The effect of moisturisers on scars: a systematic review.

Submitted by

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Thesis declaration

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Dedicated to my late Mum, who unfortunately did not make it to see this completed.

Abstract

Introduction

Scars, including keloid and hypertrophic scars, are a common and unpleasant cosmetic and sometimes functional side effect of burn injury, trauma or surgery. Moisturising is one of the most common scar management techniques recommended by health professionals. Many clinicians believe that moisturiser application to scars can hydrate, reduce itch and increase pliability. Since trans-epidermal water loss (TEWL) is thought to be the mechanism of action behind the effectiveness of silicone gel sheeting/contact media, it may be that moisturisers also impact on TEWL to have an effect on scars. Some moisturisers also contain additional ingredients, such as vitamins or pharmaceuticals, which may also have an effect on scars. This systematic review aims to assess the effect of moisturisers on scars, excepting atrophic scars. The aim is to present recommendations that are relevant and useful to consumers and clinicians.

Method

Databases searched were PubMed, CINAHL, Embase and Web of Science. Critical appraisal was conducted using Joanna Briggs Institute (JBI) tools. The search located 33 studies of low quality and high risk of bias and these were selected for inclusion: 14 RCTs, 11 quasi-experimental, seven case series and one case report. Overall there were 867 participants or scars included in the review. Data on the outcomes reported by the included studies was extracted using JBI tools.

A subset of seven studies, including a total of 82 keloids, examining the outcome of recurrence of keloids post-excision and application of Imiquimod cream was subjected to a meta-analysis utilising StatsDirect software (Cambridge, UK) and the random effects model. In an attempt to determine if the location of the keloid or the excision method and resultant method of healing (primary closure versus healing by secondary intention) impacted these results, subgroup analysis was performed.

Narrative synthesis was performed on the results of the remaining 26 included studies. The subjective nature of outcome/scar measurement was noteworthy. Despite the variable quality of the studies, all were included so as to provide a current view of the state of the evidence. Outcomes addressed in the narrative synthesis included cosmesis, scar parameters, itch and pain, TEWL and *in vitro* outcomes.

Results

Thirteen moisturisers were examined for their effects on cosmesis. Moisturisers that were reported to have statistically significant positive effects on cosmesis included Lumiere Bio-Restorative Eye Cream, Tretinoin, Scarguard® and Cetaphil®. Imiquimod was the only moisturiser found to have a statistically significant detrimental effect on cosmesis. Studies examining 18 different moisturisers

reported on scar parameters. Of these, those that reported a statistically significant effect on scar parameters were Imiquimod, Aquaphor®, Mederma®, Scarguard® HSE (hydrocortisone, silicone, vitamin E), Cetaphil®, Tretinoin, Eucerin®, Putrescine, Keratin Gel and Doxepin. Eight moisturisers were examined for their effects on itch and pain; statistically significant benefits on both outcomes were observed with Doxepin, Provase®, Mugwort lotion and Eucerin®. Only one study examined TEWL as an outcome measure and found Alhydran to have a statistically significant positive effect. Considering *in vitro* outcomes, only one moisturiser, Dermovate, did not have a statistically significant effect, whereas the others, Tretinoin, Wubeizi ointment and Imiquimod, did.

Seven studies, examining a total of 82 keloids, investigated their recurrence post excision and application of Imiquimod. The similarity in design allowed for statistical meta-analysis. Meta-analysis revealed a recurrence rate of 39% following application of Imiquimod post scar excision. This result however was imprecise (95% CI = 8.4% to 74.4%) and the analysis showed significant statistical heterogeneity (I^2 =87.5%, 95% CI = 75.7% to 92.2%). The use of primary excision and bilayer closure or shave/tangential excision did not alter the outcome as compared to when all studies were examined together. When analysis was conducted based on the location of the keloid scar, earlobe keloids had a recurrence rate of 5.4% (95% CI = 0% to 21.7%), (I^2 = 52.9 %, 95% CI = 0% to 82.6%). Remaining keloids excised were predominantly on the trunk and their recurrence rate was higher, at 76.8% (95%CI = 36.1 to 100%), (I^2 = 70.5%, 95% CI = 0% to 86.4%). Many of the included studies reported adverse events especially erythema and crusting resulting in a rest period at the two to three week mark.

Discussion

Considering the results of this review and the availability and costs of the moisturisers investigated, recommendations are provided for practice. Costly and prescription moisturisers should be selected for application to scars appearing in small and/or cosmetically sensitive areas, such as the face. Clinicians managing scars covering a large surface area should consider readily available, low cost moisturisers that show some evidence of effectiveness.

Of those classified as prescription only, based on their availability in Australia, only Doxepin and Putrescine can be recommended, but with reservations. For high cost, over the counter moisturisers, Tretinoin, Wubeize, Lumiere Bio-Restorative Eye Cream, Scarguard® HSE, Provase and Mugwort Lotion can be recommended, but with reservations. Only Alhydran can be recommended with any confidence. The low cost, over the counter moisturisers that can be recommended with reservations are Eucerin® and Cetaphil®.

Use of subjective scales far outweigh the use of objective instrumentation among relevant studies. Future research needs to utilise appropriate and available instrumentation in the measurement of outcomes. As the included studies in the narrative synthesis group examined keloid and/or hypertrophic scars, recommendations for specific scar types cannot be provided. Some studies also utilised linear scars, which are commonly normotrophic and therefore were likely to have been resolved without any intervention.

Further research is required to examine the effects of basic moisturisers that are regularly in use and readily available to the general public. A small number of these were included in studies as control. It is not known if these moisturisers are just as effective, if not more, than those that are costlier and contain additional specific ingredients.

1. Introduction

This chapter presents information regarding how this systematic review was conceptualised and why it is needed. This chapter also provides some background information to outline the different structures of the skin and how these are affected in wound healing and scar formation. The concepts of trans-epidermal water loss (TEWL), hydration and occlusion and how this is important in scar management are addressed. Different scar types and their unique characteristics are addressed in this chapter. In addition to moisturiser application there are other accepted strategies to manage scars which are often prescribed at the same time as moisturisers and these are also introduced. Since moisturisers are available as many formulations, a brief description of their characteristics is provided and an attempt to group them according to their relevance to clinicians and consumers has been outlined. The science of evidence synthesis introduces evidence based practice and the Joanna Briggs Institute (JBI) model.

1.1 Context of the review

Following burns, trauma or surgery, after immediate life and wound salvaging procedures are undertaken, a priority for the health professional is management of the scars that begin to form. Burns, trauma and all forms of surgery can cause scars that can become problematic. Scars classified as hypertrophic or keloid are particularly problematic.[1] These types of scars impact upon physical function by causing restrictions to movement and contractures, and can be overly sensitive and itchy.[2] Furthermore, they can adversely affect the psychosocial recovery of individuals by affecting the way they perceive their body image and how they feel others perceive them (cosmesis), and they can be a reminder of the trauma that had caused their scars.[3] Overall, scars can influence the quality of life of those that bear them. Therefore, the correct management of scars is of utmost importance.[4]

Health professionals that work extensively with scars commonly recommend pressure, contact media and massage as there is evidence to support this composite approach.[1] In addition to these scar management practices, moisturising is also recommended. It is commonly believed that contact media and moisturisation hydrate the scar and as a result reduce scar activity.[5]

Despite the accepted practice of applying moisturisers to scars, there is little consensus or evidence to inform clinicians about the choice of moisturisers to use.

1.2 The need for this systematic review

A recent systematic review (that was conducted by a group including this author) assessed the effects of moisturisers on scars resulting exclusively from burn injury.[6] However, as the inclusion criteria included only burn scars, only one eligible study was located.[6] Considering the results of the systematic review and in an attempt to establish international practice, this author then conducted a survey across Australia, New Zealand, Canada and the United States of America among burn therapists on what moisturisers they would recommend to their patients and why.[5]

The survey revealed that 53 therapists recommended 29 different moisturisers. Responses reflected the belief that moisturisers hydrate scars, with 85% of responders reporting this as the reason for recommending moisturisers. Recommendations for specific moisturiser use were most commonly aligned to the properties of the moisturiser and facilitation of massage. However, when the respondents were asked if they were able to cite evidence regarding their choice of moisturiser, only one could provide a reference.[5]

Due to the absence of collated research within the burns field it was decided that a systematic review that investigated and included research beyond burns treatment and management may provide the evidence necessary to inform the practice of clinicians working with scars in general. A search of PubMed, Cochrane and JBI revealed that, apart from the above systematic review on burn scars[6], there were no systematic reviews on this topic.

1.3 Skin and scar formation

1.3.1 Skin

The skin is the heaviest organ in the human body, comprising about 16% of dry mass. Its function is to maintain the physiological barrier between our internal milieu and the outside environment, but its other functions are numerous. The skin consists of three layers: the epidermis, dermis and subcutaneous tissue or panniculus.[7] The epidermis consists predominantly of cells (keratinocytes) which, as their name indicates, synthesise keratin which forms part of the waterproofing function of skin.[7] The most superficial layer of the epidermis, consisting of the dead keratinocytes, is called the *stratum corneum.* Scars have a thinner, and therefore malfunctioning, *stratum corneum* which results in increased TEWL.[8]

The dermis is a molecular structure and holds the functional structures such as hair follicles, sebaceous glands and sweat glands (although these are epidermal in origin), and is fundamentally made up of Type 1 collagen.[7] Fibroblasts are responsible for producing this collagen and are the cells responsible for scar production in the latter stages of wound healing after trauma to the dermis.

1.3.2 Wound healing and scar formation

When an injury occurs to the skin, a series of events begins instantaneously. The dermal component of wound repair is typically divided into four phases: coagulation, inflammatory response, granulation tissue formation and matrix remodelling.[9] It is in the final stage, matrix remodelling, where scar formation is considered to begin and the scar can be termed an *active scar* until this phase is complete. It is at this point that the scar is deemed to be *mature*. Scarring of other non-dermis mesodermal derivatives, such as connective tissues, muscle and tendon, for example, were excluded from this review as scarring of these structures is a different phenomenon.

The formation of a scar (also known as a cicatrix) is a normal healing response to a deep wound in the skin. Deep wounds that result in damage to the dermis will 'scar' and it is unlikely that there are adults who cannot locate a scar on their body. Despite this, most adults would not have a scar significant enough to lead to life changes or emotional distress. For those that do, however, the scar may also have other physical complications. The prevalence of contractures, for example, has been reported in a systematic review of burn scars to vary between 38% and 54%.[10]

The longer the phase of inflammation, the more likely a scar will form; time to healing is dependent on how deep the wound is.[11, 12] Acknowledgement of this relationship has led to guidelines that outline that if a wound takes longer than 14-21 days to heal it will require scar management to minimise the detrimental effects of hypertrophic scar.[13]

1.3.3 Trans-epidermal water loss, hydration and occlusion: its relationship to scar formation

As also mentioned above (section 1.3.1) the *stratum corneum* of scars is thinner and therefore the normal barrier function of the skin involved is compromised. This results in higher than normal TEWL and the underdeveloped *stratum corneum* is unable to retain optimum water levels, which is termed *hydration*.[14] When this occurs, keratinocytes produce inflammatory

cytokines that signal the fibroblasts to produce excessive amounts of collagen in an attempt to aid water retention of the stratum corneum.[14, 15]

It is hypothesised that the effect of silicone gel sheets is to return the TEWL to homeostasis at the scarred area. They have an effect of partial *occlusion* which normalises the upregulated scar formation caused by the increase in TEWL.[14] After application of moisturisers, the water content of the stratum corneum (the outermost layer of the skin) is increased, filling the spaces between partially desquamated skin flakes, making the skin smoother to touch.[16] It is for these reasons that clinicians commonly recommend moisturisers for hydration of a scar.[5]

It has been observed that a wound that has healed by secondary intention (a wound that has taken longer than 21 days to heal) and has formed a hypertrophic scar has a higher rate of TEWL than a wound that has been primarily closed, i.e. by skin graft.[17] In addition, keloid scars have an even higher rate of TEWL than other hypertrophic scars.[18] Hydration of the scar can be measured with an instrument called a Corneometer®, and TEWL can be measured with a Tewameter®, such as that by utilised by Hoeksema et al (2013).[19]

1.4 Types of scars

In their meta-analysis of scar prevention and treatment, Mustoe et al. (2002)[1] defined a classification system based on appearance and activity to assist with scar terminology. Scars were classified as linear hypertrophic (e.g. surgical/traumatic) or widespread hypertrophic (e.g. burn), minor keloid or major keloid and mature or immature (which can apply to any scars).[1] This classification system does not include atrophic scars. The recommendation is that if no hypertrophy occurs within three months, scar prevention measures can be ceased.[13]

1.4.1 Linear scars

Linear scars are those that are formed typically following surgery where the edges of the deeper sections of the wound are primarily closed. Therefore, the wound healing is by primary intention and results in a flat linear scar. This is likely due to rapid healing, within one to two weeks, which generally precludes hypertrophic scarring.[11, 12]

If there are intrinsic factors (foreign bodies, infection, bleeding, tension, etc.) or extrinsic factors (malnutrition, pharmaceutical agents, co-existing disease, etc.), the phase of inflammation is prolonged. The proliferation of collagen in the proliferative phase is excessive and the resulting scar becomes hypertrophic. While no evidence documenting the

incidence of hypertrophy in these types of scars is available, clinically, they have been observed to rarely progress to a hypertrophic scar that requires ongoing management.

1.4.2 Hypertrophic scars

Formation of a hypertrophic scar indicates there has been damage or trauma to the deeper (dermal) layer of the skin which contains structures such as sweat glands, hair follicles and associated oil glands.[20] A common observation of burn patients, who have extensive areas of hypertrophic scarring, is the subsequent failure to sweat or produce oils from their scars as a result of the loss of sweat and oil glands in the skin, which contributes to dry scars.[21]

The reported incidence of hypertrophic scarring after burn injury varies from 32% to 72%.[22] As suggested by its name, a hypertrophic scar is raised above the normal level of the skin but remains within the confines of the original wound. Their course is to generally increase in activity for the first six months, then decrease in activity until final maturity at around 18 months post injury.[23] Hypertrophic scars commonly arise from extensive wounds that are left to spontaneously heal (also termed healing by secondary intention) and where wounds are managed by skin grafting (primary closure or primary intention healing).[24] These subgroups of hypertrophic scars show different characteristics, one of which is the rate of TEWL.[17] Spontaneously healed scars have a higher rate of TEWL than skin grafted scars, and both have a higher TEWL than normal skin.[17]

Risk factors for more aggressive scarring include darker skin, female gender, site on the body (neck, chest), younger in age, longer time to healing and severity (e.g. depth) of injury.[22] Hypertrophy is a result of a local inflammatory process where the skin's immune system maintains a continuous inflammatory activated state in the hypertrophic tissue.[25] Females tend to have a higher risk for diseases of immunologic pathogenesis (e.g. arthritis) and this may be the reason for their higher risk of hypertrophic scarring.[25] People who are younger have more functional immune systems than those who are older and stronger anabolic basal activity that increases the remodelling phase of wound healing.[25] The location of the scar in regions that are regularly under tension and movement tend to contract more due to higher levels of myofibroblasts, and these scars tend to become bigger to accommodate the higher tension in the skin.[25] When there is a deeper wound and subsequently increased delay in reepithelialisation, there is a prolonged inflammatory phase and subsequent increase in the remodelling phase, i.e. a more prolific scar.[25]

1.4.3 Keloid scars

Keloid scars can be readily differentiated from hypertrophic scars. Unlike hypertrophic scars, they extend beyond the border of the original injury, have a longer course of activity, and have different pathophysiology and genetic factors.[26] Collagen production is increased 20-fold in a keloid scar and three-fold in a hypertrophic scar compared to normal unscarred skin.[27] The collagen in hypertrophic scars maintains a wavy pattern parallel to the epidermis whereas in keloids the collagen takes on a more random pattern.[28] There is a difference between the immunophenotypical profiles of keloidal and hypertrophic scar tissue, particularly, the major histocompatibility complex (MHC) genes.[29] It is unlikely that a single gene is responsible.[29] Interaction between gene pathways and environmental factors is likely, since not every scar in the one individual will become a keloid.[29] Keloidal scar tissue has a more prolonged inflammatory period with immune cell infiltrate present which may explain why keloid scars extend beyond the border of the original wound, while in hypertrophic scars the immune cell infiltrate decreases over time.[29]

People with keloids have reduced levels of interferon production.[30] Jacob et al.(2013)[31] found that genes whose expression is associated with apoptosis are altered by Imiquimod (a prescription cream that acts as immune response modifier) and the authors suggest that the keloid tissue may move toward a more normalised phenotype rather than the continued aberrant expression. They also have a high rate of TEWL, and have been measured as having a higher TEWL than hypertrophic scars.[18]

Factors that play a major role in keloid development are a genetic predisposition as darker skinned individuals are 15 times more likely to develop a keloid scar.[32] Another significant factor in keloid formation is skin tension when surgical incisions extend beyond relaxed skin tension lines.[32] However, hypertrophic scars are also exacerbated by high tension. Keloids also develop more readily during and after puberty, recede at menopause, and are enlarged during pregnancy.[32] Locations of keloids are predominantly on the ear lobe, shoulders and sternal notch/anterior chest.[32]

1.4.4 Atrophic scars

Examples of atrophic scars are those that arise from acne or chickenpox.[33] Atrophic scars have a different pathophysiology to hypertrophic and keloid scars, and perhaps this is the reason for them not being included in Mustoe et al.'s (2002)[1] classification of scars. Atrophic

scars are likely related to enzymatic degradation of collagen fibres and subcutaneous fat which support the overlying skin.[34] Considering that atrophic scars can occur from degradation of collagen but keloid and hypertrophic scars are associated with excess collagen, the resulting treatments are quite different.

1.5 Scar management

Scar management becomes a vital component of the treatment plan for clinicians treating those who acquire a hypertrophic or keloid scar. This is especially so in the field of burns, an injury which predominantly affects the skin and results in extensive hypertrophic scarring. The most commonly utilised and accepted conservative treatments to minimise the activity of scars are pressure therapy,[35] contact media (typically silicone gel),[36] massage and skin care (moisturising, sun protection and management of folliculitis).[21] Pressure therapy is commonly implemented with the use of pressure garments and contact media is commonly implemented with the use of silicone gel sheets.[21] Treatment of scars to maximise function and their final cosmetic appearance occurs while the scar is immature.[1] Once the scar is mature, it is no longer re-modelling and scar management is no longer considered effective.[1]

While there is evidence that scar massage has a positive effect on scars the evidence suggests it is less effective than the use of pressure or contact media.[37] Scar massage or soft tissue mobilisation (STM) facilitates the scar in returning to normal skin properties.[38] Scar massage alters the scar tissue matrix by breaking the strong bonds between the collagen fibres and by moving the interstitial fluid.[38] Cho et al.(2014)[39] found that massage in conjunction with moisturisers decreased pain, itch, scar thickness, melanin, erythema, TEWL and skin elasticity.

1.6 Moisturisers

Moisturisers can come in many forms, including creams, ointments, unguents, pastes, oils, lotions and salves. Creams are the most common and are usually emulsions of oil-in-water.[16] Lotions are usually less viscous than creams and have a lower oil content than creams.[16] Typical ingredients in moisturisers (in order of highest to lowest amounts) include water, oils, emulsifiers and preservatives.[16] Other ingredients for enhancement of biological effects or consumer acceptance include humectants, silicones, herbal extracts, fragrance, antioxidants and chelators.[16] Water immediately hydrates the stratum corneum but is short lived as it

quickly evaporates if not retained by the active chemical ingredients in the moisturiser.[40] Humectants increase the amount of water held by the stratum corneum, and moisturisers with humectants are superior for the treatment of dry skin disorders compared to those without humectants.[40] Glycerol is the most common humectant.[16] Others include propylene glycol, butylene glycol, panthenol, 2-pyrrolidone-5-carboxylic acid (pidolic acid), alpha-hydroxy acids (AHA), and urea.[16] However, propylene glycol is a known allergen and is found in 20% of moisturisers.[41] Fragrances and preservatives are the main sensitisers causing adverse reactions attributable to moisturiser use.[16] Despite this, fragrances are found in almost 70% of moisturisers and parabens (a preservative) are found in over 60% of moisturisers.[41]

As use of moisturisers results in increased hydration of the stratum corneum, the swelling of the desquamated cells may result in an occlusive effect; it has been proposed[15] that occlusion at the stratum corneum acts to down-regulate the pro-fibrotic signalling to the fibroblasts within the dermis.[8] Therefore, the mechanism of action of moisturisers is not only more complicated than simply 'hydrating' the skin but also has a cascading effect on the deeper scar tissue activity.

1.6.1 Characterising moisturisers by type and availability

When burn clinicians were asked why they recommended a moisturiser, the foremost general property was to facilitate massage.[5] Beyond that, clinicians recommended moisturisers as they were easy to find or were a known brand, long lasting and at a low cost or were readily available.[5] Therefore, when scrutinising all the products included in this systematic review it is clinically useful to categorise them according to their availability. For example, low volume, high cost products would be suitable for cosmetically sensitive, small facial scars. Alternatively, high volume, low cost moisturisers would be most suitable for extensive trauma or burn scars. Table 1-1 summarises this for the Australian context.

Table 1-1: Australian availability to consumers of products examined in this systematic review

Availability	Product
Prescription – high cost, low volume, high potency ingredients.	Imiquimod (immune modulator) Tacrolimus ointment (immune modulator) Doxepin (anti-histamine) Putrescine/Fibrostat (effect on collagen) Clobetasol proprionate 0.05%/Dermovate (corticosteroid) Aristocort® (corticosteroid)
High cost over the counter – small volume, limited availability e.g. 10-30millilitre tube.	Tretinoin/retinoic acid 0.05%/vitamin A Bio-Oil® Wubeizi (only available in China) Lumiere Bio-Restorative Eye Cream Onion extract gel/Mederma® Scarguard®/HSE Keratin Gel/KeragelT® Provase® Mugwort lotion Alhydran
Low cost over the counter – large volume e.g. 1-2litre.	Vitamin E creams Cetaphil® Aquatain (no longer available) Eucerin® Aquaphor® Petrolatum Aqueous cream

1.6.1.1 Prescription/Medicated Moisturisers

Prescription creams, as categorised in this review, are those that tend to be available in Australia only by prescription from a medical practitioner and contain high potency ingredients; as a result, they tend to also be high cost and come in small tubes. Therefore these moisturisers are not generally suitable for extensive, large surface area scars, but rather for small, problematic or cosmetically unappealing scars. The table below outlines the cost of the each of the creams in this category, demonstrating that they can vary from AUD$1 to just over AUD$20 per gram.

Table 1-2: Cost and usual available sizes of prescription only creams

Cream	Available size	Cost: AUD/gram
Imiquimod 5%	3g	20
Tacrolimus ointment	30g	8.10
Doxepin/Prudoxin	45g	7.27
Putrescine (Fibrostat®)	Not available	-
Clobetasol proprionate 0.05%/Dermovate	15g	3.05
Aristocort® 0.1%	90g	1.16

Prices obtained by basic internet searching in January 2018

Imiquimod 5%

Imiquimod 5% cream is an immune response modifier that is commonly utilised to treat genital warts. It is capable of inducing IFN-α, TNF-α and interleukins 1, 6 and 8.[30] A systematic review has examined the effect of Imiquimod on recurrence rates of keloids post excision.[42] Four studies on Imiquimod were analysed and they estimated the overall recurrence rate to be 24.7% (95% CI, 3.2-76.4) and in a subgroup of earlobe scar recurrence, the rate was estimated to be 13.6% (95% CI, 4.3-35.5).[42] The authors claimed that this recurrence rate was 'better than expected' as routine treatment results in 'at least approximately 50%'.[42] However, this 50% recurrence rate was obtained from only one study, albeit a large one, which was published in 1974, with earlobe only keloid excisions occurring from 1932 to 1970.[43] The other referenced study reported recurrence rates of facial keloids that had been excised and treated with a steroid but had no data on untreated excised keloids.[44] Considering that our current systematic review could not find reliable reports of a standard recurrence rate of keloids post excision, the rate of recurrence without post-operative treatment is unclear.

Tacrolimus ointment

Tacrolimus ointment contains a drug that has an effect on tumour necrosis factor, TNF-α. The tacrolimus binds to a molecule involved in cellular growth and metabolism, and inhibits the expression of TNF-α which is a profibrotic (pro scarring) cytokine, i.e. it inhibits the process that encourages scar formation (see Section 1.3).[45]

Doxepin/Prudoxin

Doxepin hydrochloride (HCl) is used for clinical depression but it has also been found to have histamine receptor blocking properties.[46] Doxepin HCl is available in a fivepercent cream – Prudoxin®.[46] Doxepin has been found to be more potent than some antihistamines in studies examining common dermatological disorders.[46]

Putrescine (Fibrostat®)

Putrescine is a polyamine that is produced in the breakdown of amino acids in living and dead organisms and is responsible for the foul odour of putrefying flesh.[47] Despite its interesting origin, it has previously been shown *in vitro* to inhibit extracellular type III collagen crosslinking – the collagen that is found elevated in hypertrophic scars.[48]

Clobetasol proprionate 0.05% /Dermovate

Dermovate is a topical corticosteroid containing the active ingredient clobetasol proprionate.[49] Corticosteroids aim to reduce the production of collagen.[49] Dermovate is considered to be 'Class 1 (super-potent)' in the potency rankings of topical steroid preparations.[50] However, the raft of atrophic changes in the skin causing thinning of the epidermis and dermis would likely be counterproductive when a scar already has a thinner stratum corneum (epidermis) than normal skin.[50]

Aristocort® 0.1%

As with Dermovate, Aristocort® A 0.1% (triamcinolone acetonide) potentially has all the side effects mentioned of a topical corticosteroid, but in comparison it is considered less potent 'Class 3 (potent)'.[50]

1.6.1.2 High cost, over the counter moisturisers

For this review, moisturisers available to the consumer from a pharmacy over the counter for a 'high cost' and contain some form of 'active ingredient' are arranged in their own category. They are generally available in small tubes similar to prescription only items. As such, they are not suitable for extensive, large body surface area scars, but instead for small, problematic or cosmetically unappealing scars. Table 1-3 outlines the cost of each of the creams in this category, varying from AUD0.17 per mL to just over AUD20 per mL.

