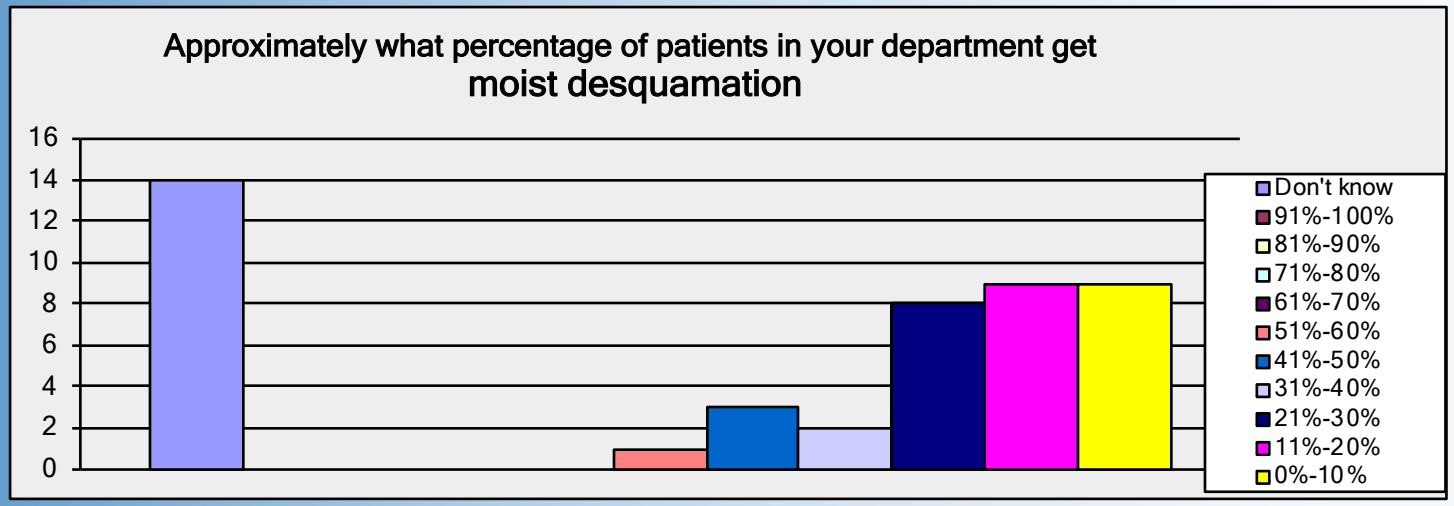
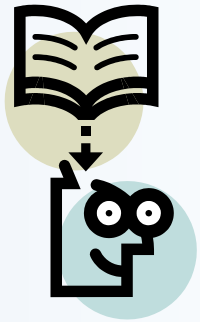




Systematic Reviews

- An extensive literature review was undertaken of over 300 articles from 1980 to October 2010.
- Two systematic reviews of skin care literature proved invaluable in determining the more robust evidence base. *(Bolderston et al., 2006; Kedge 2009)*
- 2014 systematic review undertaken using PICO method and *SIGN* to determine if, since 2010 there has been any additional evidence. Three systematic reviews also reviewed. *(Butcher and Williamson, 2012; Schnur et al., 2013; Chan et al., 2014)*
- 2019 systematic review undertaken using PICO method and pearl growing to identify new literature since 2014



2019 Systematic Review

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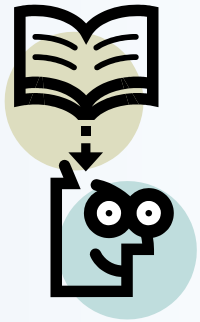
- The current review included a search of multiple databases as well as a hand search of a number of relevant journals and supplemented by searches of the grey literature to include ongoing trials. The systematic review was registered with the Prospero database (registration CRD42019148161).

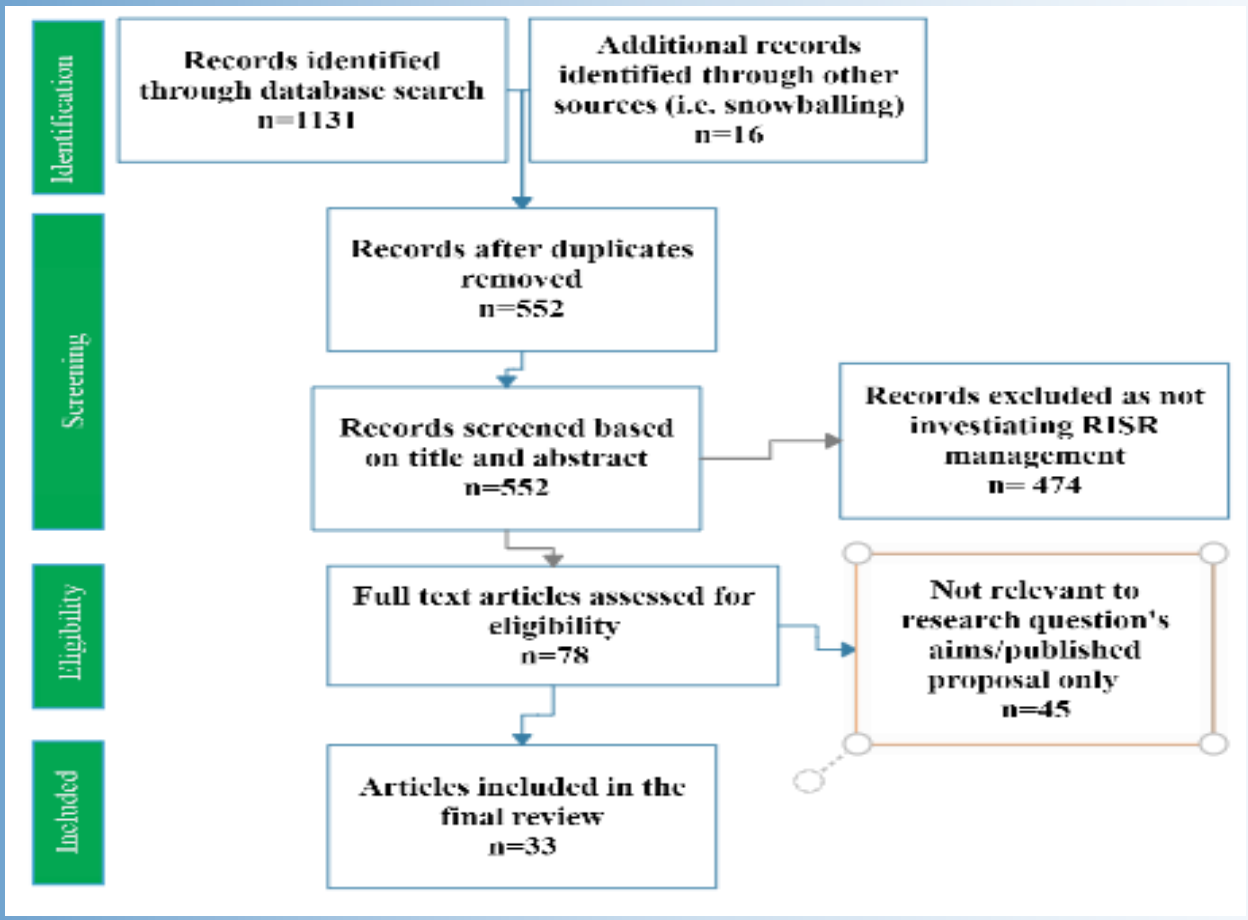
- Thirty-three studies were included in the results and discussion. All included research was assessed for quality, with recommendations based on the studies assessed as having low opportunity for bias.

- However, significant challenges still arise with respect to the research conducted.



2019 Systematic Review

Quality assessment was completed by 3 researchers assessing study quality independently; 2 independent reviews were completed on each article. The review has been reported using the PRISMA group guidelines



The review aimed to answer the following questions:

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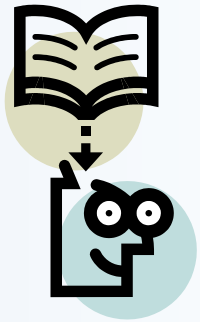
- Is there new research evidence to support a change in advice given to patients undergoing radiotherapy about how to care for their skin before during and after a course of radiotherapy in terms of washing, drying, deodorant or cream use?

- Is there new evidence to support the use of topical agents?

- Is there new evidence to support the use of dressings, medical devices, oral medications or barrier films?