Table 1-3 Cost and usual available size of high cost over the counter creams. Prices obtained by basic internet searching in January 2018.

Cream	Available size	Cost: AUD/gram or mL
Tretinoin cream/retinoic acid/vitamin A (0.05%)	50g	1.09
Bio-Oil®	60-200mL	0.17
Wubeizi	Not available	
Lumiere Bio-Restorative Eye Cream	15mL	6.27
Mederma®/onion extract	50g	1.83
Scarguard®/HSE	15g	2.30
Keratin gel/KeragelT®	20g	20.65
Provase®	59g	0.30
Mugwort Lotion	Not available	
Alhydran	250mL	0.82

Prices obtained by basic internet searching in January 2018
HSE: hydrocortisone, silicone, vitamin E

Moisturisers containing Vitamin A (Tretinoin/retinoic acid) perhaps belong in the prescription only moisturisers (Section 1.6.1.1) as the 0.05% concentration is only available by prescription in Australia, however, there are many moisturisers claiming to contain vitamin A, retinoic acid, or its less potent variant retinol, over the counter. However, vitamin A containing moisturisers require additional precautions; in particular, it is only to be used at night as it thins the stratum corneum, making the skin more susceptible to sun damage, it needs to be used for three to six months to achieve epidermal changes and nine to 12 months to see dermal changes, and permanent changes may not occur as discontinuation will cause regression of clinical gains.[51]

Bio-Oil® is a very well marketed product within Australia. Clinically this author has observed that patients with scars frequently ask about Bio-Oil®, have used it, or report that a concerned friend has recommended it. According to the Bio-Oil® website, it has a combination of plant extracts and vitamins suspended in an oil base.[52] The ingredients list includes four different ‘botanicals’ (calendula, lavender, rosemary, chamomile), an ‘oil base’ which consists of eight different ingredients too extensive to examine in detail for the purpose

of this review, 13 different ‘fragrance’ ingredients, a colour and ‘vitamins’ A (retinyl palmitate) and E (tocopheryl acetate).[53]

Mederma® is a gel containing a botanical extract *allium cepa* (onion extract) as the active ingredient. However, studies examining the effects of Mederma® provided insufficient descriptions as to which of the range of scar products advertised on the website were utilised.[54]

Alhydran is an oil in water emulsion consisting of mostly aloe vera gel, mineral oil, decyl oleate, sorbitan stearate, propylene glycol, jojoba oil, and vitamins A, C, E and B12.[19] Alhydran was only previously available in Europe and has only recently (as of May 2018) become available in Australia. An exact price is yet to be provided but it is anticipated to be available in pharmacies at a higher cost than the basic moisturisers (Section 1.6.1.3).

Moisturisers can be manufactured from other plant extracts such as the Wubeizi ointment which contains the ingredient Wu Bei Zi, a tannin produced by a tree following infestation by aphids. The mugwort lotion in the study by Ogawa and Ogawa (2008)[55] consisted of mugwort extract (from the leaves and branches of *Artemisia yomogi*) methanol, ethanol and distilled water. It is reported that mugwort extract has biologic effects such as anti-histamine, anti-oxidant, induces apoptosis and has an anti-inflammatory effect.[55] Information on the cost of this Chinese herb was difficult to find as it can come in a raw form and is then added to other ingredients to make up an ointment or cream.

Scarguard® reportedly contains 0.5% hydrocortisone, silicone and Vitamin E.[56] However, details about this product are unavailable on the internet and therefore it is suspected to be unavailable. Keratin has a role in epithelium differentiation, mechanically stabilising this layer against mechanical stress and maintaining hydration by providing a waterproof barrier.[57] Keratin gel products have been predominantly studied with regards to wound healing and have shown positive results but there is only one study on the effect of a keratin gel on scar progress.[57]

Provase® is a water and petroleum blend based moisturiser with 2% dimethicone and a blend of proteases. *In vitro* assays have shown that proteases work to degrade proinflammatory substances such as tumour necrosis factor-α, interleukin 6 and its receptor and matrix metalloproteinases.[58] This product has been previously used to resolve inflammation and itch in dermatitis and other aetiologies with improvements seen within 12-48 hours after application.[58]

1.6.1.3 Low cost, over the counter moisturisers

For this review, moisturisers that tend to be typically available to the consumer from convenience stores are categorised as low cost, over the counter moisturisers. Moisturisers in this category tend to be available in larger volumes such as 250mL to greater than 1L containers. Vitamin E creams, for example, can be as cheap as AUD3 for 1L, representing a cost of 0.3 cents per mL. Aquaphor®, Cetaphil® and Eucerin® are the most costly of this low cost group, costing around 2-4cents per mL. They therefore tend to be suitable for extensive scars covering large surface areas.

Vitamin E, or its form alpha-tocopherol, which is the only form maintained in the human body, acts as an antioxidant protecting cells from oxidative stress.[59] Since its discovery as the major lipid-soluble antioxidant in the skin, it has been used for treating many skin conditions.[59] Curran et al. (2006)[59] conducted a survey of 208 medical staff and students at their institution in Dublin, Ireland on their use and understanding of Vitamin E. They found that 68% of respondents thought that Vitamin E could be of use in improving the cosmetic appearance of scars, 25% recommend Vitamin E to patients to improve the cosmetic outcome but only 40% were aware of its biological function.[59] In contrast, this author's own survey of therapists from US, Australia and Canada found that three out of the 53 responders (6%) recommended vitamin E for scars.[5]

Cetaphil® Moisturizing Lotion (Galderma Laboratories, LP Forth Worth, TX, USA) was included in one study[56] as a placebo cream. There is a broad range of products under the name of Cetaphil®, but the moisturising lotion used in this study is water based with the second ingredient listed being glycerine.

Eucerin® (Beiersdorf AG) is a water based moisturiser. In the survey conducted by this author, 12 out of 26 (46%) of the burn therapists surveyed (predominantly from US) reported recommending Eucerin® for scar management.[5] Its ingredients include, in order of highest to lowest proportions, water, petrolatum, mineral oil, ceresin, lanolin alcohol, phenoxyethanol and piroctone olamine.[60] However, the Eucerin® brand has a broad range of moisturisers so it is difficult to ascertain which was used by Phillips et al. (1996)[61]

Aquaphor®, similar to Eucerin®, comes in a broad range of products bearing this name. 'Aquaphor® Healing Ointment' contains 41% petrolatum as its main ingredient and would therefore be quite thick and occlusive, similar to Vaseline which is 100% petrolatum.

Petrolatum is commonly referred to as ‘petroleum jelly’ in Australia, and popularised under the brand name, Vaseline. Due to Vaseline containing only one ingredient, it can be used as a control moisturiser in studies examining the effects of moisturisers with more complex formulations or active ingredients.

Aqueous cream has been found to increase TEWL in healthy skin and decreases the thickness of the stratum corneum skin.[62, 63] Since scar activity may correlate with TEWL (section 1.3.3), aqueous cream may influence TEWL in a negative direction for scar outcome. Despite this, aqueous cream was the second most commonly recommended moisturiser by burn therapists in Australia.[5] The use of aqueous cream as a control moisturiser was questioned in a critique of a study of the moisturiser, Medilixir.[64]

1.7 The science of evidence synthesis

Publications on the topic of evidence-based medicine began to rapidly increase in frequency from the mid 1990s. The term *Evidence-Based Health Care (EBHC)* has become the umbrella term to incorporate the previous terms of *Evidence-Based Practice* and *Evidence-Based Medicine.* In the literature it appears that the terms EBP and EBM are used interchangeably. At its outset, the movement was very much led by Professor David Sackett who published extensively on the topic, although he himself reports that its philosophical origins extend back to mid-19th century Paris.[65]

Sackett (1997)[65] suggested that evidence-based medicine 'is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research'.[65(p3)]

This systematic review follows JBI methodology and is informed by the JBI model of EBHC. Joanna Briggs Institute has a pragmatic and inclusive approach in terms of evidence, and understands that clinicians need summaries of the best available evidence to inform their practice. This remains true even when high quality randomized controlled trials are not available. As such, JBI reviewers are encouraged to look beyond RCTs when there are none published and include other types of evidence in their systematic reviews, where appropriate.[66]

The 2016 revised JBI Model shows that 'evidence synthesis' occurs after 'evidence generation' and includes structured outputs including ***systematic review,*** evidence summaries and guidelines.[66]

A systematic review is 'essentially an analysis of all of the available literature (evidence) and a judgement of the effectiveness or otherwise of a practice'.[67(p13)] The aim is to summarise the current state of knowledge in relation to the review question. It is termed a systematic review as it follows a systematic process including a series of steps which are transparent and reproducible for the reader. The steps are:

- Develop a protocol.
- State the review question.
- Implement the inclusion and exclusion criteria for selecting the literature.
- Detail the strategy to identify all relevant literature.

- Utilise critical appraisal to further refine included studies.
- Detail how the data is extracted from the primary research.
- Synthesise extracted data.[68]

The final step including evidence synthesis ideally takes the form of a meta-analysis, which is a statistical technique used to combine quantitative/numerical data. Where meta-analysis is not possible, a narrative synthesis, which is descriptive and summarises text from multiple studies, is the approach used. The narrative synthesis is an approach in systematic reviews where instead of synthesising and manipulating numerical data with the use of statistics, the findings of multiple studies are summarised in a structured manner in plain text which tells the story of the findings from the included studies. A meta-analysis refers to the statistical synthesis of quantitative results from two or more studies[69] and analyses whether included studies are significantly homogeneous or heterogeneous, i.e. how much similarity or variation there is between the studies. This allows for combination of data from similar studies to determine the overall effect of an intervention.[70] A forest plot is generated to allow visual inspection to assess heterogeneity.[70] A formal statistic calculates the probability (I^2) to provide the test of homogeneity.[70] These types of data synthesis were used for this systematic review.

2. Methodology and method

This chapter outlines the methods used to conduct this systematic review. The review question sets the scene for the review, and the inclusion and exclusion criteria are discussed in detail. The search strategy and how searches were conducted are clearly outlined. A description of how studies were selected and critically appraised is provided. Finally, how data is extracted and synthesised using a narrative synthesis and meta-analysis is described.

2.1 Review question

The review question is: What is the effect of moisturisers on scars?

The objectives are to provide a summary of recommendations that are relevant to clinicians and consumers regarding the effectiveness of different types of moisturisers on different types of scars, the ideal properties of the moisturisers, and/or specific ingredients that a moisturiser has in order to have a positive (or negative) effect on the scar outcome. Presenting the moisturisers according to availability and cost can aid in decision making for the clinician and consumer when working together to determine the best product for the best outcome.

2.2 Criteria for considering studies for inclusion in this review

2.2.1 Types of studies

The types of studies to be included was deliberately kept broad to capture the maximum number of studies that might address the review question. Types of studies considered for inclusion included experimental and epidemiological study designs such as randomised controlled trials, non-randomized controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case-control studies, case series and analytical cross sectional studies. Articles that were not about primary empirical research, for example, review articles, were not included.

2.2.2 Types of participants

This review considered studies including people of any age with scarring to the skin. Risk factors for more aggressive scarring, including dark skin, female gender, younger in age, increased time to healing and severity of injury,[22] were considered when analysing the results of studies.

Scars from various causes were included. This included those labelled as hypertrophic, keloid, formed from healing by secondary intention, or a linear scar (from surgery or trauma). Keloid scars are defined as extending beyond the border of the original injury and are reported to have a different pathophysiology, genetic factors[71] and a higher rate of TEWL.[18] Despite them being different from the other scars mentioned above, they were carefully considered to be included for this review as moisturisers are a management technique commonly utilised in the clinical setting. Studies examining scarring of internal structures (other than skin) such as connective tissue, muscle, tendon and nerves, for example, were excluded.

Atrophic scars were excluded as they result from damage to the underlying structures that support the skin such as fat or muscle. Acne and chicken pox scars are examples of atrophic scars and have quite different management regimes.[33] Studies conducted on animals were excluded.

2.2.3 Types of interventions

Moisturisers can come in many different forms. They are considered pharmaceutical products and can be termed cream, lotion, emollient, paste, oil, unguent or salve. These all have different properties but all versions can be considered to be under the broader banner of a 'moisturiser'. The ingredients in moisturisers can be many and varied, and when they have a specific active ingredient added can be considered a medicated cream. This review intended to include any moisturiser and therefore included all the interchangeable terms listed above, and medicated or un-medicated creams were also appropriate for inclusion.

Studies that used moisturisers in addition with another conservative means of scar management were excluded as the effect of the moisturiser could not be determined. However, studies that included an active comparison of two *different* moisturisers were included, where the method of application (including rubbing it in) was consistent, for example, Lewis et al. (2012), where aqueous cream was compared to a beeswax and herbal oil cream to reduce itch.[72]

2.2.4 Comparators

Comparisons included a moisturiser/cream with other moisturiser/creams with or without an active ingredient or medication. Alternatively, the use of moisturiser was compared to no

treatment. As scar management includes other treatment techniques, the comparators were other scar treatments such as laser therapy, pressure garments or contact media, for example, and provided they did not compromise the findings they were included as they possibly reported secondary findings related to the effect of the moisturiser.

2.2.5 Types of outcome measures

This review considered studies that included outcome measures that rated changes in the scar. Patients reporting changes to their scars such as pain, itch, pliability and hypersensitivity are subjective outcome measures which may be utilised in some studies. These included questionnaires, visual analogue scales or part of a scar assessment scale such as the Patient and Observer Scar Assessment Scale (POSAS).[73]

Subjective scar assessment scales such as the Vancouver Scar Scale,[74] Modified Vancouver Scar Scale,[75] and POSAS[73] are only a few of the scales that were used to assess the scar's physical characteristics such as colour, height, thickness/pliability and texture. They infer a measure of severity of the scar.

Physical characteristics, which demonstrate the scar's physiological activity, were measured by objective instrumentation such as goniometry (joint range of movement), tape measure (length), spectrophotometry/colorimetry (colour/vascularity), tissue tonometry (pliability),[76] standardised digital imaging and spectral modelling (vascularity and melanin),[77] and electrical hygrometers such as the Tewameter® (TEWL).

The occurrence or recurrence of a scar post surgical procedure combined with the use of a moisturiser is an outcome measure that was included. Reports on the characteristics of the moisturiser/cream such as patient acceptance, price paid by the patient, how well it spreads, fragrance, comfort and other characteristics were reported by studies. This subjective information would be of use to clinicians in their decision making when recommending moisturisers and therefore was included in this review.

2.3 Review methods

2.3.1 Search strategy

The first stage of determining the search strategy was to clarify the PICO (Population, Intervention, Comparator, Outcome) question as this then allowed for expansion of the search terms into a logic grid. The PICO model is used to define the properties of the studies to be

included in the systematic review.[70] The logic grid is completed by placing all the search terms for each component of the PICO question into a table. Each column of the table is then linked with an 'and' and the search terms within each column are linked with an 'or'.

The PICO question was: What is the effect of moisturiser use on scars?

The ***population*** included any person with any hypertrophic or keloid scar. There was no need to limit the search to adults or children, for example, therefore no terms were required to further define this concept in the search and it was not included on the logic grid.

The ***intervention*** was moisturisers. There are many different terms to describe moisturisers. These are shown in Table 2-1 below.

The ***comparators*** were any other treatment, control group or no treatment. As a result there was no need to include any search terms in the logic grid.

The ***outcomes*** were changes to the scar characteristics, patient reported outcomes or reports on the characteristics of the moisturiser. As there was no restriction to what outcomes were being sought there was no search terms included.

Additional terms were found initially by examining the keywords of published articles already known to be close to the research question. Basic definition descriptions of the term 'scar' and 'moisturiser' were sought from various sources, for example, Google search, thesaurus and research articles on moisturisers and scars. Table 2-1 provides a list of the initial keywords identified to guide database searching.

Table 2-1: Logic grid of search terms used as a basis to create searches

Scars	Moisturiser
Cicatrix, hypertrophic Cicatrix Scar Keloid Hypertrophic	Emollient Moisturiser Skin cream Cream Lubricant Ointment Salve Unguent Lotion

The databases searched were chosen with the guidance of a University of Adelaide librarian so as to be as inclusive as possible for the review. The databases chosen were PubMed,

CINAHL, Embase and Web of Science. Searches which were limited to English as there was no capacity to translate studies published in other languages. There were no date limits set to ensure maximum capture of studies.

Each database's thesaurus of subject headings or indexing terms was then thoroughly checked to customise the search terms specific to each database. With the assistance of the librarian, each of the search terms was refined to specify the field code (e.g. PubMed) to search for the term in the MeSHs (Medical Subject Heading) [mh], or as a text word [tw]. In the case of PubMed the choice was made to explode the search term. When the MeSHs were examined they demonstrated that all components under that heading were relevant to the topic. Where possible, wildcards (*) were used, for example, Moisturi*[tw]. This allowed for results to be obtained which contained US and Australian spelling of the word and different endings, for example:

- moisturisers
- moisturisers
- moisturizing
- moisturising
- moisturize
- moisturise
- moisturized
- moisturised.

Appendix 1 contains the logic grids with field codes, and the search strategy for each database. Searches of databases were completed in September 2016 and grey literature searching occurred in June 2017. Once the search was completed, the results from each database were exported to EndNote™ software (Clarivate Analytics, USA).

A search of the grey literature was also performed to identify any unpublished documents, such as technical or research reports, doctoral dissertations, theses, conference papers, etc.

The websites searched included:

- https://clinicaltrials.gov/ – a registry and results database of publicly and privately supported clinical studies of human participants.
- www.anzctr.org.au – Australian and New Zealand Clinical Trials Registry – an online registry of clinical trials being undertaken in Australia, New Zealand and elsewhere.
- www.controlled-trials.com now called www.isrctn.com – a primary clinical trial registry recognised by the World Health Organization and International Committee of Medical Journal Editors that accepts all clinical research studies (whether proposed, ongoing or completed), providing content validation and curation and the unique identification number necessary for publication.
- www.opengrey.eu – the System for Information on Grey Literature in Europe is an open access reference on grey literature produced in Europe.
- http://www.cochranelibrary.com/about/central-landing-page.html – the Cochrane Central Register of Controlled Trials. Two studies were found but both were already included from database searching.

2.3.2 Study selection and inclusion

Duplicate citations were removed in EndNote™. Further duplicates, not identified by the software, were removed manually during title and abstract screening. Screening of titles and abstracts occurred with consideration of the inclusion criteria (see Section 2.2). The full texts of studies that appeared to meet the inclusion criteria during the screening process were retrieved. When assessing eligibility of full-text articles, the specifics of the inclusion and exclusion criteria were considered to assist in decision making.

2.3.3 Assessment of methodological quality – critical appraisal

The object of critical appraisal is to 'assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis.'[70(p59)] As this systematic review utilised the JBI approach, the standardised JBI critical appraisal instruments were used to assess the quality of included studies.

Papers selected for inclusion were assessed by two independent reviewers for methodological validity prior to inclusion in the review using the predefined standardized critical appraisal instruments available on the JBI website. Appendix 2 contains the JBI critical appraisal tools that were utilised for this review.

Recruitment of a second reviewer was a similarly qualified Masters of Clinical Science candidate who had undergone critical appraisal and systematic review training with JBI. This author and the second reviewer scored the included studies independently and this author then compared the final scores. Any disagreements that arose between the reviewers were resolved through discussion. There was no need to obtain a third reviewer, however, this was an option had the need arisen if agreement could not be obtained.

2.3.4 Data extraction

Reported results of outcomes measured and conclusions were extracted from critically appraised and selected studies into a table similar in structure to that of the Included Studies (Table 3-1 and 3-2) and Excluded Studies (Appendix 3). Data extracted included type of scar, moisturiser utilised, method of the interventions, methodology of the study and results of outcomes measured.

Numerical data suitable for a meta-analysis on the recurrence rates of keloids post excision and application of imiquimod were extracted according to location of the keloid and surgical technique utilised.

2.3.5 Data synthesis

The findings of the studies were grouped and outcomes were described in terms of direction of effects, for example, negative effect of the moisturiser on scars, no effect or a positive effect of the moisturiser on scars. Actual data and effect sizes, along with confidence intervals and the results of any statistical tests, were extracted and reported in the narrative synthesis where possible.

Meta-analysis – imiquimod group

These studies were conceptually similar in that they all looked at the outcome of recurrence of keloids post excision and then application of imiquimod cream. Meta-analysis was conducted using StatsDirect software (StatsDirect Ltd., Cambridge, UK) using the Miller

approach (exact inverse Freeman-Tukey double arscine) for proportional meta-analysis.[78] Following the recommendation by Munn et al. (2015)[78] a random effects model was used.

A meta-analysis was performed presenting a forest plot to illustrate the risk or proportion of participants that will have recurrence of their keloid following use of imiquimod. Heterogeneity was assessed statistically using the standard I square. Due to the wide spread of results in the meta-analysis of all the imiquimod studies, subgroup analyses based on the location of the keloids and the surgical technique was also conducted

3. Results of searching, selection and assessment of methodological quality

This chapter outlines the results of the systematic searching and selection process. From the database searches, 1970 studies were retrieved and filtered down to a total of 33 studies. The included studies were divided into the moisturiser group and the imiquimod group which was a group of studies that investigated the recurrence of keloids post excision and application of imiquimod cream. The included studies details are presented in a table format. Critical appraisal of the included studies revealed interesting factors to consider when examining the results, presented in the next chapter.

3.1 Results of searches

Grey literature searching resulted in no eligible papers being identified.

The number of records identified in the databases searched are as follows:

- PubMed: 677
- Embase: 1162
- CINAHL: 72
- Web of Science: 59

⇒ Total 1970 studies.

A total of 552 duplicates were removed from the 1970 results, see Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart in Figure 3-1.

3.1.1 Other searches

Three studies were found in the reference lists of included articles.[79-81] All three were studies on Tretinoin cream. When examining the MeSH headings for these articles, it was apparent that they did not appear within any of the 'moisturiser' search terms utilised, despite Tretinoin cream being a topical cream.

A well marketed product and company in Australia, Bio-Oil® was approached to supply articles they self-funded.[82-84] The three studies received were considered for inclusion with two eventually being included in the moisturiser group for narrative synthesis. Another study was identified by a co-worker of this author relating to a moisturiser used within Australia.[72] This study was later excluded.

3.2 Screening of studies

The following PRISMA chart illustrates the results of the searching, screening and inclusion process of the review. A total of 1977 records were identified through searching. Once duplicates were removed the title and abstract of 1425 records were screened. Seventy-two full text studies were retrieved and assessed for eligibility; of these 39 were subsequently excluded (see Section 3.3 and Appendix 3).

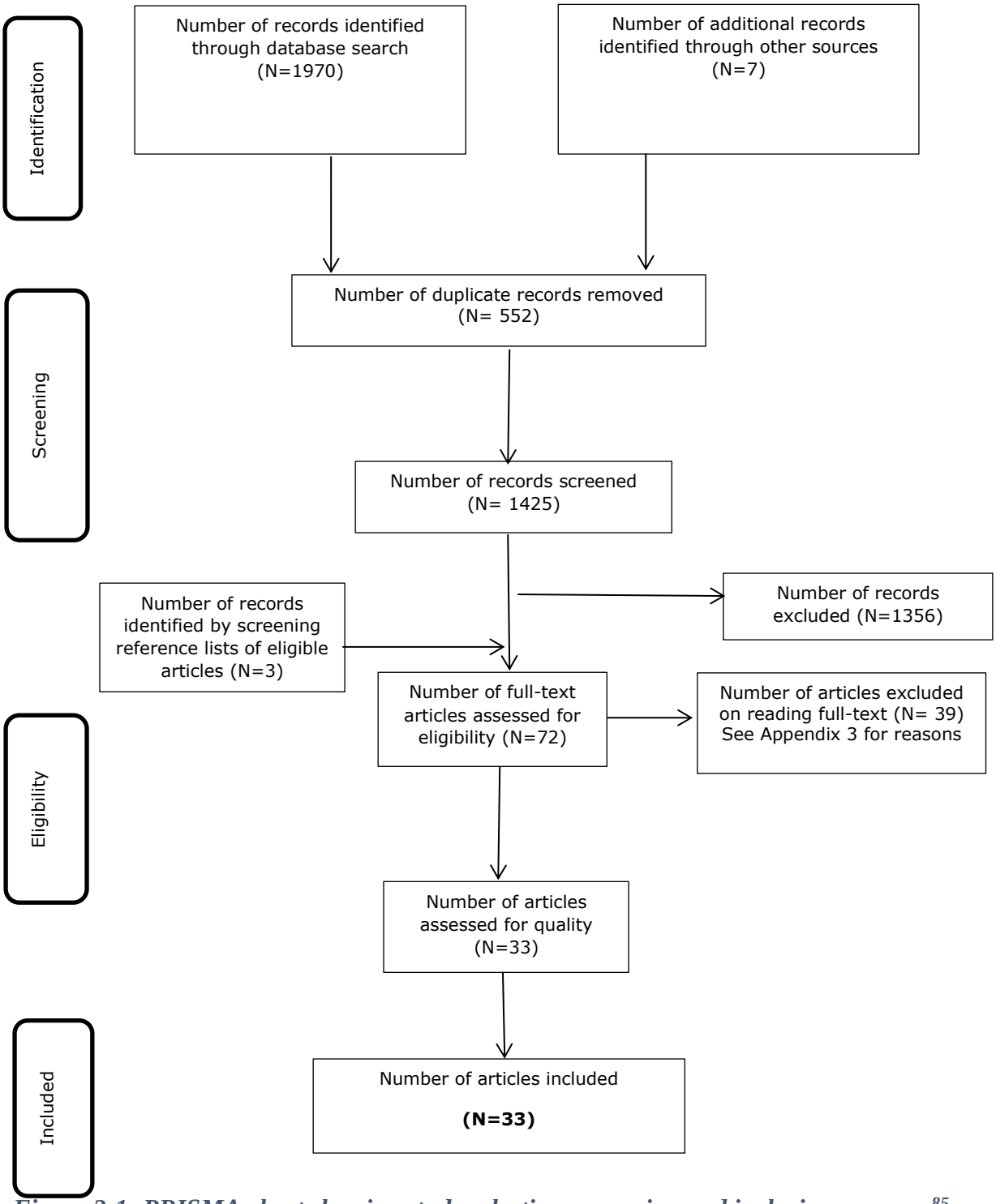

Figure 3-1: PRISMA chart showing study selection, screening and inclusion process. [85]

3.3 Excluded studies

A list of the full-text studies that were excluded with reasons is provided in Appendix 3. The most common (15 studies) reason for exclusion when reviewing the full texts was that studies were only reported as abstracts. Other common causes for exclusion were that the application of moisturiser also involved other confounding interventions affecting the final outcomes (seven studies), review articles or opinion pieces (five studies) and animal studies (three studies).