The 2019 evidence base for prophylactic skin care (1)

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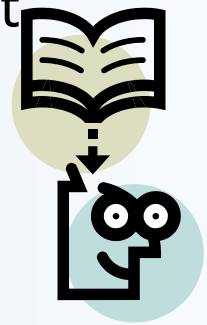
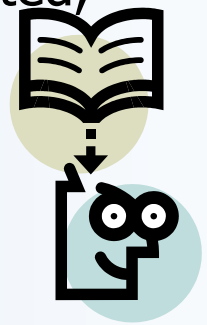
The review identified a number of key areas which have been and are currently being researched.

- Some studies have made strong recommendations for the use of **prophylactic topical steroids**. In spite of this, other published research recommends exercising a degree of caution and that there is a need for more work to be undertaken, particularly to determine any long term implications of using steroids. Therefore it is recommended that steroid creams should be reserved prophylactically for patients scored at a high risk of radiation dermatitis.
- **Photobiomodulation (laser therapy)** shows positive benefits but long-term possible consequences of this approach have not been assessed and further research is needed.



The 2019 evidence base for prophylactic skin care (2)

- **Barrier films** demonstrate mixed results due to poor patient compliance or high withdrawal rates in some studies. The positive results tend to be in studies where the dose fractionations are over 40Gy. Patients with breast cancer in the UK should be routinely treated with 40Gy in 15 fractions, therefore for patients with breast cancer treated with a hypofractionated regimen there does not appear to be any advantage of using a barrier film. For patients with cancers in the head and neck region where higher doses are utilised there may be a benefit but **the evidence base is inconclusive and weak to support this as routine practice**.
- There are a range of **other interventions** that have been tested, only a few assessed as low risk of bias and need additional research to confirm the findings before they could be recommended for wide use.



2019 systematic review

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Overall, the evidence base is not strong enough to either support or refute the use of any particular product for topical application

Consensus 2019

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There are two areas where a more general consensus on guidance is closer to being achieved.

- Firstly with respect to the use of **aqueous cream**:

This has now been reclassified in the British National Formulary (BNF) as a soap substitute and should not be used as a leave-on moisturiser.

- Secondly with respect to the use of **deodorant**:

Where a much stronger evidence base refutes the adverse impact that deodorants were once thought to have. *(Bennett, 2009; Watson et al., 2012; Wong et al., 2013)*

2019 systematic review

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1. There is a need for **more research** investigating the impact of dosimetry in modern radiotherapy planning on subsequent skin reactions.
2. Prior to the start of radiotherapy **patients should be identified as being at low, medium or high risk** based on intrinsic and extrinsic factors.
3. Where centres want to consider implementing a new topical intervention or a new device to reduce radiation dermatitis we would recommend teams first test the new product/device within **a well-designed randomised controlled trial** to ensure the research evidence is robust enough to inform practice.

Future research (1)

- There should be a **clear scientific rationale** for introduction of the new product or device.
- Where possible RCTs testing a topical agent or device should be **placebo-controlled**.
- Where **barrier films** are the focus of the investigation researchers should **use a within-subjects design** with the barrier film placed on half of the area of skin to be irradiated (on the other half of the treated area, standard skin care using simple moisturisers and standard washing instructions should be used).

Future research (2)

- Assessors should be **blinded** to the intervention as should patients if possible.
- Measure/score skin at **baseline** prior to radiotherapy.
- Researchers should measure and document **confounding factors**.
- A **standard skin toxicity scoring system** should be used, for example RTOG. Assessors should be trained to use the tool and an assessment of inter and intra-rater reliability should be undertaken.
- RTOG scores are categorical (ordinal level) data and **presentation of the data should be by percentage of each grade at each measure point** during radiotherapy and post radiotherapy. Using a mean score to make judgements about performance of an intervention can be misleading.

Future research (3)

- **Randomisation should be remote** to the staff.
- **Randomisation should consider stratification** to ensure important confounding variables are balanced.
- **Use of PROMs**, it is useful to have patient reported outcomes in addition to clinician/practitioner reported assessments.
- Researchers should employ **multivariate analysis** to control for confounding variables, and to identify the contribution of the intervention to reducing (or preventing) radiation dermatitis in the context of other intrinsic or extrinsic factors.
- Measurement and **reporting of adherence** to the intervention of new products or devices is important as is the reporting of the detail for withdrawals.