The primary authors were contacted for those studies that were only available in abstract form such as those presented at conferences.[46, 86-92] Successful contact was only made with one author who reported their studies were conducted such a long time ago that they no longer had any further data to share.[91, 92]

3.4 Included studies

Studies were included if they met the inclusion criteria detailed in the published review protocol,[93] also described in Section 2.2. Many studies reported on more than one outcome. The majority reported on scar parameters (16), followed by itch/pain (nine), cosmesis of the scar (eight), recurrence of keloids post excision and imiquimod application (seven), *in vitro* outcomes (four) and TEWL (one). To facilitate analysis and presentation of results, studies that were grouped for a meta-analysis that examined the recurrence of keloids post excision and application of imiquimod (imiquimod group) were reported separately from the others (moisturiser group). A study that appeared initially to belong to the imiquimod group was moved into the general moisturiser group as they did not follow the same structure (six weeks of imiquimod application to measure recurrence of the keloid post excision) as the other imiquimod studies.[94] All studies were appraised and included. Details of the included studies are shown in Tables 3-1 (moisturiser group) and 3-2 (imiquimod group).

3.4.1 Included studies: moisturiser group

There were 26 studies in this group, including a total of 719 participants, some with multiple scar sites. A wide variety of products were investigated, comprising a total of 23 different moisturisers. Utilising the JBI Levels of Evidence,[95] half of the studies (13/26)[48, 56, 58, 61, 82, 83, 94, 96-102] in the moisturiser group were RCTs (level 1c), the majority of the remainder (11/26)[19, 31, 46, 49, 55, 57, 79-81, 103, 104] were of a quasi-experimental design (level 2c) and 2/26[45,

[105] were case series (level 4c). The majority (16/26)[31, 45, 46, 48, 56, 58, 61, 79, 80, 94, 96-98, 100, 101, 104] of the included studies in the 'moisturiser group' were conducted in the Americas and Canada. Others were conducted in European countries (5/26)[19, 49, 81, 105] and Asian countries (3/26)[55, 99, 103]. Overall there was a total of 785 participants with scars included for narrative synthesis.

Participants in the studies had a mix of differing scar types, including keloid, linear and hypertrophic. Some studies had mixed types of scars in the patients they examined. Figure 3-2 below shows the number of the included studies with diverse scar types among included participants. The '1' in the middle represents the study that utilised a scar model (tape stripping) to simulate all scars.[19] Hypertrophic scars were the most commonly examined types of scars,[46, 48, 49, 55, 58, 79, 98, 105] followed by linear[96, 97, 100, 101, 104] and keloid[31, 45, 80, 103] scars.

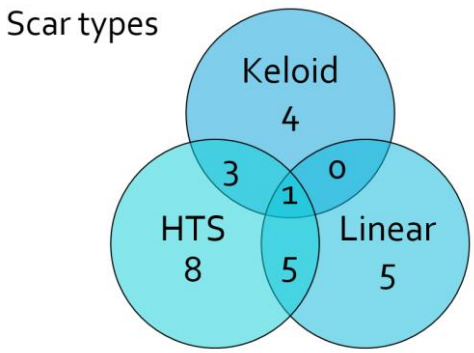

Figure 3-2: Scar types examined by studies in the moisturiser group. HTS = Hypertrophic scar. The '1' in the middle is a scar model.

The five studies in the hypertrophic/linear category did not specify the scar types.[57, 82, 83, 94, 99] Since they examined scars from small postoperative wounds, it was assumed that unless they specified otherwise the scars could be either hypertrophic or linear. Although keloid and hypertrophic scars are now known to be quite different scar types, they were examined together in the three studies.[56, 61, 81] One was published in 1980,[81] perhaps before it was established that the scars have different mechanisms for proliferation.

Further details of all these studies are included in Table 3-1 below.

3.4.2 Included studies: imiquimod group

The imiquimod group included seven studies that examined the outcome of recurrence of a keloid post excision and application of imiquimod. Over the seven studies, there were 77 total participants with 82 total keloids. All underwent excision of a keloid which was either left to heal by secondary intention or was primarily closed. The length of imiquimod application was from six to eight weeks and the frequency of application varied from daily to three times a week. Utilising the JBI Level of Evidence[95] **t**he majority of the studies (5/7)[30, 106-109] in the imiquimod group were case series (level 4c), one case report[110] (level 4d) and one RCT[111] (level 1c). The imiquimod studies were mainly from the USA (3/7)[30, 109, 111], with the others originating from South America (2/7)[107, 108] and Asia/India (2/7)[106, 110]. Details of the studies are in Table 3-2 below.

Table 3-1: Characteristics of included studies - moisturiser group

Study	Types of scars	Design	Product	Participants, setting	Intervention	Outcomes measured
Baumann & Spencer 1999[96]	Linear	Double blinded RCT	Vitamin E, Aquaphor®	Participants: Undergone Mohr's (skin cancer removal) surgery. Setting: University of Miami Department of Dermatology & Cutaneous Surgery, Miami, Florida, USA.	Given 2 ointments Aquaphor® labelled Ointment A and Ointment B which was Aquaphor® with contents of oral vitamin supplement, resulting concentration was 320 IU/gm, scars divided into parts A & B, applied twice a day for 4 weeks.	Cosmetic appearance at week 1, 4 & 12.
Berman, Frankel et al. 2005[94]	Linear/ HTS	RCT	Imiquimod 5%	Participants: Post surgical scars - removal of melanocytic nevi. Setting: University of Miami, Florida, USA.	Subjects underwent punch elliptical or punch excision. Same surgeon, all sutured in 2 planes. Each wound randomised to either receive vehicle cream or imiquimod. Apply nightly for 4 weeks. Also applied Bacitracin antibiotic cream until sutures taken out to both sites.	Evaluation at 2, 4, and 8 weeks after surgery. Plus extra follow up between week 17-46 to evaluate long term effect of imiquimod. At week 8 patient and investigator examined the scars cosmesis, induration, and pigmentary alterations using VAS.
Berman, Poochareon, et al. 2005[45]	Keloid	Case series	Tacrolimus Ointment 0.1%	Participants: Keloids >10ys old, various sites, 6F:4M, 9xblack skin:1xwhite skin. Setting: University of Miami, Florida, USA.	Open label pilot study. Applied the ointment 2x/day for 12 weeks without occlusion.	Evaluated at baseline, 2, 7, 12 weeks. Volume of keloid measured by alginate impression. Induration determined by a set of rubber discs & recorded on VAS. Patients rated pain, pruritus, erythema, tenderness, global cosmesis using VAS.

Cont…. Table 3-2: Characteristics of included studies - moisturiser group

Study	Types of scars	Design	Product	Participants, setting	Intervention	Outcomes measured
Butzelaar et al. 2015[105]	HTS	Case series	Not specified	Participants: Elective cardiothoracic surgery through median sternotomy. Setting: St Antonius Hospital Nieuwegein and University Medical Centre Groningen, The Netherlands.	Scars labelled normotrophic or HTS.	Evaluated at 4m & 1yr. Patients completed a questionnaire. Also measured blood pressure, skin types, joint mobility, standardised photos taken. Studied risk factors: 90 – combined into 17 categories.
Chung et al. 2006[97]	Linear	Prospective, double blind RCT	Mederma®	Participants: Recently undergone Mohr's or excisional surgery for BCC or SCC. Setting: Dermatologic Surgery Unit at Beth Israel Deaconess Medical Centre, Boston, Massachusetts, USA.	Split scar study. Treatment – onion extract gel (Mederma®). Control – petrolatum ointment. Provided treatments in opaque syringe & labelled. Applied 3x/day for 8 weeks.	Evaluated at 2, 8 & 12 weeks from start of treatment & 11months via phone. Physician evaluation – assessors blinded. VAS for redness, thickness, overall cosmetic appearance. Patient evaluation – used VAS rate redness, itching, burning and pain. And phone interview to rate differences between scar halves for cosmetic appearance.

Cont…. Table 3-3: Characteristics of included studies - moisturiser group

Study	Types of scars	Design	Product	Participants, setting	Intervention	Outcomes measured
Dematte et al. 2011[79]	HTS	Quasi-experimental study	Tretinoin cream	Participants: >2yrs post whole facial burn scars. Setting: Tertiary, Institutional, Sao Paulo, Brasil.	Patients applied 5 drops of Tretinoin every night on their face without massaging and washed their face in the morning.	Skin biopsies were obtained initially and after one year of treatment. The resistance and elastance of these skin biopsies were measured using a mechanical oscillation analysis system. The density of collagen fibres, elastic fibres, and version were determined using immunohistochemical analysis.
Demling & DeSanti 2003[46]	HTS	Quasi-experimental study	Doxepin	Participants: Minor burns who complained of itch, not >15%TBSA. Healed wounds. Scars 6weeks - 3months. Setting: outpatient clinic, Brigham and Women's Hospital Burn Centre, Boston, Massachusetts, USA.	Standard care group: oral antihistamine, skin moisturiser 3x/day of the patient's choice as long as it did not have antihistamine properties. Doxepin group: applied cream in a thin layer to the itchy area 4x/day (every 6 hrs), then 20min later moisturiser of choice. Treatment modality in each group continued for 3 months or until itch stopped and no longer required treatment.	Measurement of itch & erythema by research team. Initial and subsequent done by them. Itch – VAS, patients recorded daily minimum & maximum itch score for the day, averaged by the researchers and antihistamine adjusted in the standard care group. Pain – VAS, Erythema – VSS, digital photography. Participants sat in quiet temp controlled room for 20min.

Cont…. Table 3-4: Characteristics of included studies - moisturiser group

Study	Types of scars	Design	Product	Participants, setting	Intervention	Outcomes measured
Ding et al. 2015[103]	Keloid	Quasi-experimental study	Wubeizi ointment	Participants: Specimens collected from active keloids of patients. Setting: Xuzhou Central Hospital and Xuzhou Hospital of Traditional Chinese Medicine, Jiangsu, China.	Drug preparation: 1g/ml – high concentration group, 0.5g/ml medium concentration group, 0.25g/ml for low concentration group, and a control group. Fibroblasts of keloids cultured in medium. Fibroblasts then mixed with the drug.	Cell proliferation rates measured as a % of the control (no drug). DNA cycles of keloid fibroblasts also recorded at different concentrations of the drugs.
Dolynchuk et al. 1996[48]	HTS	Prospective, double blind, crossover RCT	Putrescine	Participants: Patients with one or more unrevised HTSs. Setting: University of Manitoba, Canada.	Putrescine compounded in eutectic base at 0.8% concentration (Fibrostat). Identical in odour and appearance to the sham treatment which was the ointment base alone. Patients applied the ointment daily and occluded with Duoderm CGF or Actiderm. After 1 month the patient received the other topical preparation for an additional month.	Measurements taken at baseline, 1m & 2m. Scars rated on a rating scale. Photographic analyses at 1 month and 2 months upon completion of treatment.

Cont…. Table 3-5: Characteristics of included studies - moisturiser group

Study	Types of scars	Design	Product	Participants, setting	Intervention	Outcomes measured
Hoeksema et al. 2013[19]	Scar model	Quasi-experimental study	Alhydran	Participants: Tape stripped skin on healthy normal subjects. Setting: Ghent University Hospital, Ghent, Belgium	3 silicone gels (liquid) and hydrating gel cream (Alhydran®, BAP Medical, Belgium). 2 Test areas, one on each forearm, then divided into 4 subareas. One control area – normal skin One stripped area = scar like control. Stripped subareas for application of each of the 4 products. Process: 30min of acclimatisation. Baseline measures of TEWL & hydration on every subarea. Then stripping of all the areas except the control site. 5min after stripping TEWL measured to identify increased TEWL. Application of the 4 products. TEWL measured every hour and hydration at the end after 3 hours.	TEWL and hydration.

Cont…. Table 3-6: Characteristics of included studies - moisturiser group

Study	Types of scars	Design	Product	Participants, setting	Intervention	Outcomes measured
Jackson & Shelton 1999[104]	Linear	Quasi-experimental study	Mederma® & Aquaphor®	Participants: Scars from Mohr's surgery. Setting: University of Texas, Houston, USA	Assigned to one of 2 treatment groups on a rotating basis. Group 1 – Mederma® 3x/day for 1 month. Group 2 – Aquaphor® 3x/day for 1 month.	VAS on erythema and itching and photos at onset and completion.
Jacob et al. 2003[31]	Keloid	Quasi-experimental study	Imiquimod 5%	Participants: Excised keloid scars. Setting: University of Miami, Miami, USA.	Keloids were present 6 months to 3 years and were untreated for at least 2 months. Control: no imiquimod treatment. For the treated tissue, imiquimod 5% cream had been applied to the skin once daily by the subject for a minimum of 2 weeks and a maximum of 2 months. Tissue was only included if the keloid had been excised within 48 h of cessation of imiquimod therapy. Each keloid had a confirmed haematoxylin and eosin diagnosis by a dermatopathologist. Total RNA extracted, cDNA probes synthesized.	Expression levels of genes associated with apoptosis.

Cont…. Table 3-7: Characteristics of included studies - moisturiser group

Study	Types of scars	Design	Product	Participants, setting	Intervention	Outcomes measured
Jansen de Limpens 1980[81]	HTS & Keloid	Quasi-experimental study	Tretinoin cream	Participants: Scars from multiple causes (burns, trauma, post surgery). Setting: Red Cross Hospital, The Hague, The Netherlands.	Retinoic acid (005%) as a topical application apply the solution to their scars twice a day. Several patients had received Kenacort intralesionally prior to treatment with retinoic acid. Excluded if treatment was shorter than 3months.	Three months after completion of this study all patients received a questionnaire requesting them to answer twelve questions about their subjective findings of the effectiveness of the drug. These questions included improvement or disappearance of pain and/or itching as the main parameters.
Jenkins et al. 1986[98]	HTS	RCT	Aquatain, Vitamin E, Aristocort® 0.1%	Participants: Grafting for post burn contractures of the neck and axilla and interdigital webs of the hand. Setting: Shriners Burns Institute, Cincinnati, USA.	Allocated to groups: Base cream (Aquatain), Aristocort® A (Aristocort® 0.1% in Aquatain) or base cream with Vitamin E, 200 units/gm. Used the study cream on discharge and continue for 120 days. Massaged in 3x/day for 3min.	ROM, scar thickness not he edge of the graft, cosmetic appearance. Photographs pre op and at each follow up. Graded for scarring & cosmetic appearance by independent blinded observers. Patients with neck and axillary grafts evaluated for contracture by a pliable impression cast of the grafted area 1m, 4m, 1yr post-op.
Jina et al. 2015[57]	HTS/ Linear	Quasi-experimental study	KeragelT®	Participants: Adults having an operation involving median sternotomy. Setting: Cardiothoracic Surgery Department, Christchurch Hospital, New Zealand.	At 7 days post op, each half of the patients scar was randomised to receive keratin gel (KeragelT®) or Aqueous Cream. Patients self-administered both products for twice a day 6 months.	Patients reviewed at 3 and 6 months. Assessed using Manchester Scar score and POSAS (both observer and patient rated components). Photos also taken.

Cont…. Table 3-8: Characteristics of included studies - moisturiser group

Study	Types of scars	Design	Product	Participants, setting	Intervention	Outcomes measured
Kwon et al. 2014[99]	HTS/ Linear	Single blinded RCT	Tretinoin cream	Participants: Patients with postoperative wounds. Setting: Wonkwang University School of Medicine, Iksan, Korea.	Patients randomly allocated to groups. 3 groups - Silicone gel (Dermatix), or Tretinoin cream applied both applied twice daily for 6months or no treatment. Gel, cream or nothing applied to the wound the day after removal of the stitches.	mVSS at 0, 4, 8, 12 & 24 weeks to measure scar.
Medunsa 2005[82]	HTS / Linear	Single blinded RCT	Bio-Oil®	Participants: burns and surgical scars, new - 3yrs old. Setting: Photobiology Laboratory of the Medical University of South Africa.	Subjects had matching scars or a scar large enough to allow a half-half scar application and intra-subject comparison. Product applied twice daily for 12 weeks to the targeted area.	Assessments conducted at 0, 4, 8 and 12 weeks. Change in appearance judged according to: - Vascularity (redness) - Pigmentation (difference in colour from surrounding skin) - Thickness (width) - Relief (height) - Pliability (elasticity)

Cont…. Table 3-9: Characteristics of included studies - moisturiser group

Study	Types of scars	Design	Product	Participants, setting	Intervention	Outcomes measured
Murdock et al. 2016[100]	Linear	Single blinded RCT	Lumière Bio-Restorative Eye Cream	Participants: Patients who underwent bilateral upper eyelid blepharoplasty. Setting: Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, USA.	Week 2 post-op each subject was randomized to receive treatment of Lumière Bio-Restorative Eye Cream on one upper eyelid and no treatment on the other upper eyelid. Application of the study product in the morning and at least 30 minutes prior to bed. Applied the product twice a day for 12 weeks total.	Subjects completed a diary to assess effects of product on a 4-point scale including pain, itching, redness, and peeling. Subjects returned at weeks 6, 10, and 14. Standardized photographs taken, principal investigator completed a live assessment to evaluate: scar appearance, overall appearance of eyelid skin, and comparison between eyelids. Subject completed a self-assessment with a 4-point scale to evaluate pain/soreness, tenderness, itching, swelling, redness, and eye irritation for both the treated and non-treated eyelid. Subjects also evaluated the appearance of the scar and overall eyelid. At the study exit subjects rated whether they would recommend the product.

Cont…. Table 3-10: Characteristics of included studies - moisturiser group

Study	Types of scars	Design	Product	Participants, setting	Intervention	Outcomes measured
Nedelec et al. 2012[58]	HTS	Prospective, double blind, single centre, pilot RCT	Provase®®	Participants: Patients who were experiencing itch as the result of a burn injury. Setting: Villa Medica Rehabilitation Hospital, Montreal, Canada	Participants randomly assigned to either control moisturiser or protease-containing moisturiser (Provase®). The moisturiser base used for both was identical. The investigators and participants were blinded to the treatment groups. Each participant was instructed to apply the moisturiser evenly to the pruritic area at least every 8 hours. Before applying the moisturiser, participants recorded current itch or pain at the treatment site using a VAS which - no itch (pain) and the worst itch (pain) imaginable. Thirty minutes later, participants again recorded their current itch or pain using the VAS.	The participant's demographics, history, burn and itch TBSA, burn and itch locations, skin and scar condition, baseline scoring of itch, and baseline scoring of general and localized pain severity were evaluated and recorded during the screening and on a weekly basis for 4 consecutive weeks. Measures – questionnaire on pruritus, mVSS, Mexameter quantifies erythema and melanin.
Ogawa & Ogawa 2008[55]	HTS	Quasi-experimental study	Mugwort lotion	Participants: Patients with hypertrophic burn scars. Setting: hospitalised patients, Nippon Medical School Hospital, Tokyo, Japan.	Applied mugwort lotion to 15 sites and control heparinoid ointments, two different regions of severe itchiness were selected in each patient. The lotion was applied twice daily (in the afternoon and before bedtime) to the selected itchy regions.	Questionnaire on itch severity administered at 1 week and 2 months after the commencement of treatment.
Panabiere-Castaings 1988[80]	Keloid	Quasi-experimental study	Tretinoin cream	Participants: Keloid patients, present for average 7 yrs, paediatric. Setting: Faculty of Medicine, University of San Luis Potosi, Mexico.	Cream applied twice a day for 12 weeks.	Evaluation using photos, tape measurements and volume using dental moulages. Taken prior to therapy and at 6 and 12 weeks.

Cont…. Table 3-11: Characteristics of included studies - moisturiser group

Study	Types of scars	Design	Product	Participants, setting	Intervention	Outcomes measured
Perez et al. 2010[56]	HTS/ Keloid	RCT	Mederma®, Scarguard®/HSE, Cetaphil®	Participants: adult subjects with keloid or HTS 0.5-2.5cm diameter. Setting: recruitment via advertisements in hospitals and clinics within University of Miami Miller School of Medicine and external advertisements in the Miami-Dade Metrorail, USA.	Random assignment (computer generated randomization list) to receive one of 3 creams, use for 16 weeks. Mederma®, Scarguard®/HSE (0.5% hydrocortisone, silicone and VitE) and Cetaphil® (placebo/control). Applied HSE twice daily, Applied OE 3-4x daily. Applied placebo 2x daily, i.e. as per package instructions.	Evaluate at baseline, 4, 8, 12 & 16 weeks. Adverse events, photos, scar volume using alginate impression. Subjects and investigator assessed scar parameters – volume, length, width, height, induration, erythema, pigmentation, pain, itch, tenderness, cosmetic appearance with VAS. Subjects also assessed satisfaction with treatment with a VAS.
Phillips et al. 1996[61]	HTS/Keloid	RCT	Eucerin®	Participants: Patients with HTS scar, 1 patient in each group had keloid scar, the rest were HTS's. Setting: Department of Dermatology, Boston University School of Medicine, Boston, USA.	Patients allocated to either hydrocolloid dressing group or moisturiser group. Scar cleaned with saline. HCD applied dressing and left for up to 7days or was replaced if it became dislodged. Moisturiser applied once daily.	Measurements day 0, 14, 28, 56 and subsequently 1 month after the last dressing change. Evaluations by blind assessor. Scar volume measured with alginate. Photographs. Transcutaneous oxygen measures of the skin adjacent and the scar. Parameters – size, pigmentation, vascularity, pliability, pain, itch, height, VSS, patient symptoms using VAS.

Cont…. Table 3-12: Characteristics of included studies - moisturiser group

Study	Types of scars	Design	Product	Participants, setting	Intervention	Outcomes measured
Prado et al. 2005[101]	Linear	RCT	Imiquimod 5%	Participants: post breast reconstruction surgery. Setting: Department of Plastic Surgery School of Medicine, Jose Joaquin Aguirre Clinical Hospital, University of Chile, Santiago, Chile.	First group of 5: R breast scar control - no treatment. Left breast - imiquimod beginning 2m after surgery. Gently rubbed cream on for 3-4 days once every 3-4 days for 8 weeks. Second group of 5: imiquimod on R same as others and L with petrolatum application. Third group of 5: double blind application.	Scar assessed with Strasser (cosmesis) and Beausang (scar colour & contour) scale.
proDERM 2010[83]	Unclear	Double-blind, RCT	Bio-Oil®	Participants: scars newly formed - 3yrs old, different locations. Setting: proDERM Institute for Applied Dermatological Research, Hamburg, Germany	Subjects had matching scars or a scar large enough to allow a half-half scar application and intra-subject comparison. - Product applied twice daily for 8 weeks, no additional massaging performed on the target area. - Application performed under supervision at regular intervals.	Assessments conducted at 0, 2, 4 and 8 weeks. Different scar parameters as defined in the POSAS

Cont…. Table 3-13: Characteristics of included studies - moisturiser group

Study	Types of scars	Design	Product	Participants, setting	Intervention	Outcomes measured
Riaz et al. 1994[49]	HTS	Quasi-experimental study	Dermovate (clobetasol proprionate 005% w/w)	Participants: Patients 4-8 weeks after cardiothoracic surgery involving sternotomy. Control group of patients before surgery with healthy skin. Another group of patients 1yr post surgery to provide a sample of mature scar tissue. Setting: St Mary's Hospital, London, UK.	3x3cm area at lower scar marked out. One group had a single application of Dermovate then covered with Tegaderm & returned 48hrs later for sample provision. Another group of patients applied the cream in marked areas of the scar 2x/day for 7 days.	Photo taken using standard method. Two samples of scar tissue were obtained from each patient. First was from within the marked area (where the steroid based cream had been applied) and the second sample was from an adjacent area of the scar where cream had not been applied. 2 observers independently ranked the photographs and the biopsy slides from each patient. Photos assessed for width of scar and if it was flattened/raised. Biopsy specimens were compared. Score assigned as to whether steroid resulted in an increase or decrease of PCP1. Correlation coefficient was used to test the correlation between the degree of PCP 1 staining and the severity of the scar.