Future research needed (4)

- Evaluation into **wet versus dry shaving** and **perfume** and **make-up** use is needed.
- Evaluation of treatment **aftercare** requires review to ensure local continuity and consistency of care across the patient pathway.
- Further investigations into the skin care reactions: **superficial, orthovoltage**, and **proton beam** radiotherapy are required.
- **Patient preferences** and **compliance**.

Before radiotherapy begins (baseline assessment) (1)

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- Formally assess and document **RTOG** score.
- Discuss and **document the condition of the skin** on and around the site of treatment.
- Ensure any **pre-existing skin conditions**, such as infection, sun burn, eczema, etc. are recorded.
- Discuss and document **patients' skin care routines** (including any routinely used products on or near the site of treatment).

Before radiotherapy begins (baseline assessment) (2)

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- Assess, discuss and document **intrinsic and extrinsic factors**, providing appropriate support and information (e.g. smoking cessation, extra care if skin folds in the treatment area). Those patients with intrinsic or extrinsic influencing factors are at a higher risk of developing a significant skin reaction and should therefore be monitored frequently.
- Provide **self-care advice**.
- **Discuss the likelihood** of radiation dermatitis developing and the possibility of permanent radiotherapy-related side effects to the skin, e.g. increased skin sensitivity, hyper- or hypo-pigmentation, and what precautions to take. For example, advise patients to reduce sun exposure to the treatment area and to use sunscreen with SPF 50 (sun protection factor 50).

Prophylactic skin care (1)

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A lack of evidence to support prophylactic use of any specific product

2014 data:
49% of departments do not assess what a patient currently uses

ask

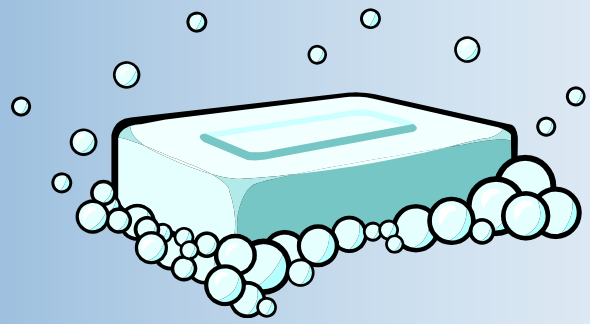
Prophylactic skin care (2)

Evidence indicates that gentle skin and hair washing should be unrestricted for patients and there should be:

no restriction to using a specific type of soap

2014 data:

74% of departments report washing restrictions



Prophylactic skin care (3)

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Evidence indicates that deodorant use should be unrestricted for patients and there should be:

no restriction to using a specific type of deodorant

2014 data:
55% departments are still saying 'no deodorant'

Breast cancer patients who are advised not to use a deodorant often cite this as one less area of control they have in their life and they note concern regarding body odour. *(Komarnicki, 2010)*

Recommendations

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- **Wash** the skin gently and gently pat dry. *(Aistars, 2006; Bolderston et al., 2006; Aistars and Vehlow, 2007; Butcher and Williamson, 2012)*
- Use a **moisturiser** that is sodium lauryl sulphate free. *(Tsang and Guy, 2013; Patel et al., 2013)*
- Continue to use normal **deodorant** (unless this irritates the skin), but discontinue if the skin is broken. *(Bennett, 2009; Butcher and Williamson, 2012; Watson et al., 2012; Wong et al., 2013)*

Health and well-being

- It will help overall health if patients have an intake of at least **6–8 glasses of water** a day and eat a **nutritionally well-balanced diet**. If patients are receiving treatment to the abdominal area a different diet may be needed.
- If the skin is **not** blistered or peeling, allow patients to go **swimming**. Advise to stop swimming if it irritates.
- **Avoid sun exposure** and protect the treated area from direct sunlight. Continue to protect the treated area from the sun for at least one year after treatment. Use sunscreen with SPF 50.
- Advise **comfortable loose-fitting clothing** made of natural fibres, such as cotton or silk.