RCT = randomised controlled trial, HTS = Hypertrophic scar, VAS = visual analogue scale, TEWL = trans-epidermal water loss, ROM = range of motion, mVSS = modified Vancouver Scar Scale.

Table 3-14: Included studies - imiquimod group

Study	Keloid location	Design	Participants, setting	Intervention	Outcomes measured
Berman & Kaufman 2002[30]	Earlobe, back	Case series	Participants: Keloids present for >1yr, free from Rx for 2m, >18yo. Setting: University of Miami, Department of Dermatology and Cutaneous Surgery, Miami, USA.	Keloids excised with primary bilayer closure. Applied imiquimod nightly beginning post op for 8 weeks.	Assessed at 4, 8, 16 & 24 weeks for erythema, pain, pruritus, erosion, hyperpigmentation.
Berman et al. 2009[111]	Earlobe, upper back, abdomen	Double blind RCT	Participants: Keloids >1yo and stable in size over last 6m, patients >12yo. Setting: University of Miami, Department of Dermatology and Cutaneous Surgery, Miami, USA.	Tangentially shaved keloids between 0.25cm and 2cm. Treatment group - imiquimod nightly. Control group - vehicle cream nightly. Both nightly for 2 weeks post-op then 3 nights a week under a semi-occlusive non-silicone dressing for 4 more weeks.	Tolerance assessed by patient self-assessment on VAS (0=best, 10=worst) of pain, tenderness and pruritus at week 2, 6 and 6m.
Cacao et al. 2009[107]	Posterior shoulder, anterior chest	Case series	Participants: Stable keloids. >18yo. Duration of keloids 1.5-30yrs. Size ranged from 90-882mmsq. Setting: General Hospital of Sao Paulo University Medical School, Sao Paulo, Brazil.	Keloids excised and wounds sutured with bilayer closure. Applied imiquimod for 8 weeks nightly.	Evaluated at week 2, 4, 8, 12 & 20 weeks post op. Occurrence of erythema, pain, erosion, systemic symptoms. Pictures taken before surgery and during follow up visits.
Chuangsuwanich & Gunjittisomrarn 2007[106]	Ear, chest, back, neck, shoulder	Case series	Participants: Keloids >1yr old, no treatment for 2m, patients >18yo. Setting: Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.	Keloids primarily excised, sutured in two layers. Applied imiquimod on alternate nights for 8 weeks starting from 1 week post stitch removal.	Assessments at week 4, 6, 8, 16, 24. Assessment of erythema, pain, pruritus, erosion and hyperpigmentation. Follow-up 6-9m.
Martin-Garcia & Busquets 2005[108]	Earlobes	Case series	Participants: Keloids with no treatment for last 3m. Age 15-29. Size 0.15-10.5cmsq, mean 3.86cmsq. Setting: Dermatologic surgery clinic at University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico.	Keloid parallel shave removal. Then apply thin film of imiquimod without occlusion nightly, wash off in morning, for 8 weeks then just soap & water for remaining 16 weeks.	Evaluation at 2, 4, 6, 8 for adverse events, then monthly until completion. If both earlobes - compared to intralesional steroid inj.

Malhotra et al 2007[110]	Sternal	Case report	Participants: 2 patients, keloids free from any treatment over the last 3m. Setting: Department of Dermatology and Venereology, All India Institute of Medical Sciences, New Delhi , India	Keloids excised with radiofrequency under local anaesthetic. Imiquimod applied immediately, daily, for 8 weeks. Left to heal by secondary intention.	Examination every 2 weeks for 12 weeks to check for recurrence.
Stashower 2006[109]	Earlobes	Case series	Participants: Keloids with no treatment for last 6m. Duration 4-10yrs, size 1.2-2.9cmsq. Setting: The Clinical Centre of Northern Virginia, Fairfax, USA.	Tangential excision to non-keloidal tissue but some could not be completely excised. No sutures, allowed to heal by secondary intention. Post-op imiquimod applied for 6 weeks with dressing if not healed.	Follow-up every 3-8 weeks for 12 months - patients report on itch, pain & discomfort.

RCT = randomised controlled trial, VAS = visual analogue scale

3.5 Critical appraisal

All of the 26 studies in the moisturiser group and seven in the imiquimod group were critically appraised using the process detailed in Section 2.3.3. The critical appraisal tools utilised are shown in Appendix 2 and outline the questions asked.

3.5.1 Methodological quality of included studies – moisturiser group

Although the majority are RCTs the average total score of each study was 66% (Table 3-3). The included RCTs generally performed well with blinding of the outcome assessors (question 6) and measuring the outcomes the same way for the treatment groups (question 10).

Bio-Oil® studies were sourced by this author direct from the company for this systematic review since it is a product that has been extensively marketed in Australia, and is one that patients frequently ask about. The company provided reports of three unpublished studies. It is known that at least one study was funded by the owner and developer of Bio-Oil®, who engaged a private laboratory to run the trial. This study was excluded from further review when the brand owner and developer declined a request to provide more details. The other two studies[82, 83] were of a similar nature, from a private laboratory and only available from the company, and were likely also to be funded by Bio-Oil®'s owner. Apart from the concerns regarding the funding source of these studies, upon critical appraisal they scored lowest and third lowest among the included studies. The studies reported improvements in scar parameters reported as a percentage of improvement but statistical significance was not provided.

In the RCT by Dolynchuk et al. (1996)[48] they compounded Putrescine in a eutectic base at 0.8% w/v concentration to make Fibrostat. The reported results indicated that the Fibrostat resulted in significantly better scar rating scores in comparison to the base cream as a control.[48] However, there were a number of issues with the methodology. The description of the scars was only that they were hypertrophic, with no indication of age of scar. There was also no detail provided on whether the treatment groups were similar at baseline, although the cross over design may have eliminated this issue. The outcome measure was a scar rating scale that has not been published although the authors reported that the scale had a high kappa coefficient for inter-observer reliability.[48]

Jenkins et al. (1986)[98] was not clear on whether the treatment groups all received the same treatment as the author referred to the fact that some applied 'braces' but it was not specified which subjects had and which had not. It is likely that these would have had an effect on the scar parameters being measured.

Critical appraisal of the Baumann et al. (1999)[96] study resulted in low scores due to lack of detail in the description of the study but also because clinically it would have been difficult to make comparisons as they did not specify the duration post-surgery of each patient at the start of the study.

In the study examining Lumiere Bio-Restorative Eye Cream with linear scars, the comparison was an 'untreated side' and therefore received no moisturiser at all.[100] However, an outcome measure, that is, whether they would recommend the product, was flawed, as the participant had no comparison.

The study by Perez et al. (2010)[56] had some methodological issues as the subjects had different scar types (keloid or hypertrophic scar), different skin types and were in variable locations. There was no record of the age of the scars, and whether they were active or mature scars. In addition, there were small numbers (five) in each of the three groups.

Nedelec et al. (2012) examined whether Provase® would reduce post burn itching relative to the base moisturiser in Provase®.[58] They were able to demonstrate that itch was reduced in duration, weekly frequency, number of itch episodes per day, itch total body surface area (TBSA), and the reported affective burden of itch.[58] However, there were only nine subjects in each group. The author reported that the study was likely statistically underpowered.[58] They also acknowledged that larger studies were required to determine the effect of prolonged use of Provase® as this study was only over four weeks and that stratifying the subjects according to time post burn was required to examine the effects on acute and chronic scars.[58]

Phillips et al. (1996)[61] reported on Eucerin® and was based in the US. However, this study had some methodological issues and did not score well in the critical appraisal process (8/13, 62%) as details of how the RCT was conducted were unclear. Of note, there was a reported mix of hypertrophic and keloid scars with no clear reporting of the outcomes of each of the types of scars. The progression of the scars within the moisturiser group which applied Eucerin® may have been due to natural scar progression but without details of the types of scars or the age of the scar this was difficult to determine.

It was difficult to determine the outcome of the petrolatum in the study by Prado et al. (2005)[101] as there were two control groups, one with petrolatum and one with no treatment, and the data from both of these 'control' groups was combined to compare against the scores of the imiquimod group.

The quasi experimental set of studies performed better in critical appraisal with an average total score for each study of 78% (Table 3-4). These studies generally performed well in question 1 by clarifying what was the cause (e.g. scar) and the effect (e.g. cosmesis, scar erythema, itch, etc.), and in question 7 by measuring the outcomes of participants in the same way. The Jacob et al. (2003)[31] and Ding et al. (2015)[103] studies received a 'N/A' score for question 6, which asked if follow-up was complete as the studies examined gene markers and cell proliferation post-intervention *in vitro* and therefore there was no follow-up as such. The lowest scoring study was the oldest study to be retrieved, dated 1980.[81] The data was so poor that in a section of the study the percentages did not appear to add up. The study was still included to ensure the full breadth of data collated on the topic.

There are concerns with the methodology of the Demling et al. (2003)[46] study. There was no control group using a non-medicated cream. The patients were selected as being at six weeks to three months post-burn when itching is at its worst. However, this period is also the period of highest scar activity so the participants will have a high level of erythema. As the study extended over three months, this is an adequate time frame for scars to naturally begin to reduce in their activity and for a reduction in erythema and itch intensity as well.

In Riaz et al. (1994),[49] some details in the publication were not entirely clear, such as the incidence of any adverse events, whether patients had or had not applied any other treatments to their scars during the course of the study and the demographics of all participants.

The Dematte et al. (2011)[79] study of Tretinoin (Retinoic Acid/Vitamin A) had a significant positive effect on cosmesis as it improved the overall pliability of extensive full facial scars. The study scored well in critical appraisal as it appeared to have a robust methodology. In addition, clinically it was most relevant as it utilised subjects with full facial scars, who represent the most challenging and severe cases treated by burn therapists.

Jina et al. (2015)[57] conducted a study over six months to determine the effects with a keratin gel product, KeragelT®, on median sternotomy scars by comparing it to aqueous cream. Critical appraisal of this study resulted in a score of 100%. However, the use of aqueous cream as a control moisturiser may not have been a wise choice since aqueous cream has

been shown to increase TEWL[62] and therefore may impact negatively on the developing scar. The study examined scar scale scores post median sternotomy, which is at a higher risk of hypertrophic scarring. There was no mention of whether the nine subjects provided enough statistical power.

Ogawa et al. (2008)[55] did not perform as well in critical appraisal as it lacked details on methodology. The control lotion was not described, making it difficult to assess the comparison of the two groups.

Two studies were classified as case series (Table 3-5). They performed relatively well but both were unclear on whether they had consecutive and complete inclusion of participants (questions 4 and 5). Berman et al. (2005)[45] did not report outcomes clearly (question 8) on tacrolimus ointment, and an important observation that was not highlighted by the critical appraisal tools was that the study was funded by the manufacturer of the moisturiser, Fujisawa Healthcare Inc. Similarly, it was noted that the Berman et al. (2005)[94] RCT primary author was a consultant for 3M Pharmaceuticals, which manufactures imiquimod.

The critical appraisal tools, outlining the questions they contain, are in Appendix 2.

Table 3-15: Critical appraisal scores for Randomised Controlled Trials in moisturiser group

Question	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**Score**	**%**
Study															
Baumann 1999[96]	N	U	U	Y	Y	Y	Y	Y	Y	Y	U	N	U	7/13	54
Chung 2006[97]	U	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11/13	85
Dolynchuk 1996[48]	U	U	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10/13	77
Jenkins 1986[98]	Y	N	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	10/13	77
Kwon 2014[99]	U	U	Y	U	U	U	Y	N	Y	Y	Y	Y	N	6/13	46
Murdock 2016[100]	U	U	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	9/13	69
Nedelec 2012[58]	Y	Y	N	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	11/13	85
Perez 2010[56]	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	11/13	85
Phillips 1996[61]	U	U	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	8/13	62
Berman, Frankel 2005[94]	U	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	11/13	85
Prado 2005[101]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	12/13	92
Medunsa 2005[82]	U	U	U	N	U	Y	Y	U	U	U	U	U	U	2/13	15
proDERM 2010[83]	U	U	U	U	U	Y	Y	U	U	Y	Y	N	U	4/13	31
Scores	4/13	3/13	7/13	8/13	8/13	12/13	11/13	8/13	11/13	12/13	11/13	9/13	8/13		Ave 66%
%'s	31	23	54	62	62	92	85	62	85	92	85	69	62		

Refer to Appendix 2 for details of questions. Y=Yes, N=No, U=Unclear

Table 3-4: Critical appraisal scores for Quasi Experimental studies in moisturiser group

Questions	1	2	3	4	5	6	7	8	9	Score	%
Study											
Demling 2003[46]	Y	Y	Y	Y	Y	U	Y	Y	U	7/9	78
Hoeksema 2013[19]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9/9	100
Jacob 2003[31]	Y	U	Y	Y	Y	NA	Y	Y	U	6/8	75
Jina 2015[57]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9/9	100
Riaz 1994[49]	Y	N	Y	Y	Y	U	Y	Y	Y	7/9	78
Dematte 2011[79]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9/9	100
Janssen de Limpens 1980[81]	Y	U	U	N	N	N	Y	N	N	2/9	22
Panabiere-Castaings 1988[80]	Y	U	U	N	Y	Y	Y	U	Y	5/9	56
Ding 2015[103]	Y	Y	Y	Y	Y	NA	Y	Y	Y	8/8	100
Jackson 1999[104]	Y	U	U	Y	Y	Y	Y	Y	Y	7/9	78
Ogawa 2008[55]	Y	U	U	Y	N	Y	Y	Y	Y	6/9	67
Scores	11/11	5/11	7/11	9/11	9/11	6/9	11/11	9/11	8/11		Ave 78%
%	100	45	64	82	82	67	100	82	73		

Refer to Appendix 2 for details of questions. Y=Yes, N=No, U=Unclear, N/A=Not applicable

Table 3-5: Critical appraisal scores for Case Series in moisturiser group.

Questions	1	2	3	4	5	6	7	8	9	10	Score	%
Study												
Berman, Poochareon 2005[45]	Y	Y	Y	U	U	Y	Y	N	Y	U	6/10	60
Butzelaar 2015[105]	Y	Y	Y	U	U	Y	Y	Y	Y	Y	8/10	80

Refer to Appendix 2 for details of questions. Y=Yes, N=No, U=Unclear

3.5.2 Methodological quality of included studies – imiquimod group

The group of studies that measured the outcome of recurrence of keloids post excision and imiquimod application contained one RCT (Table 3-6).[111] It did not perform well in the critical appraisal, scoring only 54% of 'Yes' for the questions. The follow-up was not complete (question 8) and did not use appropriate statistical analysis (question 12). In addition, many components were unclear such as concealment of allocation to treatment groups (question 2), similarity of treatment groups at baseline (question 3), and blinding of participants (question 4) and those delivering treatment (question 5).

The case series in general performed satisfactorily for inclusion in this review with an average score of 82% (Table 3-7). They regularly performed well in reporting of the outcomes (question 6), definition of the condition (question 7), and reporting on the demographic (question 4) and clinical information (question 5) of the participants. Only one study fulfilled all of the appraisal criteria.[108]

The one case report by Malhotra et al. (2007)[110] study was considered a case report as even though there were two patients, they were reported as two separate cases (Table 3-8). It failed to get a 'Yes' for all questions as it did not clearly describe the patients' history (question 2), assessment methods were not clearly described (question 4) and it was unclear if there were adverse events (question 7).

The critical appraisal tools, outlining the questions they contain, are in Appendix 2.

Table 3-6: Critical appraisal scores for randomised controlled trial in imiquimod group. Refer to Appendix 2 for details of questions. Y=Yes, N=No, U=Unclear.

Questions	1	2	3	4	5	6	7	8	9	10	11	12	13	Score	%
Study															
Berman, Harrison 2009 [111]	Y	U	U	U	U	Y	Y	N	Y	Y	Y	N	Y	7/13	54

Refer to Appendix 2 for details of questions. Y=Yes, N=No, U=Unclear

Table 3-7: Critical appraisal scores for case series studies in imiquimod group

Questions	1	2	3	4	5	6	7	8	9	Score	%
Study											
Berman, Kaufman 2002[30]	Y	Y	U	Y	Y	Y	Y	Y	Y	8/9	89
Cacao 2009[112]	N	Y	U	Y	Y	Y	Y	Y	Y	7/9	78
Chuangsuwanich 2007[106]	Y	Y	Y	Y	Y	Y	Y	N	N	7/9	78
Martin-Garcia 2005 [108]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9/9	100
Stashower 2006 [109]	U	U	U	Y	Y	Y	Y	Y	N/A	5/8	63
Scores	3/5	4/5	2/5	5/5	5/5	5/5	5/5	4/5	3/4		Ave 82%
%'s	60	80	40	100	100	100	100	80	75		

Refer to Appendix 2 for details of questions. Y=Yes, N=No, U=Unclear, N/A=Not applicable

Table 3-8: Critical appraisal scores for case report in imiquimod group

Questions	1	2	3	4	5	6	7	8	Score	%
Study										
Malhotra 2007 [110]	Y	N	Y	N	Y	Y	U	Y	5/8	63

Refer to Appendix 2 for details of questions. Y=Yes, N=No, U=Unclear

4. Review findings

This chapter describes the included studies by drawing out their findings on the effect of moisturisers on scar outcomes. The outcomes of cosmesis, scar parameters, itch/pain, TEWL, and *in vitro* findings are described utilising a narrative synthesis. The outcome of recurrence, particularly of keloids post excision and application of Imiquimod cream, is described using a meta-analysis. Amongst the results we also highlight the adverse events reported for many products.

Narrative synthesis of the effect of moisturisers on scars

When examining all 26 studies it became apparent that studies could be grouped according to the *outcomes* they reported on. This included cosmesis, scar parameters, itch and pain, trans-epidermal water loss, and *in vitro* outcomes.

4.1 Cosmesis of the scar

There were a number of studies that specifically reported on cosmesis of the scar (Table 4.1). Murdock et al. (2016)[100] studied the effects of Lumiere Bio-Restorative Eye Cream after upper eyelid blepharoplasty in a split face randomised study. Patients were asked to choose which eyelid had a better appearance. The number of patients who selected the treated side as better than the control side increased from 50% (10/20) to 70% (14/20) from week 2 to week 10, which was a statistically significant improvement (p=0.001). The investigator rated assessment observed 60% (12/20) of treated side eyelids to be better than the control side at week 10.[100] The treated side achieved its final appearance earlier which ended up being the same as the control/untreated side by the end of the study at week 14 (p=1.00).[100]

There was little to no cosmetic benefit found when using tacrolimus ointment in five out of six subjects with keloids.[45] Patients rated the improvement in the keloid on a five-point scale. Overall improvement was rated as 4 – 'poor'. Only one patient rated the improvement as 3 – 'satisfactory'.[45]

Baumann et al. (1999)[96] found that cosmesis was no better with the use of vitamin E added to Aquaphor® (a basic moisturiser) and, in a few patients, the outcome was superior to the control side (Aquaphor® only). After 12 weeks of use, the physician assessment was that 10% (1/10) of scars were assessed as having a better cosmetic outcome from use of the vitamin E cream, 30% (3/10) of control scars were better than vitamin E and 60% (6/10) showed no difference between use of the control cream and the vitamin E cream.[96] When the patients assessed their scar for cosmetic outcome at 12 weeks, 30% (3/10) felt the control was

better and the remaining 70% (7/10) felt there was no difference.[96] Jenkins et al. (1986)[98] also failed to find a significant difference (reported as 'not significant', no p value given) in the cosmetic outcome of vitamin E cream when compared to its base cream and Aristocort® cream (a topical steroid). The data on the cosmetic outcome after one year for axillary and neck grafts with the use of each cream was spread evenly across the ratings of excellent, good, fair and poor for all three creams.

Dematte et al. (2011) reported that skin distensibility, measured as a decrease in resistance 31.4% (p=0.003) and elastance 14.8% (p=0.047), improved with prolonged use of Tretinoin cream and this would impact upon cosmesis.[79]

Onion extract gel (Mederma®) was found to have no significant effect on cosmetic appearance when compared to petrolatum at all time points of a study.[97] At 12 weeks 86% (12/14) were rated as having no difference between Mederma® and petrolatum, and one subject from each group had an overall cosmetic appearance that was better (T-test p=0.9806, Wilcoxon test p= 0.9583). Perez et al. (2010)[56] also reported only a ~25% improvement (taken from graph – Figure 1 in the publication) in keloid and hypertrophic scars (p value not reported, but reported as not statistically significant) cosmetic outcome with Mederma® cream at 16 weeks compared to baseline. However, they did find improvements in investigator rated cosmesis for the Scarguard®/HSE moisturiser (~67%, p=<0.01) subject rated cosmesis Scarguard®/HSE (~48% improvement, p<0.01) and the 'placebo' – Cetaphil® (~58% improvement, p=0.01).

When the cosmetic outcome of imiquimod cream was assessed (VAS, 0=best, 10= worst) with its use on linear or hypertrophic scars, it was found that in comparison to just its vehicle cream as the placebo, the results were often worse and occasionally the same.[94] At week 8 the mean scores for the patient cosmetic assessment was 3.2 and 2.7 (p=0.140) for the imiquimod cream and placebo, respectively.[94] Investigator assessment of cosmesis was 4.4 for the imiquimod cream and 2.9 for the placebo (p=0.005).[94] The results for the patient related cosmetic assessment for the five patients who were evaluated in the longer term between 39 and 46 weeks was scored as 2.6 for the imiquimod cream and 1.5 for the placebo (p=0.309), and the investigator scores were 3.9 and 2.6 (p=0.191).[94]

A summary of the studies examining moisturisers that have an effect on the cosmesis of the scar is outlined in Table 4-1 below.

Table 4-1: Summary of cosmesis outcomes of different moisturisers

Moisturiser type	Study / Design / Scar type	How it was measured	Effect
Lumiere Bio-Restorative Eye Cream	Murdock et al. 2016[100]/RCT/Linear	6 point scale developed by the authors, investigator assessment of wrinkles and texture.	At week 14 10/20 treated eyelids looked better & 10/20 control eyelids looked better (p=1.00)
			At week 10 60% (12/20) treated eyelids appeared better (p=0.039)
	Murdock et al. 2016[100]/RCT/Linear	Subjects recorded which eye had a better scar appearance. Measured before treatment and again after.	From 50% (10/20 scars) week 2 to 70% (14/20 scars) week 10, P=0.001
Tacrolimus ointment	Berman, Poochareon, et al. 2005[45]/case series / Keloid	Scale 1 to 5, 1=excellent, 2=good, 3=satisfactory, 4=poor, 5=worse than the original keloid	5/6 patients reported no or little improvement. Overall rated 4 (poor).
Vitamin E Aquaphor®	Baumann et al. 1999[96]/ RCT/Linear	Unclear. Investigator and patient evaluated whether scar cosmesis was superior or no different for the Aquaphor®/control and study moisturiser (Aquaphor® + Vit E)	At 12 weeks: 90% (9/10) with investigator evaluation reported Aquaphor® was better or no different than Vit E. 100% (10/10) when patients evaluated reported Aquaphor® was better or no different than Vit E.
Vitamin E Aristocort® A 0.1% Aquatain	Jenkins et al. 2006[98]/RCT/HTS	Photographs pre-op and at each follow up and graded for ultimate cosmetic appearance by independent blinded observer.	No significant difference in cosmetic appearance for any of the 3 creams (p value not reported).
Tretinoin cream (Retinoic Acid/Vit A)	Dematte et al. 2011[79]/quasi experimental/HTS	Skin elasticity and resistance of skin biopsies measured with a mechanical oscillation analysis system.	Decreased resistance 31.4% (p=0.003) and elastance improved 14.8% (p=0.047)
Mederma® (onion extract gel)	Chung et al. 2006[97]/RCT/Linear	Physician evaluated overall cosmetic appearance if one half was better than another, VAS, 0=no difference to 10=significant difference. Phone interview with patients - rate if one scar better than other for overall cosmetic appearance and whether difference minimal, moderate or significant. Also asked if scars overall appearance poor, okay or excellent.	86% (12/14) rated no difference between Mederma® and petrolatum. One subject reported Mederma® was better, one subject reported Petrolatum was better. T test p=0.9806, Wilcoxen test p=0.9583
	Perez et al. 2010[56]/RCT/HTS & Keloid	VAS, 0=best to 100=worst overall cosmetic appearance. Investigator and subject rated.	~25% improvement in keloid and HTS (not statistically significant, no p value).
Petrolateum	Chung et al. 2006[97]/ RCT/Linear	As above.	86% (12/14) rated no difference between Mederma® and petrolatum. One subject reported Mederma® was better, one subject reported petrolatum was better. T test p=0.9806, Wilcoxen test p=0.9583
Scarguard®/HSE	Perez et al. 2010[56]/ RCT/HTS & Keloid	VAS, 0=best to 100=worst overall cosmetic appearance. Investigator rated cosmesis.	~67% improvement in keloid and HTS (p=<0.01)
	Perez et al. 2010[56]/RCT/HTS & Keloid	VAS, 0=best to 100=worst overall cosmetic appearance. Subject rated cosmesis.	~48% improvement in keloid and HTS (p=<0.01)
Cetaphil® (used as placebo)	Perez et al. 2010[56]/ RCT/HTS & Keloid	VAS, 0=best to 100=worst overall cosmetic appearance. Investigator rated cosmesis.	~15% improvement in keloid and HTS (not statistically significant, no p value)
	Perez et al. 2010[56]/RCT /HTS & Keloid	VAS, 0=best to 100=worst overall cosmetic appearance. Subject rated cosmesis.	~58% improvement in keloid and HTS (p=0.01)
Imiquimod 5%	Berman, Frankel, et al. 2005[94] / RCT/Linear & HTS	VAS, 0=best, 10=worst. Investigator assessment.	At week 8: mean score for Imiqu. 4.4 & control 2.9 (p=0.005)
			At wk 39-46 mean score for Imiqu. 3.9 & control 2.6 (=0.191)
	Berman, Frankel, et al. 2005[94] / RCT/Linear & HTS	VAS, 0=best, 10=worst. Subject assessment.	At week 8: mean score for Imiqu. 3.2 & control 2.7 (p=0.140). At wk 39-46 mean score for Imiqu. 2.6 & control 1.5 (p=0.309)

No shading = no effect, green shading = positive effect, red shading = negative effect
HTS = hypertrophic scar, VAS = Visual Analogue Scale, RCT = randomised controlled trial

4.2 Scar parameters

Scar parameters are measurements of the features of a scar which indicate scar activity or severity. The parameters are usually measured with standardised scales (Vancouver Scar Scale [VSS],[74] Manchester Scar Scale [MSS],[113] Patient and Observer Scar Assessment scale [POSAS]),[73], photographs of scars, or visual analogue scales (usually created up by the author). They measure items such as scar height, pliability/thickness and colour/induration/erythema.