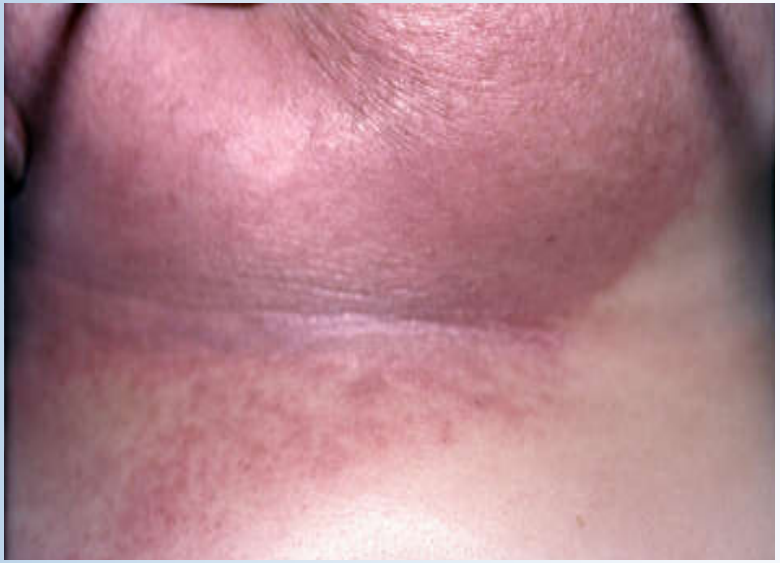
During radiotherapy

Throughout radiotherapy, the skin should be checked every day and patients should be asked if they have noticed any changes to their skin. The following assessments are recommended on (at least) a weekly basis:

- Assess, discuss and **document any changes** to the patients' skin or skin care routines.
- Encourage **self-monitoring** of skin changes and support documentation and discussion of these with the radiotherapy team.
- Ask about any symptoms experienced including pain, itching or sleep disturbance.
- Formally assess and document the **RTOG** score.
- Provide advice and support to **promote comfort**.
- Consider over-the-counter or prescription medicines such as analgesics as appropriate.

Erythema

Erythema tends to occur at 2000-4000 cGy



Recommendation 2019:

Continue with own self care skin moisturiser

2014 data:

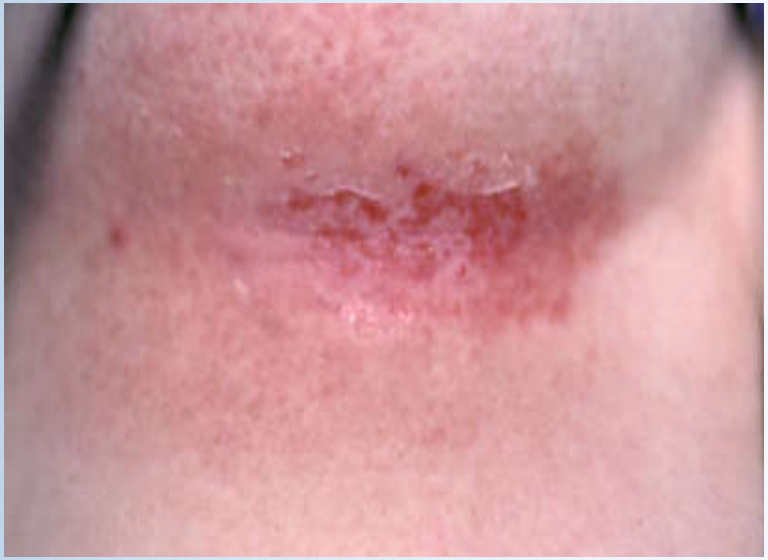
29 ISSUED the product

15 products cited

Dry desquamation

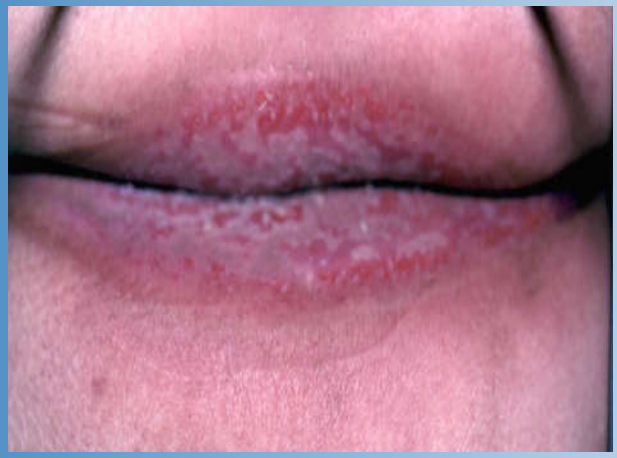
Dry desquamation occurs mainly at 3000 cGy and higher