Imiquimod 5% when compared to its vehicle cream as the control was found at week 8 to have worse outcomes for pigmentation (mean 0.8 for imiquimod group vs. 0.4 for vehicle cream, p=0.021), erythema (imiquimod 5.4 vs. vehicle cream 3.9, p=0.004) and induration (imiquimod 0.8 vs. vehicle cream 0.2, p=0.65).[94] However, by the end of the study (week 39-46) the two groups were close to being the same – pigmentation (imiquimod 1.8 vs. vehicle cream 2.1, p=0.122), erythema (imiquimod 1.8 vs. vehicle cream 2.1, p=0.753) and induration (imiquimod 0 vs. vehicle cream 0.4, p not available).[94] However, imiquimod treated scars resulted in significantly improved mean scar scores, p<0.001, (Beausang scale: 9.5-10.4, Strasser scale 2.7-3.3) when compared to no treatment or a petrolatum cream (Beausang scale: 14.8-16.2, Strasser scale 6.7-8.7).[101]

Chung et al. (2006)[97] reported no significant differences in redness/erythema when a physician evaluated the scar halves at the end of study assessment, week 12, when comparing Mederma®/onion extract to petrolatum (onion extract=0.39+/-0.36, petrolatum=0.16+/-0.13, p=0.3356). Similarly, the patient evaluated each scar half as not being any different from the other with regards to redness (onion extract=0.29+/-0.11, petrolatum=0.29+/-0.13, p=0.9142) which was treated with Mederma®/onion extract gel on one half and petrolatum on the other. A similar result occurred for the thickness of the scar assessed by the physician (onion extract=0, petrolatum=0, p=1.00).[97] Earlier results at week 2 and week 8 were similar.[97] Similarly, another study found no difference in erythema between pre- and post-treatment of linear scars with Mederma®/onion extract after one month.[104] However, in the same study the other group which applied Aquaphor® (petrolatum-based ointment) had a significant (p<0.01) reduction in erythema after one month.[104]

Perez et al[56] reported improvements from the use of Mederma® in four of the scar parameters measured. Values and percentages were taken from the graph and were an estimation of the true value. For Mederma® the mean percentage improvement of volume was 42% (p=0.01),

length 12% (p=0.02), width 16% (p=0.02) and induration 50% (p=0.03).[56] It also showed improvement over the placebo (Cetaphil®) for induration, which was only 4%, (p<0.001) and pigmentation, which was worsened by 11% (no p value).[56]

In the same study it was demonstrated that compared to baseline measures, scars treated with Scarguard®/HSE (0.5% hydrocortisone, silicone and vitamin E) resulted in a reduction in volume 40% (p=0.01), length 14% (p=0.02), induration 68% (p<0.01) erythema 74% (p<0.01) and pigmentation 62% (p<0.01).[56] However, width showed 18% worsening (no p value).[56] It also showed improvement over the placebo (Cetaphil®) for induration which was improved by only 4% (p<0.001), and erythema which only showed 1% improvement (p=0.01) with the Cetaphil® treatment.[56] Cetaphil® did show a positive result but only for a mean reduction in volume of 32% (p=0.02).[56]

When comparing Tretinoin cream 0.05% (retinoic acid/vitamin A) to a liquid silicone gel (Dermatix) on hypertrophic scars, no differences between the scar scale scores of the two groups were observed at any time. However when comparing to the control group which was no treatment at week 8 after removal of sutures there was a statistically significant difference (p<0.05) in the total scores of the Modified Vancouver Scar Scale (mVSS) between the treatment groups (Tretinoin score = 3.23, silicone score = 3.25, control group = 6.00).[99] Height was also reported to be significantly different (p<0.05) at (and beyond) week 8 from the treatment groups (Tretinoin score = 0.23, silicone score = 0.25) and the control (week 8 score = 0.80). These scars were linear or hypertrophic scars.

Tretinoin cream effects were also examined, with keloids of an average age of seven years (range one to 16 years) shown to significantly reduce the scar mean surface area from 864mm^2 (SD=1266.3) at week 0 to 392mm^2 (SD=634.9) at week 12 (p=0.01).[80] Mean volume/weight of the scar changed from 2.6gm (SD=3.9) at week 0 to 2.1gm (SD=3.0) at week 12 (p=0.04).[80] Jansen De Limpens[81] also reported Tretinoin cream reduced the colour and height of 13 out of 21 patients (13/21=61%), but the study reported this as 64% of patients and there was no report of statistical significance. This study was on hypertrophic and keloid scars.[81]

Berman et al. (2005)[45] measured the effect of Tacrolimus ointment on stable keloid scars and found no significant benefit with height and induration but reported some satisfactory, but not significant, improvement in erythema. The percentages of patients who benefited from using

the ointment varied from ~15% for improvements in volume to ~67% reporting improvements in erythema and induration (values obtained from graph).[45]

Jenkins et al. (1986)[98] comparing the effect of three creams – base cream, Aristocort® A 0.1% and Vitamin E cream – used on post burn reconstructive surgery found there were no significant differences (p values not reported) between the groups for range of motion, scar thickness and graft size, and all were rated as having a good result. Similarly, in an evaluation of a basic moisturiser, Eucerin®, it was found that it also had some minor effects on scar pliability.[61] It did not have an effect on pigmentation, elevation and vascularity, and it was reported to significantly ($\alpha<0.05$) increase pliability by 10%.[61]

A significantly positive effect ($p<0.0025$) (means not provided) was found in a study looking at the effects of adding putrescine to a base moisturiser and comparing it to the base alone on the scar parameters of erythema and height using a scale the authors designed themselves.[48]

Use of a keratin gel (KeragelT®) when compared to aqueous cream on median sternotomy scars was found to result in more favourable scar scale scores ($p>0.05$) but was only statistically significant in a subset of subjects who initially had poor scarring.[57] The mean scores for the keratin gel versus aqueous cream groups were: MSS 12.00 vs. 12.58, patient-POSAS 16.70 vs. 17.85, observer-POSAS 15.00 vs. 16.55.[57] In that subset of poor scarring subjects, the MSS, patient-POSAS and observer-POSAS were statistically significant ($p=0.025$, <0.01 and 0.01), with scores in the treatment half being 12.22, 17.33 and 15.33 and in the control half being 14.22, 23.67 and 22.33, respectively.[57]

Provase® was shown to have a significant impact on itch (see Section 4. 3), however it failed to demonstrate any difference in comparison to the base cream for measures on the VSS and Mexameter (data was not provided).[58]

Demling and DeSanti[46] investigated the effect of doxepin cream which contains doxepin HCl. It acts to block histamine receptors. Its use was compared to a group who were using oral antihistamines and a skin moisturiser that did not have antihistamine properties. Erythema was measured using the VSS. The scar is rated from 0 to 3, with 3 being red to purple in colour. Erythema was reported as being scored at 2 +/- 1 as the initial value and stayed the same for the standard care group, whereas the doxepin group showed a significant (p value not reported) decrease over the one-, eight- and 12-week time points to a final value of 0.5 +/- 0.5.[46]

An unpublished study on Bio-Oil® described percentages of subjects who reported improvements in their scars redness (65%), pigmentation (62%), width (42%), height (42%), and elasticity (46%), with 65% overall seeing improvement in their scars.[82] There was no report on whether these numbers were statistically significant. Similarly the other unpublished study on Bio-Oil® reported results as the percentage of subjects who saw improvements in pigmentation (72%), pliability (67%), relief (67%) and thickness (61%), with 92% of subjects overall seeing improvement.[83] There was also no report on whether this result was statistically significant.

A summary of the studies that reported on scar parameter outcomes is outlined in Table 4-2 below.

Table 4-2: Summary of scar parameter outcomes of different moisturisers

Moisturiser type	Study/design/scar type	How it was measured	Effect
Imiquimod 5%	Berman, Frankel et al. 2005[94]/RCT/linear & HTS	VAS, 0 = best to 10 = worst. Induration.	Mean scores: Wk 8 - Imiqu. = 0.9, control = 0 (p=0.065). Beyond wk 8 - Imiqu = 0.4, control = 0.1 (p=0.078). Wk 39-46 - Imiqu = 0, control = 0 (p= N/A).
		VAS, 0 = best to 10 = worst. Erythema.	Mean scores: Wk 8 - Imiqu. = 5.4, control = 3.9 (p=0.004). Beyond wk 8 - Imiqu = 2.6, control = 2.1 (p=0.467). Wk 39-46 - Imiqu = 1.8, control = 2.1 (p= 0.122).
		VAS, 0 = best to 10 = worst. Pigmentary alterations.	Mean scores: Wk 8 - Imiqu. = 0.8, control = 0.4 (p=0.021). Beyond wk 8 - Imiqu = 2.6, control = 2.1 (p=0.467). Wk 39-46 - Imiqu = 1.8, control = 2.1 (p= 0.122).
	Prado et al. 2005[101]/RCT/linear	Beausang scale evaluating colour & contour of scar assessed by blinded surgeon, nurse and surgeon.	For all 3 assessors: treated scar scores - ranged from 9.5-10.4 & 2.7-3.3. Untreated scar scores - ranged from 14.8-16.2 6.7-8.7. All p <0.001.
Mederma® (onion extract gel)	Chung et al. 2006[97]/RCT/linear	VAS, 0=absent to 10= severe. Patient evaluated redness & Physician evaluated scar redness and thickness for each of the scar halves.	At 12 weeks differences between the 2 sides: Physician evaluation of redness (Onion extract=0.39+/-0.36, Petrolatum=0.16+/-0.13, p=0.3356), thickness (onion extract=0, Petrolatum=0, p=1.00). Patient evaluation redness (Onion extract=0.29+/-0.11, Petrolatum=0.29+/-0.13, p=0.9142).
Petrolatum			
Mederma® (onion extract gel)	Jackson & Shelton 1999[104]/quasiexperimental/linear	Patients rate erythema on a 5 point VAS. Photos taken.	No statistical difference between pre- & post-treatment scores (p-value not provided).
Aquaphor®		Patients rate erythema on a 5 point VAS. Photos taken.	Reduction in erythema between pre- & post treatment scores (p<0.01)
Mederma® (onion extract gel)	Perez et al 2010[56]/RCT/HTS & keloid	Scar volume measured with an alginate impression. Subjects and investigator rated the scar parameters volume, length, width, height, erythema, pigmentation on VAS 0-100, 0=best, 100=worst.	Reduction in volume (p=0.01), length (p=0.02), width (p=0.02) & induration (p=0.03). Showed improvement over the placebo (Cetaphil®) for induration (p<0.001) & pigmentation (p<0.001).
Scarguard®/HSE (0.5% hydrocortisone, silicone and VitE)			Reduction in volume (p=0.01), length (p=0.02), induration (p<0.01) erythema (p<0.01) & pigmentation (p<0.01). Showed improvement over the placebo (Cetaphil®) for induration p<0.001), pigmentation (p<0.001) & erythema (p=0.01).
Cetaphil® (as a placebo/control)			Mean reduction in volume (p=0.02)
Tretinoin Cream	Kwon et al. 2014[99]/RCT/HTS & Linear	Modified Vancouver Scar Scale (mVSS)	mVSS scores total significantly better for treatments compared to no treatment for weeks 8, 12 & 24. p<0.05.
			mVSS scores comparison between Tretinoin and Dermatix (liquid silicone) - no difference at any time points.
	Panabiere-Castaings 1988[80]/quasi experimental/keloid	Tape measure to measure area and volume assessed by taking impressions with dental moulages.	Mean change in volume over 12 weeks 2.6 (SD=3.9) to 2.1 (SD=3.0) - reduced p=0.04. Mean change in size over 12 weeks 864 (SD=1266.3) to 392 (SD=634.9) - reduced p=0.01.
	Jansen De Limpens 1980[81]/quasi experimental/HTS & keloid	Patient reported "improvement" also reported on colour, height and pigmentation. Objective result in "improvement".	Subjective improvement in 14 patients - reported as 79%. Objectively 23/28 in the excellent, good and fair category - reported as 77%. 13/21 patients reported decreased discolouration and height - reported as 64%. No statistical significance calculated.**

Continued next page

Tacrolimus ointment	Berman, Poochareon, et al. 2005[45]/case series / keloid	Volume of keloid measured by alginate impression. Induration determined by a set of rubber discs & recorded on VAS. Patient rated erythema.	% of patients who benefited by improvements in diameter - 50-30%, height 50%, volume 15%, erythema 67%, induration 67%. N=6. Percentages taken from a graph. Of those that showed improvement the percentage of change of the parameters measured that were greater than 40% were diameter, erythema, pain, tenderness (60% reduction) and pruritus (80% reduction). Not statistically significant.
Aristocort® A 0.1%	Jenkins et al. 1986[98] /RCT/HTS	Range of motion (ROM), average scar thickness at the edge of the graft and total surface area of the graft to measure contracture.	ROM increased, scar thickness reduced, graft size increased but no significant difference between all 3 moisturisers.
Vitamin E			
Aquatain (base cream)			
Eucerin®	Phillips et al. 1996[61]/RCT/HTS & keloid	VSS, scar size and volume measured with alginate impressions, photographs to record colour & texture.	Pigmentation, elevation and vascularity remained unaffected (α=0.23).
			Scar pliability increased 10% (α<0.05).
Putrescine	Dolynchuk et al. 1996[48]/RCT/HTS	Photographs of scars evaluated and given numeric rating using scale where descriptors include erythema (no erythema-erythema) and irregularity (flat-nodular).	The difference between the base cream only and base cream with putrescine was significantly lower scar ratings in the presence of the putrescine cream (p<0.0025) regardless of the order given.
Keratin gel (Keragel T)	Jina et al. 2015[57]/quasi experimental /HTS & linear	Manchester Scar Score (MSS) and Patient and Observer Scar Assessment Scale (POSAS).	At 6 months scar scores for all patients were more favourable in the treatment group compared with the Aqueous group, not statistically significant, p>0.05. Keragel vs Aqueous: MSS 12.00 vs 12.58, patient-POSAS 16.70 vs 17.85, observer-POSAS 15.00 vs 16.55.
Aqueous Cream			In the subgroup of patients with poor scars at 6 months there was an improvement with the keratin treatment that was statistically significant, p range <0.01-0.025. Keragel vs Aqueous: MSS 12.22 vs14.22, patient-POSAS 17.33 vs 3.67, observer-POSAS 15.33 vs 22.33.
Provase®	Nedelec et al. 2012[58]/RCT/HTS	Modified Vancouver Scar Scale (mVSS) and Mexameter (quantifies erythema and melanin).	The mVSS and Mexameter measurement of erythema did not vary significantly with time or treatment.
Doxepin	Demling et al. 2002[46]/quasi experimental/HTS	VSS colour component only 0-3, 3=red/purple	Erythema decreased from 2+/-1 to 0.5+/-0.5 over 12 weeks and was significantly (no p value) better than standard care group.
Bio-Oil®	MEDUNSA 2005[82] /RCT/HTS & linear	Changes in vascularity/redness, pigmentation, thickness/width, relief/height, & pliability/elasticity judged by the assessor.	The percentages of subjects who report improvements in their scars: redness (65%), pigmentation (62%), width (42%), height (42%), and elasticity (46%). Statistical significance not reported.
	proDERM 2010[83]/RCT/ unknown	POSAS - pigmentation (observer), pliability (observer), colour (patient) and relief/height (patient).	The percentage of subjects who saw improvements in: pigmentation (72%), pliability (67%), relief (67%) and thickness (61%). Statistical significance not reported.

No shading = no effect, green shading = positive effect
HTS = hypertrophic scar. VAS = Visual Analogue Scale. RCT = Randomised Controlled Trial
**% calculations reported in the published study do not match numbers of patients reported

4.3 Itch and pain

Scars are notoriously itchy or pruritic (a more scientific term used for itch) and keloid scars in particular have been observed to be painful. Itch is a common outcome measure in studies on scars and treatment for scar management. In an analysis of risk factors for hypertrophic scaring, it was found that itch correlated with moisturiser use with hypertrophic scars but felt this may have been due to patients seeking relief from itch by applying a moisturiser.[105] The authors found that there was a higher prevalence of hypertrophic scar formation in those patients who utilised scar treatment in the form of ointments, creams or lotions (p=0.038; chi-square test, data not clarified).[105] However, they also found that there was a significant difference between those with a hypertrophic scar and normotrophic scar regarding factors such as pain and itch (p=0.008; chi-square test, data not clarified).[105]

Studies reporting itch as the primary outcome and demonstrating a positive effect include Demling et al. (2002),[46] Nedelec et al. (2012)[58] and Ogawa et al. (2008)[55] Topical doxepin cream applied to the itchy area of a scar immediately decreased itch compared to the standard pharmacological approach, which was to take an oral antihistamine.[46] The Doxepin cream reduced the itch from 5 +/- 2 (measured on a VAS of 0-10) to 1 +/- 1 by week 12, whereas itch in the standard care group reduced to 3 +/- 1.[46] The differences between the doxepin and standard care group were significant at each time point of week 1, 8 and 12 but no p value was reported.[46]

Nedelec et al. (2012)[58] also found an improvement in itch in post burn scars with the use of Provase®, a protease containing moisturiser, when compared to the control, the base component only of Provase®. Due to the extent of the data produced the significant outcomes are summarised in Table 4-3.

Table 4-3: Summary of itch outcomes of Provase® used with scars, from Nedelec et al. (2012).[58]

Effect	Significance level
Reduction in duration of itch	p<0.05
Reduction in days per week participants experienced itch	p=0.03
Comparison between control and treatment group for number of times per day itch experienced from week 2.	p=0.03
Difference between baseline and week 2 for treatment group for number of times per day itch experienced	p=0.03
Mean itch TBSA when compared to baseline for treatment group at week 1	p=0.02
Mean itch TBSA when compared to baseline for treatment group at week 2	p=0.04
Mean itch TBSA when compared to baseline for treatment group at week 3	p=0.03
Patients reporting itch as bothersome in treatment group at all times compared to baseline	p=0.02-0.04
Number of patients reporting itch as bothersome in treatment group compared to control group at week 4	p<0.05
Reduction in how annoying itch was in treatment group in week 3	p=.0.05
Reduction in how annoying itch was in treatment group in week 3	p=0.03
Reduction in how unbearable itch was in treatment group	p=0.002-0.04
When comparing treatment to control with how unbearable itch was at week 2	p=0.03

TBSA: total body surface area

Ogawa and Ogawa[55] also found an improvement in itch but only after two months of treatment with Mugwort lotion where 11/14 (78.6%) of subjects showed improvement, compared to the control heparinoid ointment regions where 5/14 regions showed improvement (p=0.027). The authors also noted that most participants had previously tried systemic anti-allergenic drugs and found them to be ineffective.[55]

Onion extract (Mederma®) was no different to petrolatum for the management of itch (at 12 weeks mean scores onion extract 0.86 +/- 0.047 vs petrolatum 0.57 +/- 0.027, p=0.4533), burning and pain (same scores for both at 12 weeks: onion extract 0.043 +/- 0.02 vs. petrolatum 0.043 +/- 0.02, p=1.0000) on post-surgical scars.[97] Jackson et al. (1999)[104] also found Mederma® to have no statistically significant difference in the degree of itch reported by patients' pre- and post-treatment with the cream (p value not provided).

Base creams used in studies as a control or placebo can also generate results on their effect, or lack thereof, on scars. Aquaphor® was found to cause no statistically significant change to itch (scores and p value not provided). [104] Eucerin® was found to improve itch initially in hypertrophic scars and keloids but then it returned to near initial values.[61] Rating of the itch on a VAS from 0-10 changed from 1.7 +/-3.1 in week 0 to 0.9 +/- 1.3 (week 2), 1.5 +/- 2.1

(week 4) to 1.4 +/- 2.11 and was significantly reduced, $p<0.03$.[61] Scar pain also showed a similar pattern with VAS scale mean scores ranging from 1.4 to 0.7 but was reported to be somewhat reduced, $p<0.08$.[61]

Tacrolimus ointment resulted in approximately 30% of patients reporting improvements in pain, approximately 60% reporting a decrease in tenderness, and approximately 80% reporting a decrease in pruritus but the result was reported as not statistically significant (p value not reported).[45] The values were approximate as they were obtained from the graphical representation of percentage of patients reporting improvements in those symptom.[45]

Tretinoin cream was reported to have improved pain in 14 patients out of 21 participants; statistical significance was not reported. This was reported as 79% but the actual calculation was 67%.[81]

A summary of the studies examining moisturisers that had an effect on itch and pain experienced by patients with scars is outlined in Table 4-4.

Table 4-4: Summary of itch and pain outcomes of different moisturisers

Moisturiser type	Study / Design / Scar type	How it was measured	Effect:
Doxepin	Demling et al. 2002[46]/quasi experimental/HTS	VAS 0-10 to quantify the degree of itch.	Itch scores decreased from 5 +/- 2 to 1 +/- 1 in the Doxepin group compared to the standard care group which reduced to 3 +/- 1. Differences were significant at wk 1, 8 & 12, no p value.
Provase®	Nedelec et al. 2012[58]/RCT/HTS	VAS 0-10 itch intensities (before moisturiser and 30min after), description of itch during the past week based on units of duration and Questionnaire for Pruritus Assessment for Burn Survivors.	See table 4-3 for summary of outcomes and statistical significance.
			No difference between groups reporting their itch as annoying. For itch intensity at its worst or best and for general or local pain intensity - no significant difference between control and treatment (p value not given).
Mugwort Lotion	Ogawa & Ogawa 2008[55]/quasi experimental/HTS	Survey of itch severity on a scale of 0-4, 0 = no symptoms, 4 = severe itch.	After 1 week: 40% (6/15) treated regions were improved, 21.3% (2/15) control regions improved. No difference between treatment and control - p=0.107.
			At 2 months: 78.6% (11/14) treated regions were improved, 35.7% (5/14) control regions were improved. Significant difference between treatment and control p=0.027.
Mederma® (onion extract gel)	Chung et al 2006[97]/RCT/linear	VAS rate itch, burning and pain from 0 (absent) to 10 (severe)	No statistical difference between Mederma® and petrolatum for itching burning and pain. At 12 weeks: itchiness - onion extract 0.86 +/- 0.047 vs petrolatum 0.57 +/- 0.027 (p=0.4533), burning – onion extract 0.043 +/- 0.02 vs petrolatum 0.043 +/- 0.02 (p=1.0000), pain - onion extract 0.043 +/- 0.02 vs petrolatum 0.043 +/- 0.02 (p=1.0000).
Mederma® (onion extract gel)	Jackson & Shelton 1999[104]/quasi experimental/linear	VAS, 5 point scale, rate itch (no details of which features of itch)	No statistical difference (no p value) between pre and post treatment with Mederma® when evaluating itch.
Aquaphor®			No statistical difference (no p value) between pre and post treatment with Aquaphor® when evaluating itch.
Eucerin®	Phillips et al. 1996[61]/RCT/HTS & keloid	VAS rate itch, pain. 0=none, 10=unbearable.	Scar itching mean scores significantly reduced (p<0.03): week 0: 1.7 +/-3.1, week 2: 0.9 +/- 1.3, week 4: 1.5 +/- 2.1, week8: 1.4 +/- 2.11.
			Scar pain mean scores somewhat reduced (p<0.08): 1.4 +/- 3.1, week 2: 0.7 +/- 1.43, week 4: 0.9 +/- 1.8, week 8: 0.8 +/- 1.8.
Tacrolimus ointment	Berman, Poochareon et al. 2005[45]/case series/keloid	Patients assessed their keloid for tenderness, pain and pruritus using a VAS.	Around 30% of patients had improvement in pain. Of those that had improvements there was a 60% decrease in tenderness, 80% decrease in pruritus, results not statistically significant (p value not provided).
Tretinoin cream	Janssen De Limpens 1980[81]/quasi experimental/HTS & keloid	Questionnaire (12 questions) completed by patients at completion of the study on improvement of pain and/or itching.	Improvement in 14 patients (reported as 79% but number of participants is 21, e.g. should be 67%).

No shading = no effect, green shading = positive effect
HTS = hypertrophic scar, VAS = Visual Analogue Scale, RCT = randomised controlled trial

4.4 Trans-epidermal water loss and hydration

There was only one study that reported TEWL comparing the moisturiser Alhydran against the performance of liquid silicone gels and silicone gel sheets.[19] Hoeksema et al.[19] used a tape stripping model to simulate a scar. They found that when compared to the control area, Alhydran performed significantly better ($p<0.05$, scores not provided) in terms of decreasing TEWL than Dermatix and Kelocote (liquid silicone gels). It also worked just as well as the BAP Scar Care gel (liquid silicone gel) in how occlusive it was and these both lasted longer than the other liquid silicones ($p<0.05$, scores not provided).[19] They also demonstrated that Alhydran could increase hydration or water content of the skin to the same level as thin silicone gel sheets and Dermatix liquid silicone gel (but not Kelocote liquid silicone gel) but all values were the same one hour after removal.[19]

4.5 *In vitro* outcomes

Four studies examined the effects of moisturisers by using *in vitro* methods. Dematte et al. (2011)[79] applied Tretinoin cream for one year on facial hypertrophic scars then obtained skin biopsies. They then examined resistance, elastance, collagen density and elastic fibre density of the skin biopsies. They found that there was a significant decrease in the mean values of resistance by 31.4% ($p=0.003$) and elastance by 14.8% ($p=0.047$), but there were no histological differences in the distributions of the extracellular matrix components between treated and untreated specimens.[79]

Riaz at al.[49] obtained samples of skin tissue from patients with hypertrophic or linear sternotomy scars. They found that increasing staining for type 1 procollagen (PCP1) correlated with increased macroscopic severity of scar (Spearman rank correlation coefficient = 0.604, $p<0.001$).[49] However, after they applied Dermovate (steroid based) cream for seven days to scars and examined samples for a change in PCP1 staining, they found there was no effect on PCP1 staining when compared to control sites.[49]

Ding et al. (2015)[103] obtained fibroblasts from active keloid scars, mixed them with different concentrations of Wubeizi ointment and measured cell proliferation rates as a percentage of the control cells. They found with increasing concentration the inhibitory effect on proliferation increased with a significant difference between the high and low dose groups.[103] For example, the mean OD (optical density value) at 12 hours of the control group was 0.701 +/- 0.104 compared to the high dose group which was 0.364 +/- 0.999 ($p<0.01$).[103] At 24 hours, the mean OD values for the control group were 0.554 +/- 0.130 compared to the high

dose group which was 0.233 +/- 0.041 ($p<0.01$), and at 36 hours the values for the control and high dose group were 0.413 +/- 0.033 and 0.126 +/- 0.018, respectively ($p=<0.01$).[103] The inhibition was demonstrated by an increased percentage of fibroblasts in the S phase resulting in phase arrest and reduced numbers of dividing cells.[103] The percentages of keloid fibroblasts for the control group was 37.32 +/- 2.93 compared to 60.35 +-/ 5.75 ($p<0.01$).[103]

Jacob et al. (2003)[31] also examined keloid scars. These were treated for two to eight weeks with imiquimod, or no treatment, and then the tissue was excised, the ribonucleic acid (RNA) extracted and complementary DNA (cDNA) probes synthesised.[31] Findings demonstrated that there was a statistically significant alteration in the expression of the genes associated with apoptosis.[31] Capsase 3 reduced from a mean value of 0.81 with the vehicle cream, to 0.05 with Imiquimod ($p<0.05$). In addition, DNA fragment factor 45 was elevated in patients treated with Imiquimod (0.52) compared to those treated with the vehicle cream where the mean value was <0.01 ($p<0.05$).[31] These results were felt to suggest a mechanism of action for imiquimod cream.

A summary of the studies examining moisturisers that have an effect on *in vitro* outcomes of scars is outlined in Table 4-5.

Table 4-5: Summary of in vitro outcomes of different moisturisers

Moisturiser type	Study/design/scar type	How it was measured	Effect
Tretinoin	Dematte et al 2011[79]/quasi experimental/HTS	Measured elastance and resistance of excised skin samples post treatment using a mechanical oscillation analysis system.	Resistance: decrease in mean values by 1.4% (p=0.003). Elastance: increased 14.8% (p=0.047)
		Microscopically examined collagen and elastic fibre density.	No difference in the extracellular matrix between treated and untreated samples.
Dermovate	Riaz et al 1994[49]/quasi experimental/HTS	Samples obtained after application of Dermovate, staining of tissues for type 1 procollagen (PCP1).	No effect on PCP1 staining when compared to control site.
Wubeizi ointment	Ding et al 2015[103]/quasi experimental/keloid	Cell proliferation rates of fibroblasts subjected to different concentrations of the Wubeizi ointment.	Increased concentration inhibits proliferation of fibroblasts. Control vs high dose group: At 12 hrs - 0.071+/-0.104 vs 0.364+/-0.076, 24hr – 0.554+/-0.130 vs 0.233+/-0.041, 36hr – 0.413+/-0.033 vs 0.126+/-0.018. All p<0.01.
		Measurement of the DNA cycles at different Wubeizi concentrations.	Increased number of fibroblasts in the S phase arrest at higher concentration. Control vs high dose: 37.32+/-2.93 vs 60.35+/-5.75 (p<0.01)
Imiquimod 5%	Jacob et al 2003[31]/quasi experimental/keloid	RNA extracted to measure expression of genes associated with apoptosis.	Significant change in expression of genes associated with apoptosis, Capsase 3 (reduced from 0.81 to 0.05) and DNA fragment factor 45 (increased from 0.52 to <0.01) when compared with control (p<0.05).

No shading = no effect, green shading = positive effect
HTS = hypertrophic scar

4.6 Recurrence of excised keloids treated with 5% imiquimod – a meta-analysis

All seven studies included in meta-analysis involved excising a stable keloid. A stable keloid was usually defined as one which had been present for more than one year and which had not had any treatment for the previous three months. Post excision, subjects were instructed to immediately begin application of imiquimod cream for six[109, 111] or eight[30, 106, 108, 110, 112] weeks. All studies, except one,[106] instructed subjects to apply the cream nightly or daily. Participants in the study by Berman et al. (2009)[111] applied imiquimod for a period of six weeks: nightly for two weeks then three times a week for the next four weeks. As such, it was deemed that there was clinical homogeneity and meta-analysis was possible. In terms of methodological heterogeneity, the studies were different in their design, however all were included so as to provide the most comprehensive overview of the effect of imiquimod. To obtain this final determination, all studies were included in a meta-analysis forest plot (Table 4-6), outlined below in Section 4.6.1. However, as there was variation in the data (see Figure 4.1), further subgrouping was employed to determine whether the surgical technique (Section 4.6.2) or the location of the keloid (Section 4.6.3) had effects on the outcome.

4.6.1 Meta-analysis of all included studies in imiquimod group

As mentioned above, all seven studies examined treated stable keloids for either six or eight weeks with a similar dosage by applying the cream daily.

As shown by Figure 4-1, meta-analysis revealed that 39% (95% CI = 8.4% to 74.4%) of subjects had scar recurrence when using imiquimod post excision of a keloid scar. Based on the guide to interpretation of the I^2 value described by Deeks et al. (2008),[114] the I^2 value of this meta-analysis of 87.5% (95% CI =75.7% to 92.2%) is greater than 75% and therefore indicates *considerable heterogeneity*. Essentially, given this heterogeneity, there is no confidence in the final effect size.

Due to this variation, the results of this meta-analysis should not be considered as clinically informative but does not represent trustworthy information regarding the average number of participants who will have a recurrence of their keloid following treatment with imiquimod. To further investigate the heterogeneity seen in this meta-analysis, subgroup analyses were conducted and are reported below.

Table 4-6: Meta-analysis of all imiquimod studies

Study	Responding	Total	% weight (random)
Berman et al. 2009	3	8	14.3
Berman & Kaufman 2002	0	11	14.9
Cacao et al. 2009	9	9	14.5
Chuangsuwanich 2007	10	35	16.2
Malhotra et al. 2007	3	3	11.7
Martin-Garcia 2005	3	8	14.3
Stashower 2006	0	8	14.3

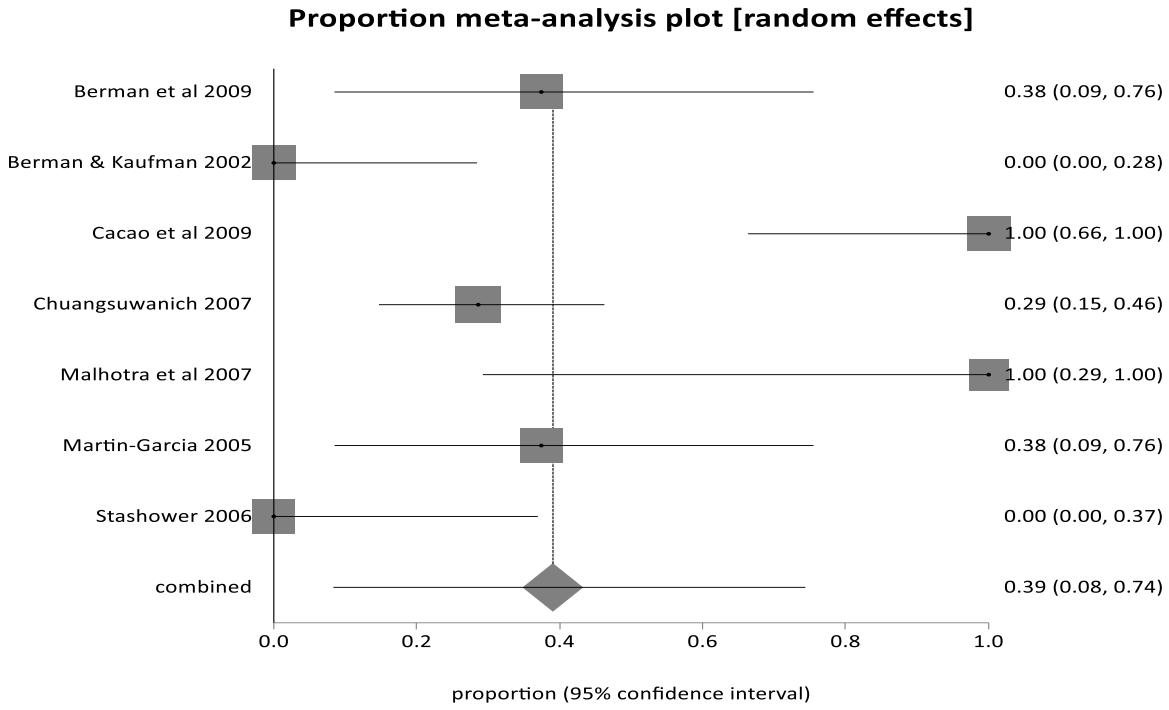

Figure 4-1: Meta-analysis of all imiquimod included studies, I2 (inconsistency) = 87.5% (95% CI = 75.7% to 92.2%)

4.6.2 Meta-analysis – surgical technique

On closer analysis of the studies, it was noted that some studies utilised different excision techniques and this may in turn have affected healing times and resultant scarring, as discussed in Section 1.3.2. As such, subgroup analysis of three[30, 106, 112] studies that utilised primary excision with bilayer closure was possible. Meta-analysis of these studies is shown in Table 4-7 and Figure 4-2.

Similar to the results for the whole group (Figure 4-1), the forest plot in Figure 4-2 demonstrates that a mean of 41.2%, (95% CI = 0 to 96.1%) of subjects who had a primary excision and bilayer closure would have a recurrence of their keloid. Statistically this is shown by the I^2 value being 94.2% (95% CI = 86.4% to 96.6%), demonstrating that the results have *considerable heterogeneity*. Essentially, given this heterogeneity, there is no confidence in this final effect size.

Table 4-7: Meta-analysis of studies utilising primary excision and bilayer closure as the surgical technique

Study	Responding	Total	% weight (random)
Berman & Kaufman 2002	0	11	32.9
Cacao et al. 2009	9	9	32.4
Chuangsuwanich 2007	10	35	34.7

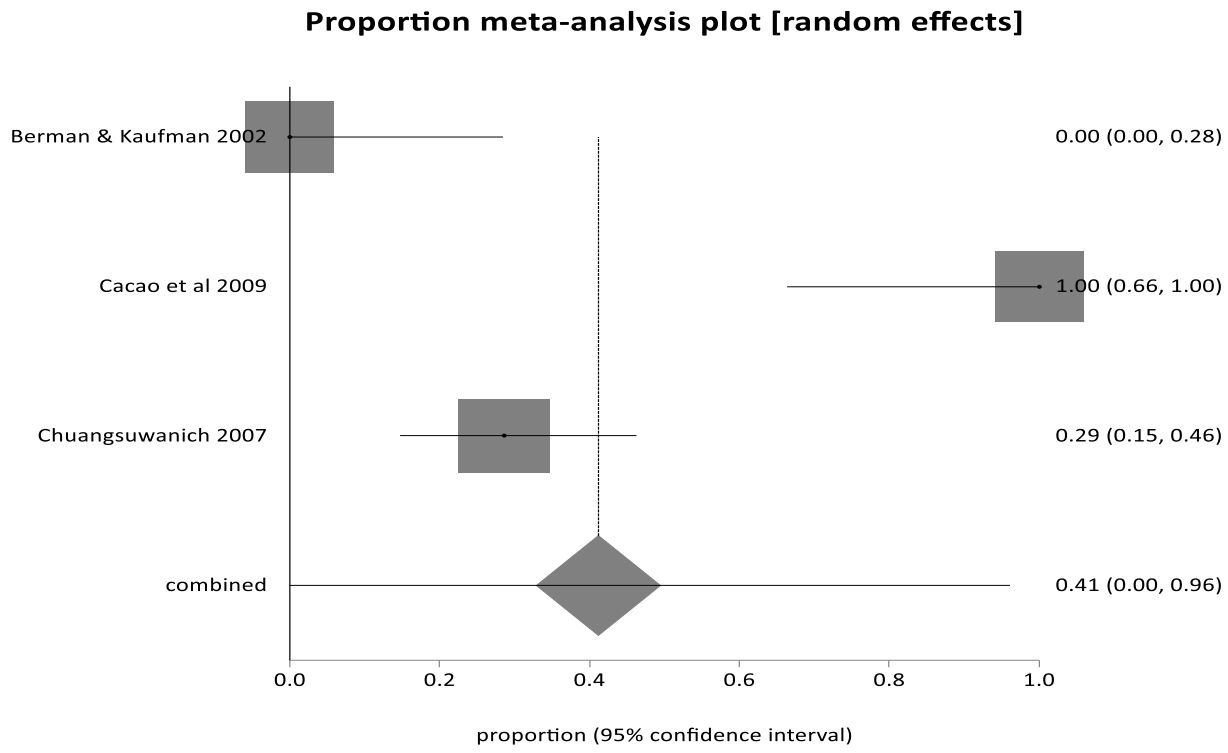

Figure 4-2: Meta-analysis of studies utilising primary excision and bilayer closure as the surgical technique, I2 (inconsistency) = 94.2% (95% CI = 86.4% to 96.6%)

There were four studies[108-111] that utilised surgical methods where the keloid was excised by shaving or tangential excision leaving an open wound to heal by secondary intention (Table 4-

8). The imiquimod cream was then applied to the wound despite it still being open. These studies are represented on a forest plot (Figure 4-3). The meta-analysis of those studies demonstrates that 36.9% (95% CI = 1.9% to 81.2%) of subjects had recurrence of their keloids. As these studies produced an I^2 value of 78.1% (95% CI = 0.5% to 90%), the results have *considerable heterogeneity*. Essentially, given this heterogeneity, there is no confidence in this final effect size.

Table 4-8: Meta-analysis of studies utilising shaving or tangential excision that result in healing by secondary intention

Study	Responding	Total	% weight (random)
Berman et al. 2009	3	8	26.4
Malhotra et al. 2007	3	3	20.8
Martin-Garcia 2005	3	8	26.4
Stashower 2006	0	8	26.4

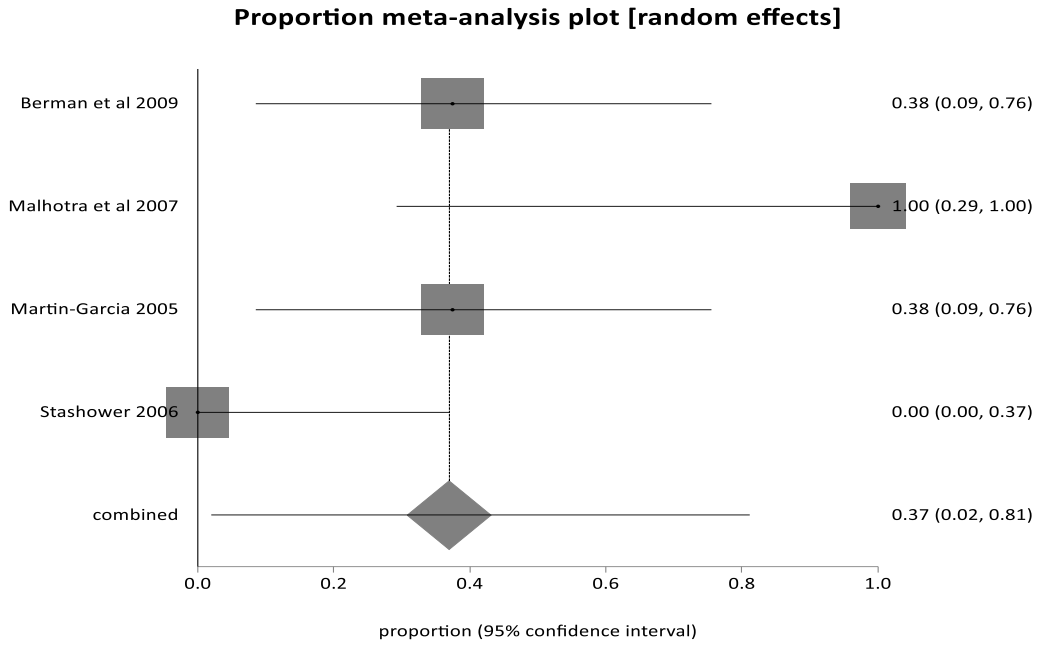

Figure 4-3: Meta-analysis of studies utilising shave/tangential excision that result in healing by secondary intention, I2 (inconsistency) = 78.1% (95% CI = 0.5% to 90%)

4.6.3 Meta-analysis – location of keloid

Some authors of these included studies noted that body location may have had an effect on the outcome of recurrence of a keloid post excision. Certain areas of the body under tension may be prone to recurrence (such as the chest) whilst those areas of low tension (such as the earlobe) may be prone to less recurrence (see Section 1.4.3). To further investigate whether this is a reasonable assumption, those studies that specified earlobe keloids were plotted together (Figure 4-4), and studies on keloids in other locations, mostly on the trunk, were plotted together (Figure 4-5).

Table 4-9 and Figure 4-4 collate and plot the studies which examined earlobe keloid excision. An assumption was required for the Berman and Kaufman[30] study where there were initially 12 patients with 13 keloids – 12 earlobe keloids and one back keloid. Two patients were lost to follow-up resulting in 10 patients with 11 keloids. It was assumed that the two patients lost to follow-up had single earlobe keloids and that the final 10 patients therefore comprised 10 earlobe keloid and one back keloid. Although they had a variety of locations in their study, Chuangsuwanich and Gunjittisomrarn[106] did report a 1/22 recurrence rate for those keloids on the earlobes. The other two studies[108, 109] included subjects with only earlobe keloids.

The meta-analysis of earlobe keloid subjects (Figure 4-4) shows that 5.4% (95% CI = 0% to 21.7%) of these patients showed recurrence of keloids on the earlobe with post-operative imiquimod application. The I^2 value is less than the previous forest plots, with a value of 52.9% (95% CI = 0% to 82.6%), demonstrating a greater degree of similarity but still having *substantial heterogeneity*.

Table 4-9: Meta-analysis of earlobe keloids

Study	Responding	Total	% weight (random)
Berman & Kaufman 2002	0	10	24.1
Chuangsuwanich 2007	1	22	32.8
Martin-Garcia 2005	3	8	21.6
Stashower 2006	0	8	21.6

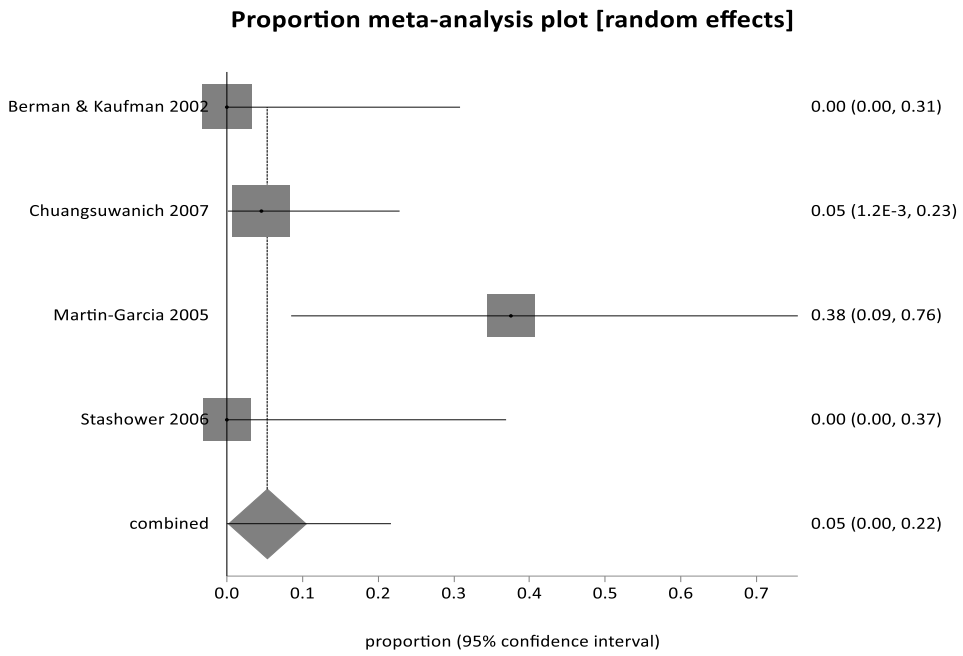

Figure 4-4: Meta-analysis of earlobe keloids, I2 (inconsistency) = 52.9% (95% CI = 0% to 82.6%)

A meta-analysis of recurrence of keloids located in other areas of the body under higher tension than the earlobe resulted in generation of a forest plot (Table 4-10 and Figure 4-5). Of the studies included, Berman et al[111] did not report the exact location of keloids but did report them as being in many different locations. Berman and Kaufman[30] had one back keloid which did not recur and this was included in the meta-analysis. On examination of the results reported by Chuangsuwanich and Gunjittisomrarn,[106] it was found that there was recurrence of 5/6 keloids on the chest, 4/7 keloids on the neck and shoulder, resulting in 9/13 recurrences for this study in the areas other than the earlobes. The other included studies investigated keloids on the chest[110, 112] and shoulder.[112]

The meta-analysis shows that 76.75% (95% CI = 36.1% to 100%) of all subjects had recurrence of their keloids on other areas of the body, particularly the trunk, with the use of imiquimod post-operatively. However, as the I^2 value is 70.5% (95% CI = 0% to 86.4%), this represents *substantial heterogeneity*. Essentially, given this heterogeneity, there is no confidence in this final effect size.