Recommendation 2019:
Continue with own self care skin moisturiser and assess if steroid cream required



2014 DATA:
33 ISSUED the product
13 products cited

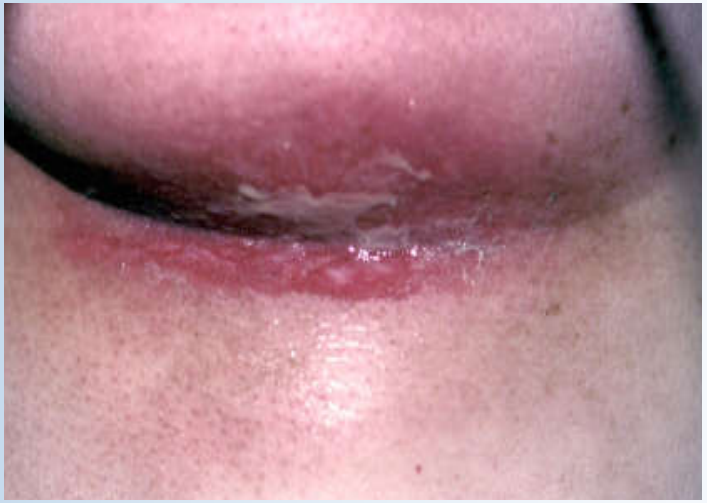
Moist desquamation



Recommendation 2019
Use appropriate dressing/product on broken skin to reduce further trauma and infection.

Suitable products would be non-adhesive, silicone low adhesion, non or low paraffin/petroleum jelly based.

Moist desquamation tends to occurs at 4000 cGy and higher



2014 data:
40 ISSUED the product
22 products cited

Things to consider as an issuer

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With a wide variety of products currently available there are bound to be variations in product utilisation and availability; therefore, careful assessment and justification is paramount.

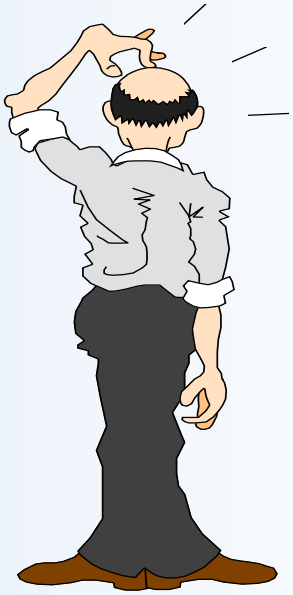
? What are the variation of ingredients in products that use the same generic name e.g. aloe vera?

? Is a product actually worth the cost?

? How available and reliable is the supplier?

? How often does a product need to be applied?

? How easily is the product applied?



At the end of radiotherapy

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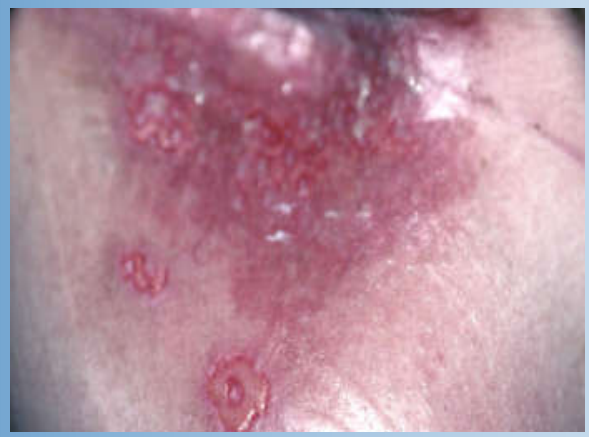
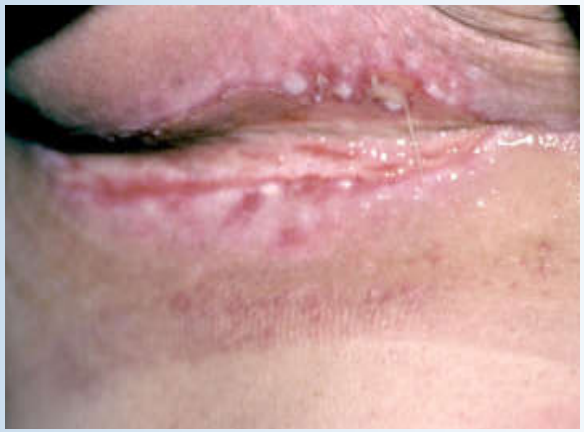
- Inform patients of the potential for skin reactions to worsen and **'peak' around 10–14 days after** the last treatment session.
- If patients require ongoing wound management, ensure this is communicated to **primary care teams**.
- Encourage patients to contact the radiotherapy department or clinical nurse specialist if they have ongoing skin reactions that they are concerned about or that are not as expected.

Late effects of radiotherapy

There is a small risk that patients may have a delayed skin reaction months or years after their treatment. There is an increased risk for patients that received SACT in addition to radiotherapy. You may encounter patients with long-term complications at follow-up clinics, in the community, or when seeing a patient for a re-treatment. Examples of late effects include:

- Fibrosis, Lymphoedema, Cellulitis (an infection which requires antibiotic treatment),Telangiectasia





Late effects of radiotherapy

Late effects can impact on the quality of patients' lives and may not resolve over time; therefore, they should be included in any local site-specific patient information where particularly relevant. Referral to a dermatologist or appropriate lymphoedema management service may be required. There are also local community and charity support groups able to offer support in managing these conditions.

The current position

- Overall, the **evidence base is not strong enough to either support or refute the use of any particular product for topical application**.

- Currently, some of the skin care provided may not actually alleviate the problem and indeed may even compound the effect.

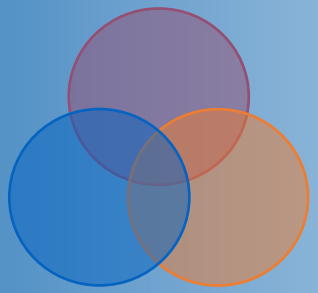
- Are we actually providing skin care advice to patients based on traditional knowledge and a paternalistic approach to healthcare? *(Harris, 2002)*

The patient perspective

Health is:

" ... a state of complete physical, psychological, and social well-being, and not merely the absence of disease or infirmity."

WHO (1978)



" We are people, not just bodies."

Patient 7: Harris (1995)

As *Gosselin, et al. (2010)* noted:

"patients prefer to take action rather than do nothing"

Key principles of effective skin-care management (1)

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- Knowledge of **intrinsic and extrinsic factors** that may affect the development and severity of radiation dermatitis.
- Documentation of **current skin care regimen** and existing skin conditions, including sensitivities and allergies to certain products.
- Use of a **standardised tool** for radiation dermatitis assessment for all patients undergoing a course of radiotherapy (RTOG is recommended).
- Adherence to a **standardised assessment process** that includes a baseline assessment and weekly assessments during treatment using the standardised assessment tool.

Key principles of effective skin-care management (2)

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- Mandatory **local training** for all staff assessing skin toxicity, to ensure accurate reporting and maintenance of consistent management protocols.
- **Regular audit** of skin reactions to collate accurate data on frequency and severity.
- An emphasis on **empowering patients** to use products they are familiar with and to self-monitor their skin, being proactive to improve comfort and minimise the risk of developing severe skin reactions.
- Testing within **well-designed randomised controlled trials** any new product or device designed to reduce radiation dermatitis, before its implementation.

Conclusion

- The extent of skin conditions is largely unknown. Although the majority of skin reactions subside after a few weeks, some can be prolonged and affect a patient's quality of life.

- It may not be possible to stop or even reduce the rates of skin reaction from occurring, but there may be comfort and psychosocial benefits that skin care products provide.

Working party (1)

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Core group

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Gemma Burke (lead for systematic review) Sheffield Hallam University

Rosemary Davies (Patient/user representative and lead for patient information)

Professor Sara Faithfull (Nursing representative and systematic review) University of Surrey

Dr Rachel Harris (Core group lead) The Society and College of Radiographers

Professor Heidi Probst (Systematic review and patient and staff information) Sheffield Hallam University

Lynda Samuels (**Lay person representative from CoR Patient Advisory Group and patient information**)

Mark Reed (Proton beam adviser and background information for guidelines lead) The Christie NHS Foundation Trust

Sue Robins (Patient Activist and patient information)

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Samantha Bostock Gloucestershire Oncology Centre

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Michele Cardoso (representative from Canada comparing advice)

Angela Cashell (representative from Canada comparing advice)

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