Table 4-10: Meta-analysis of keloids in other (not earlobe) locations on the body

Study	Responding	Total	% weight (random)
Berman et al. 2009	3	8	23.1
Berman & Kaufman 2002	0	1	10.7
Cacao et al. 2009	9	9	23.7
Chuangsuwanich 2007	9	13	25.4
Malhotra 2007	3	3	17.1

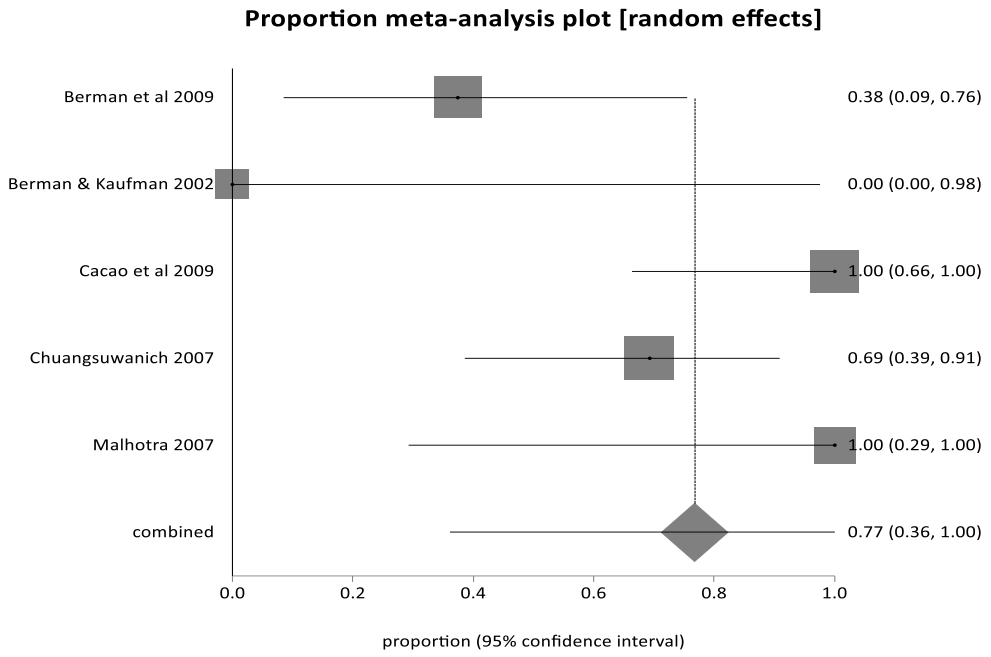

Figure 4-5: Meta-analysis of keloids in other (not earlobe) locations on the body, I^2 (inconsistency) = 70.5% (95% CI = 0% to 86.4%)

4.7 Adverse events

Adverse events were frequently reported in studies examining moisturiser effects on scars. Even basic moisturisers such as Aquatain can elicit adverse reactions in 6% of participants.[98] Eucerin® caused increased itching in one participant out of ten in the moisturiser group.[61] Berman et al. (2005) also reported two out of 18 participants in the control group who were given the 'vehicle cream' had adverse reactions.[94] Nedelec et al. (2012), when looking at itch and pain, reported that the base moisturiser resulted in an adverse event: two participants experiencing increased pain and itch. This helped to strengthen the argument for the effect of itch by the treatment moisturiser (Provase®) as they had no such adverse events.[58]

One person stopped using the Mugwort lotion because it caused a cold sensation.[55] Interestingly the vitamin E addition to a basic moisturiser resulted in a large proportion of

participants – 33%[96] and 20%[98]– having reactions. However, these adverse events may have been related to the type of vitamin E added to the base cream, that is, oral vitamin E capsule contents were physically added to the cream. Doxepin resulted in mild and transient somnolence (drowsiness) in 15% of patients which resolved after two to three days with continued use and one patient had a localised skin reaction and was removed from the study.[46]

The studies investigating the effects of imiquimod 5% on scar parameters and cosmesis appear to consistently report participants needing a rest period at around week 2-3.[94, 101] The studies included in the imiquimod group for meta-analysis also reported the same issue. Tacrolimus ointment had a high incidence of causing an adverse reaction as one patient was removed from the study for flu like symptoms, itch, burning and pain at the treatment site.[45] In addition, five out of the six participants experienced localised itch for up to two hours for the first few days of treatment.[45]

Of the topical steroids, putrescine caused only one person to have a rash and withdraw and 13.5% of participants in the Aristocort® A 0.1% study had adverse reactions including striae and delayed healing of open areas but it was reported the reactions resolved with discontinued use and removal from the study.[48, 98] The use of Mederma® (topical onion extract) resulted in three (50%) of subjects discontinuing the study when it was being evaluated for its effectiveness on scars post skin cancer removal.[104] However there was only one subject with an acneiform-like eruption at the site of application in another study.[56]

Tretinoin cream resulted in contact dermatitis in two out of nine participants which resulted in them abandoning the study.[80] It also caused a burning sensation in three out of seven participants during its first week of use but resolved without any special treatment.[99] It resulted in half of the patients in another study needing to reduce their application frequency after redness and/or scaliness of the skin.[81] In the longer term study of tretinoin cream, one third of the subjects exhibited temporary signs of dermatitis but continued on without any recurrence after a one-week rest period.[79] In addition, in the same study, three patients had hyperpigmentation and one exhibited mild telangiectasis (dilation of capillaries).[79]

In the study testing Lumiere Bio-Restorative Eye Cream, three subjects withdrew due to redness and itching at the application site.[100]

5. Discussion and conclusions

This chapter discusses the results of the systematic review presented in the preceding chapters. To aid clinicians and consumers to apply the results clinically, the effects of moisturisers are grouped according to the cost and availability of the product. This review has a number of limitations that impact on the conclusions that can be drawn; these limitations include the quality of the included studies and the means and methods used to measure outcomes. Suggestions for further research especially for common or basic moisturisers are outlined.

5.1 Effect of moisturisers on outcomes

The results of this systematic review provide no definitive evidence to inform a decision about which moisturiser has outstanding overall effectiveness to manage scars. Rather, to obtain a specific outcome, the clinician may recommend a specific moisturiser. Conversely, the results of this systematic review can inform the clinician as to which moisturisers are not effective.

Patients frequently have questions or opinions about a product they have seen advertised or have heard about from other clinicians, family and friends. The clinician will consider and discuss with the patient many factors such as the scar size, the effect on the person's emotional and physical wellbeing, and the cost of various options, and subsequently formulate a recommendation. One of the most significant factors influencing a service (if a product is provided) or the consumer's choice (if they are required to self-fund) is the cost and availability of a product. Therefore, the clinician should be armed with the knowledge outlined below to guide their decision when selecting a product.

5.1.1 Treatments with an effect

The moisturisers that have a significantly positive effect on *cosmesis* includes Lumiere Bio-Restorative Eye Cream, Tretinoin, Scarguard®/HSE, and Cetaphil® (see Table 4-1). The moisturisers which have a significantly positive effect on *scar parameters* include Scarguard®/HSE, Cetaphil®, Tretinoin, Eucerin®, putrescine and Doxepin (see Table 4-2). Those that have a significantly positive effect on *itch and pain* include Doxepin, Mugwort Lotion and Eucerin® (see Table 4-4). Tretinoin and Wubeizei ointments were shown to have a significant positive effect on *in vitro* outcomes (see Table 4-5). Although imiquimod also

had a positive effect, it had not been included in the group to be recommended as it had no effect on many of the other outcomes as mentioned above.

Moisturisers that can be recommended are presented according to availability and cost. This is clinically relevant for clinicians and consumers to determine which is best for their needs. A summary of the recommendations, outcomes and scar types is contained in Table 5-1 at the end of this section.

5.1.1.1 Prescription only moisturisers that have an effect on scars

There were only two prescription-only moisturisers that can be recommended as they had a statistically significant beneficial effect on scars: putrescine (Fibrostat®) and Doxepin. Putrescine may be beneficial in reducing the parameters of hypertrophic scars but further studies are needed with clear descriptions of the study design and subjects. Despite the author reporting that a total of 128 patients had been treated with topical putrescine and minimal adverse events (one person with a rash),[48] this treatment has not been investigated in any further studies, nor become part of current regular management of scars. A search of Fibrostat via Google (May 2018) revealed that a clinical trial had been registered for December 2017 at the same location (University of Manitoba) as the original study but no results have been posted.[115] There is also an article suggesting that recruitment was occurring in 2004 for another study by the same author of the original study but this did not proceed to publication.[116] However, a website (www.fibrostat.com) was located, containing documents, one of which is a word document of a paper delivered in 2016. This contains minimal detail on the results an unpublished RCT examining the effect of Fibrostat® on post breast reduction scars. The reported results were significantly favourable when subjectively reported by patients and objectively measured by durometry (measures hardness) but not when measured by a scar scale (MSS). Cost data could not be obtained for this prescribed moisturiser, however, considering it contains an active drug it is likely to be costly and can therefore only be recommended for small cosmetically sensitive hypertrophic scars.

Topical Doxepin appeared to be more effective than an oral antihistamine in the reduction of burn scar itch and it was also shown to reduce erythema of the scars. However, as mentioned previously (section 3.5.1) patients were six weeks to three months post burn when the itching was at its worst and this period was the point of highest scar activity and erythema.[46] There is also potential for scars to naturally begin to reduce in activity and therefore in erythema and itch intensity. Topical Doxepin may be recommended to reduce early burn scar itch but a

study utilizing a control group would be recommended to clarify the significance of its effect in comparison to a basic moisturiser.

5.1.1.2 High cost/over the counter moisturisers that have an effect on scars

There were seven high cost/over the counter moisturisers which showed significantly positive effects on scars. They are tretinoin/retinoic acid/vitamin A, Wubeizei, Lumiere Bio-Restorative Eye Cream, Scarguard® HSE, Provase®, Mugwort Lotion and Alhydran. Considering their high cost, they are unlikely to be recommended for large scars but would be more suited to smaller, cosmetically sensitive scars.

There were four studies that examined the effects of tretinoin/retinoic acid/vitamin A on scars.[79-81, 99] Three studies used the moisturiser at a concentration of 0.05%, whereas Kwon et al. (2014)[99] used the 0.025% variation of the moisturiser. They found that patients with postoperative wounds had no difference in scar scale scores when comparing the scores to those subjects that used Dermatix, a liquid silicone gel.[99] Hoeksema et al. (2013)[19] also measured the effects of Dermatix. They reported that Dermatix reduced TEWL and hydrated the stratum corneum (however, Alhydran and a silicone gel sheet were more effective in this regard).[19] As a result, the 0.025% variation of tretinoin may have been no more effective than Dermatix, and both were inferior to Alhydran. Tretinoin can be recommended for small (due to cost) cosmetically significant hypertrophic or post-surgical scars which cause cosmetic concerns due to tightness or contracture of the scar. However, patients should be advised regarding the risk of hyperpigmentation and that continued use would also be required to ensure clinical gains.

Wubeizi ointment contains the ingredient Wu Bei Zi, a tannin produced by a tree when infected by aphids. The author referenced his own previous study (not in English) in the introduction to claim that Wubeizi ointment was effective in treating keloids and therefore completed a study to examine the effects of different concentrations of Wubeizi ointment on keloid fibroblast proliferation and demonstrated significant effects.[103] Wubeizi cannot be strongly recommended for the management of keloid scars without further investigation of its effects on scars and any adverse events.

Eyelids treated with Lumiere Bio-Restorative Eye cream was found to have a better cosmetic outcome than its control (no moisturiser) as they reached maturity earlier but only in the early stage of the study (week 10). At completion of the study, just four weeks later, there was the

same improvement in all of the eyelid scars.[100] As the patients were not applying a control moisturiser they may have been biased in their ratings of the cosmetic effect. Considering the cost and the additional four weeks required to achieve the same outcome, Lumiere Bio-Restorative Eye Cream is not recommended for patients with new post-operative linear scars.

Scarguard® HSE did show significant improvement in investigator and subject rated cosmesis of keloid and hypertrophic scars.[56] Hypertrophic and keloid scars also had a reduction in volume, length, induration, erythema and pigmentation over the 16-week period of the study.[56] Scarguard® HSE showed improvement over the placebo (Cetaphil®) for induration, pigmentation and erythema.[56] However, as Scarguard® HSE is not available and the study had a mix of scar types and small numbers in each group it is not strongly recommended as a consideration for scar treatment.

The study on Provase® was reported as being a pilot study, however, there was an extensive data set that allowed the authors to conclude that the treatment group was having the itch cycle interrupted compared to the control group.[58] Provase® can be recommended for reducing itching of post burn scars in the early phase (one to three months). However, more data is needed to determine whether it is effective in scars more than three months post injury. The authors also acknowledged that the study was not statistically powered and was only conducted over a four-week period.[58] Had the study been extended, the following could have been determined: if the effect had worn off, if the itch had returned or if the itch had been resolved. In addition, it would be of interest to establish if the itch returned after cessation of application.

Although Ogawa et al (2008)[55] found no difference in severity of itch between treatment and control (a heparinoid ointment – no further details). After one week they did find a difference between the groups after two months of applying the lotion to hypertrophic burn scars. This is in contrast to the study by Nedelec et al. (2012)[58] on Provase® who noted a much more rapid response to the moisturiser. The authors concluded that topically applied antihistamines may be more effective than systemic ones as many of the participants had trialled systemic antihistamines with no effect.[55] Mugwort lotion may be effective in reducing itch of post burn hypertrophic scars but the effect may take anywhere between one week and two months. Other side effects or adverse events were not clearly outlined and require clarification before recommending this product.

Alhydran was included in the study by Hoeksema et al. (2013)[19] as it had reportedly been used by patients at the author's clinic, and the patients reported that they preferred it over other moisturisers. The study was based in Belgium and included products, except Kelocote and Dermatix, not available in Australia. It has only been recently (May 2018) that Alhydran has become available in Australia. The effect of Alhydran on TEWL and hydration of tape stripped skin of normal subjects was examined.[19] The authors compared the outcomes to those of silicone gel sheets and the liquid silicones, including Dermatix and Kelocote, that are also available in Australia.[19] This first study of its kind demonstrated that Alhydran was able to reduce TEWL more effectively than Dermatix and Kelocote.[19] Alhydran also increased hydration as effectively as a thin silicone gel sheet and Dermatix, but Kelocote was not as effective as either of these.[19]

The measurement of TEWL is an important outcome measure in the management of scars. It has been proposed that the effectiveness of silicone gel sheets is attributed to their capacity to reduce and normalise the rate of TEWL[18, 117] which is elevated in hypertrophic and keloid scars.[17, 18] Alhydran can hydrate and reduce the TEWL of skin that has had its barrier function of the stratum corneum disrupted so that there is a high rate of TEWL such as that which occurs in scars. As a result, it can be recommended to patients with hypertrophic and keloid scars. The Hoeksema et al. (2013) study is also useful for those that utilise the products Dermatix and Kelocote as they would now have to question their effectiveness.

5.1.1.3 Low cost/over the counter moisturisers that have an effect on scars

In some studies, moisturisers that were included as controls showed they could also have a significant effect on improving scar outcomes. These included Cetaphil® and Eucerin®, in particular. These moisturisers are readily available from retail outlets and are of low cost (as outlined in Section 1.6.1.3) and are therefore most suited to those patients with a large scar surface area such as major burns.

Cetaphil® was shown to have a significantly positive effect on reducing scar volume and subject rated cosmesis but the improvement in cosmesis was not significant when measured by the investigators.[56] Considering the low cost and ease of availability of this moisturiser, it may well be that this basic moisturiser may have a positive outcome on the cosmesis and scar parameters of hypertrophic and keloid scars. Nonetheless, the quality issues identified in this study makes it difficult to recommend Cetaphil® with any confidence.

Eucerin® is commonly recommended to burn patients in the US.[5] In a study aimed to examine hydrocolloid dressings, Eucerin® as a control was found to not have a significant effect on scar parameters but reduced itch and pain, and increased scar pliability.[61] However, the itching was initially reduced in this study but later stabilised to near initial values.[61] As Eucerin® is likely to be recommended to a large number of burn scar patients, further well-structured studies would be of benefit. For the interim though it is reasonable that it continues to be recommended as part of scar management in the US.

5.1.1 No or limited effect

Moisturisers that cannot be recommended to have a statistically significantly positive effect on *cosmesis* include Imiquimod, Tacrolims ointment, Aristocort® A 0.1%, Mederma®, vitamin E, Aquatain, Aquaphor® and petrolateum. The moisturisers which do not have a significantly positive effect on *scar parameters* includes Imiquimod, Tacrolimus ointment, Aristocort® A 0.1%, Mederma®, Keratin Gel, Provase®, Bio-Oil®, Vitamin E, Aquatain and Petrolateum. Mederma®, Aquaphor®, Tacrolimus and Tretinoin do not have a significant effect on *itch* and/or *pain*. Dermovate was the only study investigating *in-vitro* outcomes that showed no significant effect.

The following section outlines the moisturisers that do not have a statistically significant effect grouped according to the cost and availability as outlined earlier (see Section 1.6.1).

5.1.2.1 Prescription only moisturisers that do not have an effect on scars

Imiquimod was the only moisturiser found to have a negative effect on cosmesis in comparison to control.[94] However, it is difficult to ascertain if a 1.5 point difference in the mean score between control and imiquimod on a VAS is clinically significant. This result was measured at week 8 of the study and the difference between the groups became insignificant later.[94] Although Berman et al. (2005)[94] reported no difference when comparing imiquimod to a control moisturiser when measuring induration, erythema and pigment, Prado et al. (2005)[101] did find differences in the colour and contour of scars. They both examined post-surgical linear scars but Berman et al. (2005)[94] implemented a maximum 14-week time frame and the Prado et al [101] study had a 24-week timeframe. The Prado et al. (2005)[101] study had as a control no treatment whereas Berman et al. (2005)[94] used vehicle cream as a control. As Berman et al. (2005)[94] found no difference between the two groups and Prado et al. (2005)[101] did, it may well be that the vehicle cream alone had some effect and not necessarily the

imiquimod within the cream. Therefore, Imiquimod cannot be recommended to improve scar cosmesis and scar parameters.

For keloids, imiquimod application post excision did not appear to have an effect on recurrence rates and is therefore not recommended as a treatment option. Imiquimod application post excision of a keloid results in highly variable recurrence rates (see Section 4.6). These highly variable rates of recurrence remained even when subgroup analysis investigating differing surgical technique was performed. Some of the variation observed appeared to be explained when data were analysed according to location of the keloid; the recurrence for earlobe keloids was 6.2% compared to the other areas of the body (particularly the trunk) which was 69.1%. This is a different result to a recent meta-analysis[42] which calculated recurrence rates as 13.6% (earlobes) and 24.9% (all areas) as discussed in Section 1.6.1.1. In Shin et al (2017),[42] despite the authors' claim that a strength of their meta-analysis was that they conducted a thorough search, it only located and included four of the seven studies included in this review. Investigating subgroups based on body location of the scar is supported by the clinical and documented observation that earlobe keloids have a lower recurrence rate compared to other areas of the body, particularly the chest.[118] There is some evidence that the tension in the wound bed determines the type of scar at different body sites, for example, there is high tension at the chest and low tension on the skin at the earlobe post excision of a keloid.[119]

AristocortA 0.1%® cream which has Aquatain as a base was compared to Vitamin E added to Aquatain, and to Aquatain alone, on burns scar reconstructions.[98] There was no difference between all three groups for all scar outcomes of cosmesis and scar parameters.[98] Topical Aristocort A 0.1%® cannot be recommended for scar cosmesis and scar parameters as it appears to have no effects and comes with a raft of potential side effects that would exacerbate a negative scar outcome. Similar to Aristocrt A 0.1%®, Clobetasol proprionate 0.05%/Dermovate is a topical corticosteroid. It is not recommended for hypertrophic scars as it has no effect and is accompanied by significant local and systemic side effects.

Finally, in the prescription group, Tacrolimus ointment cannot be recommended as a treatment that has any effect on keloid scar cosmesis, scar parameters, itch or pain.

5.1.2.2 High cost/over the counter moisturisers that do not have an effect on scars

Mederma® was examined in a total of three studies[56, 97, 104], two of which found no significant effect on cosmesis.[56, 97] Chung et al. (2006)[97] found no difference between Mederma® and Petrolateum and the poor quality study by Perez et al (2010)[56] found no significant

improvement with Mederma®. Considering the high cost of Mederma® and that it appears no more effective than petrolatum, it would not be value for money. The low cost petrolatum is no different in its effectiveness to the more costly Mederma®. However, neither have strong data to back any confident recommendations for or against using them for managing cosmesis and scar parameters of linear scars.

Considering the methodological quality of the Bio-Oil® studies (see section 3.5.1) where the studies were self-funded and not published in peer review journals, and where the manufacturer would not release further details about these studies, there is no adequate evidence to indicate that Bio-Oil® has an effect on scar parameters and therefore cannot be recommended at this point in time. It was also interesting to note that the company website reports that the formulation 'contains the breakthrough ingredient PurCellin Oil™',[52(para 1)] yet this ingredient is not listed in the list of ingredients[53] on the same website. Studies implementing an appropriate control group, objective outcome measures and careful subject selection are needed to clarify the effect of this well marketed scar lotion.

When the authors examined all results on the effects of keratin gel (Keragel T), they did not identify a significant difference between the treatment and control groups.[57] It was only when they isolated the 'poor' scars that the treatment group obtained significance over the control. However, aqueous cream as the control may not have been the wisest choice due to concerns about its effects on normal skin. Due to the ambiguity of the results, keratin gel cannot be recommended. A repeat of the study with an alternative control moisturiser and a larger number of subjects to enable a strong conclusion would be beneficial.

5.1.2.3 Low cost/over the counter moisturisers that do not have an effect on scars

It was interesting to note that despite the widespread acceptance[59] of vitamin E, there was no significant positive effect on the moisturisers containing it. The results of this systematic review indicate that vitamin E's reputation as a beneficial addition to a moisturiser is not warranted. It was also noted that the addition of Vitamin E from an oral capsule to a base moisturiser might have been the reason for the high occurrence of adverse events.[96] Therefore, patients should be advised to not add oral vitamin E capsules to a basic moisturiser.

A systematic review examining the role of vitamin E in scar management was found after this author's systematic review was completed.[120] In this review, Tanaydin et al. (2016)[121] included six studies, among which were Baumann et al. (1999),[96] Jenkins et al. (1986),[98] and Perez et al. (2010)[56] which are all in the current systematic review. Also included was Zampieri et al. (2014)[122] which was excluded from the current systematic review as the

ointment containing vitamin E (Lipogel) was applied prior to surgery (for 30 days) and from day 1 post-operatively, and therefore may have had an effect on wound healing rather than scar development as such. The second study not included in this systematic review was Khoo et al. (2011)[123] This study could not be located in the searching as it does not refer to the topical vitamin E, in the form of tocotrienol, as being a moisturiser except for once in the description of how it was prepared where it was referred to as being a cream. They found there was no difference between the vitamin E group and the placebo when the creams were applied to early post-surgical linear scars. The third study not included in the current systematic review was Palmieri et al.(1995)[124] who investigated the effect of adding vitamin E to silicone gel sheets. Therefore, it was not a study that investigated the effect of a moisturiser on a scar. Finally, Tanaydin et al (2016)[121] also concluded that there was insufficient evidence that vitamin E had a beneficial effect on scars to justify its widespread use.

Baumann et al (1999)[96] used Aquaphor® as a control and base moisturiser to add vitamin E from supplement capsules. The Aquaphor® alone performed better through the early stages of the study likely due to the vitamin E side of the scar having a high incidence of local reactions. The final outcome at 12 weeks was predominantly no difference. However, this study lacked detail on cosmetic measurement, only asking if one side was better or no different to the other. Additionally, being linear scars, after 12 weeks, all scars are likely to look similar whether they have treatment or not. Jackson and Shelton (1999)[104] utilised Aquaphor® as a control moisturiser when examining the effects of Mederma® (onion extract gel). They reported the Aquaphor® group to have a significant reduction in erythema scores but it had no effect on itch in pre and post scores of linear scars.[104] However, there were methodological issues with this study including small sample sizes, insufficient information on the scar age and subject characteristics. Aquaphor® may be utilised to reduce erythema of linear scars. However, due to the low quality and lack of detail of the study it cannot be recommended with any confidence.

A search of the internet yielded only a material safety data sheet from 2007 but no further information on the availability of Aquatain that was utilised by Jenkins et al.(1986)[98] as a placebo cream and as a base to add to Aristocort® 0.1%. As this study was conducted in 1986, it is suspected that this moisturiser is no longer available. The study did not provide any details on the composition of this moisturiser to enable comment on its effectiveness or allow comparisons with other moisturisers.

Petrolateum was utilised in two studies as a control for comparison against Mederma®[97] (as mentioned above) and imiquimod.[101] The low cost petrolatum is no different in its effectiveness to the more costly Mederma®. There is inadequate data to enable confident recommendations to be made for or against petrolatum for managing cosmesis of linear scars.

Although aqueous cream was included as a control moisturiser in one study,[57] its effects alone were not measured as they were for some other control moisturisers. However, considering that previous studies on aqueous cream demonstrated that it increased TEWL in healthy skin and decreased the thickness of the stratum corneum[62, 63] (see Section 1.3), this product cannot be recommended. Aqueous cream should not be utilised as a control moisturiser in studies examining the effectiveness of a moisturiser on scar outcomes.

Table 5-1: Summary of recommendations for all included moisturisers ordered according to availability

	Recommendations	Outcomes					Scar types		
		C	SP	I&P	IV	T&H	Linear	Hyper-trophic	Keloid
Prescription only									
Imiquimod 5%	-	✓	✓		✓		✓		✓
Tacrolimus Ointment	-	✓							✓
Doxepin/Prudoxin	++		✓	✓				✓	
Putrescine (Fibrostat®)	++		✓					✓	
Clobetasol proprionate 0.05%/Dermovate	-				✓			✓	
Aristocort® 0.1%	-		✓					✓	
High Cost OTC									
Tretinoin cream/retinoic acid/vitamin A (0.05%)	+++	✓	✓	✓	✓		✓	✓	✓
Bio-Oil®	-		✓				✓	✓	
Wubeizi	+				✓				✓
Lumiere Bio-Restorative Eye Cream	+	✓					✓		
Mederma®/onion extract	-	✓	✓	✓			✓	✓	✓
Scarguard®/HSE	+	✓	✓					✓	✓
Keratin gel/KeragelT®	-		✓				✓	✓	
Provase®	+++		✓	✓				✓	
Mugwort Lotion	+			✓				✓	
Alhydran	++++					✓	*	*	*
Low cost OTC									
Vitamin E	-	✓	✓				✓	✓	
Aquaphor®	-	✓	✓	✓			✓		
Cetaphil®	++	✓	✓					✓	✓
Eucerin®	++		✓	✓				✓	✓
Aqueous	-		✓				✓	✓	
Petrolateum	-	✓	✓				✓		
Aquatain	-	✓	✓					✓	

Recommendations:
++++ Able to recommend
+++ recommend but with minor reservations
++ recommend but with moderate reservations
+ recommend but with major reservations
- not able to recommend
Outcomes: C = cosmesis, SP = scar parameters, I&P = itch and pain, IV = *in vitro*, T&H = TEWL and hydration.
✓=negative effect, ✓=no or mixed positive/no effect, ✓=significantly positive effect.
*= scar model, tape stripped skin

5.2 Assumptions, limitations and delimitations

This review was initiated due to the desire to explore the question of what moisturisers to use for burn patients. However, to ensure that maximum study outcome data was collected, the assumption was made that scars that arise from burn injury are similar to those that arise from trauma or surgery. This is due to the anatomical basis for the scarring in that hypertrophic scars are arising from trauma to the dermis in both instances, regardless of the cause, thereby justifying this assumption.

A limitation of this review is the quality of outcomes measured in the literature. It is only recently that researchers have used instrumentation to measure scar outcomes compared to using scar scales and observer rated VASs or questionnaires. This review only identified one study that utilised instrumentation to objectively measure outcomes.[19] Instrumentation such as a cutometer to measure skin elasticity, evaporimeters to measure TEWL, and colorimeters to measure the colour are needed to provide studies with valid, objective data. The scar scales may provide reasonable intra-rater reliability and measures of change over time but may have questionable inter-rater reliability. Subjective scar scales and VASs have been popular as they are easily utilised by clinicians as part of their usual clinical workload and most studies are performed by a researcher who is also attempting to juggle a clinical and research portfolio. The exception is *in vitro* studies where the measurements are quite robust and quantitative but *in vitro* studies may not necessarily transfer over to clinical practice.

A limitation of the results of this systematic review may be that research that is typically conducted in this field is predominantly conducted on specialised ingredients within moisturisers but there is limited findings on the low cost, over the counter moisturisers. These specialised ingredients are usually drugs that can have some significant effects on cellular processes such as the immune modulators (imiquimod, Tacrolimus ointment and Doxepin) and the effectors of collagen synthesis or topical steroids (Putrescine/Fibrostat, Clobetasol proprionate 0.05%w/w / Dermovate, Aristocort® 0.1%). Some of the moisturisers included in this review have potentially less toxic effects but are exceptionally expensive (high cost, over the counter group) compared to the basic moisturisers. The cost to the consumer of these creams would prohibit their use on larger scars and by those with limited finances and would therefore only be of interest to those undergoing small cosmetic surgeries.

The moisturisers that may be considered basic moisturisers due to their cost and non-toxic ingredients that appeared in this systematic review were outlined in the “low cost, over the

counter" category. These moisturisers were often not the primary focus of the study being conducted but were used as control moisturisers. Although a consumer with large areas of scarring (such as burns patients) use arguably the greatest volume of moisturisers for their scars there is limited data available on their effectiveness.

Since the searches were completed in September 2016 there may be new articles of relevance that have been published. An updated search has not been performed but an article was identified in the Australian Hand Therapy Association newsletter which identified a systematic review and other articles on vitamin E creams.[120] The systematic review that this review identified found some studies that the current systematic review had not identified.[121] On closer examination of PubMed's MeSH headings, this was due to the search term 'topical application' not being utilised in the current systematic review. It is unknown if there are other broader search terms that could have identified articles for inclusion. Another limitation related to the searches is that searches were limited to English language only, thereby excluding potentially valuable studies in other languages.

To ensure quality and depth of data to from which conclusions can be drawn, only complete studies were included in this systematic review. This potentially could be a limitation on the results of the review as there were many studies that were retrieved that were abstracts only, usually from conference proceedings (see Appendix 3). These may have contained valuable data and further knowledge. Despite contacting authors, no further information was retrieved.

5.3 Implications for research

Of note in the articles sourced for this systematic review, there was a lack of robust measurements of scars. Scar scales provide little objective detail with scales often only spanning a scale of 0 to 4. Although patient perspectives are important for clinical outcomes, patient rated scales are also quite subjective. Instrumentation to measure scar parameters are required to accurately measure scar progress. Measurement tools such as spectrophotometry/colorimetry (colour), tissue tonometry (pliability),[76] standardised digital imaging and spectral modelling (vascularity and melanin),[77] electrical hygrometers such as the Tewameter® (TEWL), to name a few, are required to accurately and objectively measure scars. There was only one study in this systematic review that utilised a Tewameter® to measure TEWL and a Corneometer® to measure hydration of the stratum corneum.[19] What is needed are more studies reporting on the effects of the most popular and widely available moisturisers on TEWL and hydration of scars or scar models. De Paepe et al.(2015)[125]

reported in their study the effect of petrolatum on TEWL and hydration and referred to a number of other studies that did the same. However, in their study, the application was to normal skin.[125] It is unknown whether this data can be translated to scars that have obvious altered characteristics to normal skin.

In the selection of subjects, scars need to be the same in type (e.g. linear, hypertrophic or keloid), location, and age or stage of development, and this needs to be clearly documented in the study. An alternative to choosing appropriate scars would be to utilise a scar model such as the tape stripping method employed by Hoeksema et al.(2013)[19] as they reported that this resulted in more reliable TEWL readings compared to taking TEWL readings from scars.

Linear scars are not a useful scar type for determining the effectiveness of scar management techniques. These have been observed clinically to be non-problematic with minimal to low incidences of hypertrophy and contracture. Results of studies employing subjects with linear scars are treated with caution as these scars often produce favourable scar scores without intervention. These procedures result in a linear wound where normal skin closely approximates normal skin on the other side of the wound. Since wound closure and epithelialisation occurs within 10-14 days, it does not stimulate hypertrophic scar formation.[11, 12] Some studies retrieved in this systematic review contained a mix of keloid and hypertrophic scars. Ideally, they should not be combined. The understanding of the underlying mechanisms of both types of scars is now more developed and it would be unlikely that a study would combine them in future.

Although statistical significance is important, research should provide comment on clinical significance of results. Scar scales are often totalled or combined when there is no clear basis for doing so. Total scores that then differ by a few points are reported as a statistically significant result and researchers have been implying this as clinically significant in their conclusions. If scar scales are to be used, then interpretation of their results and what constitutes a clinically relevant difference should be clarified.

The methodology of the studies also needs to be carefully considered when performing research. Studies should be adequately powered and have an appropriate comparison group which is as similar as possible to the treatment group. They should also be randomised where possible with the technique of randomisation clearly documented.

5.4 Conclusions

Problematic scars such as keloid and hypertrophic scars are commonly an unpleasant cosmetic and functional side effect from burns, trauma and surgery. Moisturising is one of the standard scar management techniques recommended by health professionals.

Of the six prescription moisturisers, Imiquimod, Tacrolimus, Dermovate and Aristocort® are not recommended for scars. Doxepin may be useful to control itch and topical putrescine may assist in reducing scar parameters. High cost, over the counter moisturisers that cannot be recommended with any certainty are Bio-Oil®, Wubeizei, Lumiere Bio-Restorative Eye Cream, Mederma®, and Scarguard®. Keratin gel may be useful to reduce scar parameters and Mugwort lotion for itch. More confident recommendations can be made for Tretinoin cream/vitamin A or scar parameters, Provase® for itch and Alhydran for improving TEWL and hydration.

No basic moisturisers stood out that can be recommended with great confidence. Except for vitamin E containing moisturisers, there were no studies looking primarily at their outcomes, rather observations were made when they were used as a control moisturiser. However, they were low cost and had minimal adverse events and should not be ruled out, as yet, to have an effect. The exceptions were aqueous cream and vitamin E containing moisturisers which increased TEWL and adverse events, respectively.

Recommendations for research include careful selection of subjects and especially outcome measures. In particular, measurement of TEWL and hydration, and use of instrumentation as opposed to scar scales and other scales or questionnaires would result in more reliable research that could confidently be transferred into clinical practice. Many patients with scars want recommendations from clinicians on what moisturiser they can easily purchase and the data on these basic moisturisers is still severely lacking.

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Appendices

Appendix 1: Logic grids for database searching

PubMed Logic Grid. No filters used

Scar[tw] OR Scars[tw] OR Scarring[tw] OR Cicatrix[mh] OR Cicatrix[tw] OR Cicatrization[tw] OR Cicatrisation[tw] OR Keloid[mh] OR Keloid*[tw] OR hypertrophic[mh] OR hypertrophic[tw]	Moisturi*[tw] OR Emollients[mh] OR Emollient*[tw] OR Skin cream[mh] OR Skin cream*[tw] OR Cream[tw] OR Lotion*[tw] OR Ointments[mh] OR Ointment*[tw] OR Salve[tw] OR Salves[tw] OR Unguent[tw] OR Unguents[tw] OR Lubrica*[tw]	English[la]

Embase logic grid. English filter enabled

Scar:de,ti,ab OR Scars:ti,ab OR Scar:ti,ab OR Scarring:ti,ab OR Cicatrix:de,ti,ab OR Cicatrix:ti,ab OR Cicatrization:de,ti,ab OR Cicatrization:ti,ab OR Cicatrisation:ti,ab OR Keloid:de,ti,ab OR Keloid*:ti,ab OR 'Hypertrophic scar':de,ti,ab OR 'Hypertrophic':ti,ab	Moisturi*:de,ti,ab OR Moisturi*:ti,ab OR Emollient*:de,ti,ab OR Emollient*:ti,ab OR 'skin cream*':ti,ab OR Lotion*:de,ti,ab OR Lotion*:ti,ab OR Cream:de,ti,ab OR Cream:ti,ab OR Creams:ti,ab OR Ointment*:ti,ab OR Salve:de,ti,ab OR Salve:ti,ab OR Salves:ti,ab OR Unguent:ti,ab OR Unguents:ti,ab OR 'lubricating agent':de,ti,ab OR Lubrica*:ti,ab

CINAHL logic grid. English filter enabled

TI Scar OR AB Scar OR TI Scars OR AB Scars OR TI Scarring OR AB Scarring OR MW Cicatrix OR TI Cicatrix OR AB Cicatrix OR TI Cicatri?ation OR AB Cicatri?ation OR TI Keloid* OR AB Keloid* OR TI Hypertrophic OR AB Hypertrophic	TI Moisturi* OR AB Moisturi* OR TI Emollient* OR AB Emollient* OR TI Cream OR AB Cream OR TI Skin cream OR AB Skin cream OR MH creams OR TI Lotion* OR AB Lotion* OR MH Ointment OR TI Ointment* OR AB Ointment* OR TI Salve OR	AB Salve OR TI Salves OR AB Salves OR TI Unguent OR AB Unguent OR TI Unguents OR AB Unguents OR MH Lubricants OR TI Lubrica* OR AB Lubrica*

Web of Science logic grid

Scar OR Scars OR Scarring OR Cicatrix OR Cicatrization OR Cicatrisation OR Keloid* OR hypertrophic	Moisturi* OR Emollient* OR “Skin cream*” OR Cream OR Lotion* OR Ointment* OR Salve OR Salves OR Unguent OR Unguents OR Lubrica*

Appendix 2: Critical appraisal tools

These are the critical appraisal tools that were used in this systematic review and are available at:
http://joannabriggs.org/research/critical-appraisal-tools.html

JBI Critical Appraisal Checklist for Randomized Controlled Trials

Reviewer_____Date_____

Author _____Year_____Record Number_____

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	☐	☐	☐	☐
2. Was allocation to treatment groups concealed?	☐	☐	☐	☐
3. Were treatment groups similar at the baseline?	☐	☐	☐	☐
4. Were participants blind to treatment assignment?	☐	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	☐	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	☐	☐
7. Were treatments groups treated identically other than the intervention of interest?	☐	☐	☐	☐
8. Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized?	☐	☐	☐	☐
9. Were participants analysed in the groups to which they were randomized?	☐	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	☐	☐	☐	☐
11. Were outcomes measured in a reliable way?	☐	☐	☐	☐
12. Was appropriate statistical analysis used?	☐	☐	☐	☐
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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THE JOANNA BRIGGS INSTITUTE

JBI Critical Appraisal Checklist for Quasi-Experimental Studies (non-randomized experimental studies)

Reviewer_____Date_____

Author _____Year_____Record Number_____

	Yes	No	Unclear	Not applicable
1. Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?	☐	☐	☐	☐
2. Were the participants included in any comparisons similar?	☐	☐	☐	☐
3. Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	☐	☐	☐	☐
4. Was there a control group?	☐	☐	☐	☐
5. Were there multiple measurements of the outcome both pre and post the intervention/exposure?	☐	☐	☐	☐
6. Was follow-up complete, and if not, was follow-up adequately reported and strategies to deal with loss to follow-up employed?	☐	☐	☐	☐
7. Were the outcomes of participants included in any comparisons measured in the same way?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

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THE JOANNA BRIGGS INSTITUTE

JBI Critical Appraisal Checklist for Case Series

Reviewer_____Date_____

Author _____Year_____Record Number_____

	Yes	No	Unclear	Not applicable
1. Were there clear criteria for inclusion in the case series?	☐	☐	☐	☐
2. Was the condition measured in a standard, reliable way for all participants included in the case series?	☐	☐	☐	☐
3. Were valid methods used for identification of the condition for all participants included in the case series?	☐	☐	☐	☐
4. Did the case series have consecutive inclusion of participants?	☐	☐	☐	☐
5. Did the case series have complete inclusion of participants?	☐	☐	☐	☐
6. Was there clear reporting of the demographics of the participants in the study?	☐	☐	☐	☐
7. Was there clear reporting of clinical information of the participants?	☐	☐	☐	☐
8. Were the outcomes or follow up results of cases clearly reported?	☐	☐	☐	☐
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	☐	☐
10. Was statistical analysis appropriate?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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THE JOANNA BRIGGS INSTITUTE

JBI Critical Appraisal Checklist for Case Reports

Reviewer_____Date_____

Author _____Year_____Record Number_____.

	Yes	No	Unclear	Not applicable
1. Were patient's demographic characteristics clearly described?	☐	☐	☐	☐
2. Was the patient's history clearly described and presented as a timeline?	☐	☐	☐	☐
3. Was the current clinical condition of the patient on presentation clearly described?	☐	☐	☐	☐
4. Were diagnostic tests or assessment methods and the results clearly described?	☐	☐	☐	☐
5. Was the intervention(s) or treatment procedure(s) clearly described?	☐	☐	☐	☐
6. Was the post-intervention clinical condition clearly described?	☐	☐	☐	☐
7. Were adverse events (harms) or unanticipated events identified and described?	☐	☐	☐	☐
8. Does the case report provide takeaway lessons?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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Appendix 3: Excluded studies and reasons for their exclusion

Agbenorku, P. Triple keloid therapy: A combination of steroids, surgery and silicone gel strip/sheet for keloid treatment. European Journal of Plastic Surgery. 2000;23(3):150–1.

Reason for exclusion: Treatment is steroid injection and surgery and a cream. Reports on the overall results of re-occurrence, does not report on effect of cream used alone. It is a triple therapy regime.

Berman, B.; Poochareon, V. N.; Villa, A. M. Novel dermatologic uses of the immune response modifier imiquimod 5% cream. Skin therapy letter. 2002;7(9):1–6.

Reason for exclusion: A review article that has only one paragraph relating to keloids and references only one reference in that paragraph.

Berman, B.; Viera, M.; Perez, O.; Huo, R.; Amini, S. Tolerability and efficacy of two marketed topical preparations versus placebo for the treatment of keloids and hypertrophic scars: Interaction and end of study analysis. Journal of the American Academy of Dermatology. 2009;60(3):AB194.

Reason for exclusion: Abstract only. Contains the data for article published later with Perez as lead author (2010).

Bordalo, O.; Brandao, F. M. Contact allergy to palmitoyl collagenic acid in an anti-keloid cream. Contact Dermatitis. 1991;24(4):316–7.

Reason for exclusion: A single case study demonstrating the reaction of an ingredient in an anti-keloid cream. Does not discuss any effects on scars at all.

Daly, T. J.; Golitz, L. E.; Weston, W. L. Keloids and Hypertrophic Scars in Patients Treated with Tretinoin Cream. Journal of Cutaneous Pathology. 1986;13(6):439–439.

Reason for exclusion: Abstract only. Attempted contact with authors – no reply

Daly, T. J.; Golitz, L. E.; Weston, W. L. A Double-Blind Placebo-Controlled Efficacy Study of Tretinoin Cream 0.05-Percent in the Treatment of Keloids and Hypertrophic Scars. Clinical Research. 1986;34(2):A744–A744.

Reason for exclusion: Abstract only. Attempted contact with authors – no reply

De Paepe, K.; Sieg, A.; Le Meur, M.; Rogiers, V. Silicones as non-occlusive topical agents. Pharmazeutische Industrie. 2015;77(9):1370–9.

Reason for exclusion: Effect of creams on normal skin. Creams are used in scar management in a clinical setting but this study does not use scars as the test environment.

Draelos, Z. D.; Hardas, B.; Kaur, M.; Jones, W.; Murray, W. Development and assessment of onion extract cream with sun protection factor for the improvement of the appearance of post surgical scars. Journal of Investigative Dermatology. 2009;129:S42.

Reason for exclusion: Abstract only. Attempted contact with authors – no reply

Draelos, Z.; Kaur, M.; Jones, W.; Murray, W.; Hardas, B. A comparison of onion extract gel with onion extract cream for the improvement of the appearance of postsurgical scars. Journal of the American Academy of Dermatology. 2009;60(3):AB82.

Reason for exclusion: Abstract only. Attempted contact with authors – no reply

Fitzpatrick, R. Repigmentation of hypopigmented scars. Lasers in Surgery and Medicine. 2010;42:30–1.

Reason for exclusion: Abstract only. Attempted contact with authors – no reply

Gao, J.; Tao, J.; Zhang, N.; Liu, Y.; Jiang, M.; Hou, Y.; Wang, Q.; Bai, G. Formula optimization of the Jiashitang scar removal ointment and anti-inflammatory compounds screening by NF-kappaB bioactivity-guided dual-luciferase reporter assay system. Phytother Res. 2015;29(2):241–50.

Reason for exclusion: Animal study

Garcia, A.M., Vila, T.O., Pulido, L.F., Martin, J.J.R. Hypertrophic and keloid scars after the application of 5% Imiquimod Cream: A report of 2 cases. Actas Dermosifiliogr. 2014;105(8):795–7.

Reason for exclusion: Scarring caused by imiquimod. Cases are not about a moisturiser to treat a scar.

Gupta, J, Patel, A, Jain, P. Alteration in transforming growth factor-beta1 gene expression in hypertrophic scar. Indian Journal of Biotechnology. 2014;13(July):314–7.

Reason for exclusion: No identification of 'herbal cream' that used in the study.

Gupta, J.; Patel, A.; Jain, P. Alteration in transforming growth factor-β1 gene expression in hypertrophic scar. Indian Journal of Biotechnology. 2014;13(3):314–7.

Reason for exclusion: Excluded after critical appraisal as noted it does not measure effect of the moisturiser in the scar, just the levels of TGF-B1 gene expression. Since VSS measures changes, could assume they were still active scars despite being >18m old, or else the VSS scale scores would be very low to start with. Therefore, TGF factors would reduce anyway with scar activity. Also, no description of the 'herbal cream'.

Jain, P.; Kumar, S.; Patel, A.; Jain, V.; Kostopoulos, N. G.; Barot, A. Three-dimensional assessment of the efficacy of a herbal cream on postburn hypertrophic scars: A prospective study. Wound Repair and Regeneration. 2012;20(5):A96.

Reason for exclusion: Abstract only. Attempted contact with authors – no reply

Janicki, S.; Sznitowska, M. Effect of ointments for treating scars and keloids on metabolism of collagen in scar and healthy skin. European Journal of Pharmaceutics and Biopharmaceutics. 1991;37(3):188–91.

Reason for exclusion: Animal study

Jina, N. H. Midline sternotomy wound healing using a keratin based product. Wound Repair and Regeneration. 2011;19(2):A29.

Reason for exclusion: Abstract of the 2015 study which is a full publication of the results of the study.

Jones, W.; Kaur, M.; Drewes, S.; Heberer, M.; Hardas, B. Rationale and formulation development of cream with sun protection factor with onion extract for therapy of scars. Journal of Investigative Dermatology. 2007;127:S45–S45.

Reason for exclusion: An earlier version of the Draelos study 2009 but this one is just the rationale for the study. Other authors are the same as the 2009 study. An abstract only.

Juckett, G., Hartman-Adams, H. Management of keloids and hypertrophic scars. American Family Physician. 2009;80(3):253–60.

Reason for exclusion: A review article, not original research.

Karimi, K.; Jadidian, A.; Adelson, R. Prevention of head and neck keloid with 5% Imiquimod cream. Otolaryngology - Head and Neck Surgery. 2011;145:142.

Reason for exclusion: Abstract only. This abstract reports what will be done – a retrospective review of the charts of patients. There are no further publications. May not have ever been done.

Lewis, P., Wright, K., Webster, A., Steer, M., Rudd, M., Doubrovsky, A., Gardner, G. A randomized controlled pilot study comparing Aqueous Cream with a beeswax and herbal oil cream in the provision of relief from postburn pruritus. Journal of Burn Care and Research. 2012;33(4):e195-200.

Reason for exclusion: No identification of the subjects as having a scar. Only referred to as 'burn wound'.

Liuzzi, F.; Chadwick, S.; Shah, M. Paediatric post-burn scar management in the UK: A national survey. Burns. 2015;41(2):252–6.

Reason for exclusion: A review of treatment strategies only.

Manca, M. L.; Matricardi, P.; Cencetti, C.; Peris, J. E.; Melis, V.; Carbone, C.; Escribano, E.; Zaru, M.; Fadda, A. M.; Manconi, M. Combination of argan oil and phospholipids for the development of an effective liposome-like formulation able to improve skin hydration and allantoin dermal delivery. International Journal of Pharmaceutics. 2016;505:204–11.

Reason for exclusion: Animal study.

McPartland, F. M. Use of capsaicin cream for abdominal wall scar pain. American Family Physician. 2002;65(11):2211–2211.

Reason for exclusion: No real data, just opinion piece, letter to editor.

Niedner, R. Effects of a Symphytum-Peregrinum extract containing ointment. Acta Therapeutica. 1989;15(3):289–97.

Reason for exclusion: Not in English.

Ong, A.; Orozco, F.; Sheikh, E. S.; Anmuth, C.; Alfaro, A.; Kathrins, R.; Grove, G. L.; Zerweck, C.; Madden, A. M.; Raspa, R.; Weis, M. T. An RCT on the effects of topical CGP on surgical wound appearance and residual scarring in bilateral total-knee arthroplasty patients. Journal of Wound Care. 2011;20(12):592–8.

Reason for exclusion: Treatment begins at day 3 post op and is more a measure of effect of wound healing. Cannot tease apart if the cream affect wound healing and resulting scar or if cream has an effect at scar development stage.

Romo, E. M.; Fundora, F. P.; Albajes, C. R.; López, L. E.; Hana, Z. The effectiveness of cream with Centella Asiatica and Pinus Sylvestris to treat scars and burns. Clinical Trial. Dermatologia Kliniczna. 2012;14(3):105–10.

Reason for exclusion: No control group. Huge mixture of subjects. More a test of adverse reactions than outcomes or 'effectiveness' of the cream.

Sawada, Y.; Sone, K. Beneficial effects of silicone cream on grafted skin. British Journal of Plastic Surgery. 1992;45(2):105–8.

Reason for exclusion: Cream is covered with a plastic film so it is actually a study looking at occlusion with cream.

Selden, S. T. Urea healing of surgical scars. The Journal of dermatologic surgery and oncology. 1983;9(9):712.

Reason for exclusion: A letter only, and opinion piece. Not even a case study.

Serghiou, M. A.; Holmes, C. L.; McCauley, R. L. A survey of current rehabilitation trends for burn injuries to the head and neck. J Burn Care Rehabil. 2004;25(6):514–8.

Reason for exclusion: A survey, no mention of moisturisers.

Shin, S.; Shin, J.; Chung, W.; Nam, K.; Kwon, T.; Lee, J. Preventive and treatment effects of multi-growth factors-containing cream on post-thyroidectomy scars: A single-blinded randomized controlled study. Thyroid. 2015;25:A152.

Reason for exclusion: Abstract only. Attempted contact with authors – no reply

Taheri, A.; Moradi Tuchayi, S.; Alinia, H.; Orscheln, C. S.; Mansoori, P.; Feldman, S. R. Topical clobetasol in conjunction with topical tretinoin is effective in preventing scar formation after superficial partial-thickness burn ulcers of the skin: A retrospective study. Journal of Dermatological Treatment. 2015;26(4):361–4.

Reason for exclusion: Cream used with an occlusive dressing which can also have an effect on the scar. Cream not used on its own.

Visser, H. J.; Harris, E.; Hurwitz, P.; Dietze, D.; Viereck, C. Patient-Reported Outcomes and Perceptions Following Use of Compounded Scar/Burn Cream: Interim Results from an Observational Survey Study. Wound Repair and Regeneration. 2015;23(4):A33–A33.

Reason for exclusion: Abstract only. Attempted contact with authors – no reply

Yii, N. W.; Frame, J. D. Evaluation of cynthaskin and topical steroid in the treatment of hypertrophic scars and keloids. European Journal of Plastic Surgery. 1996;19(3):162–5.

Reason for exclusion: Product cynthaskin dries to form an occlusive film so unlikely to be considered a moisturiser, more of a contact media.

Zampieri, N.; Castellani, R. Topical application of lipophilic anhydrous gel rich in Vitamin E in the management of scars in patients surgically treated for neck cysts. Journal of the American Academy of Dermatology. 2014;70(5):AB194.

Reason for exclusion: Abstract only. Attempted contact with authors – no reply

Zampieri, N.; Zuin, V.; Burro, R.; Ottolenghi, A.; Camoglio, F. S. A prospective study in children: Pre- and post-surgery use of Vitamin E in surgical incisions. Journal of Plastic, Reconstructive and Aesthetic Surgery. 2010;63(9):1474–8.

Reason for exclusion: Vitamin E cream is used from day 1 – could affect wound healing and therefore have an effect on scar outcome because of effect on wound healing.

Chandawarkar RY, Piorkowski J, Amjad I, Deckers PJ. Combination therapy of a large, recurrent keloid. Dermatologic Surgery. 2007;33(2):229–35.

Reason for exclusion: A single case study with no comparison and multiple surgical techniques that can affect outcome e.g. VAC and Integra.

Laftah Z, Ujam A, Baksh N, Huppa C, Fan K, Bashir S. A case series on the use of topical imiquimod 5% for severe and recurrent keloid scarring. British Journal of Dermatology. 2014;171:68.

Reason for exclusion: Abstract only and surgery also involves injection of steroid. Use of imiquimod is also from day 3 until wound heals.

Shapiro SD. Imiquimod 5% cream as a novel agent in the treatment of skin scarring. Journal of the American Academy of Dermatology. 2004;50(3):P36–P36.

Reason for exclusion: Abstract only - Attempted contact with authors – no reply.