NICE National Institute for Health and Care Excellence

NICE guidance

The ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury

Medical technologies guidance
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Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

1.1 The ReCell Spray-On Skin system shows potential to improve healing in acute burns. However, there is insufficient evidence on its use in clinical practice, particularly in relation to which patients might benefit most from its use, to support the case for its routine adoption in the NHS.

1.2 Research is recommended to address uncertainties about the claimed patient and system benefits of the ReCell Spray-On Skin system. Clinical outcomes should include time to 95% healing, length of hospital stay, cosmetic appearance of the scar and function of the burned area, compared with standard care. As relevant databases and registers are available, the research might include analysis of data generated from these. NICE will explore the development of appropriate further evidence, in collaboration with the technology sponsor and with clinical and academic partners, and will update this guidance if and when new and substantive evidence becomes available.

2 The technology

Description of the technology

2.1 The ReCell Spray-On Skin system (Avita Medical; 'ReCell') is a rapid, autologous cell harvesting, processing and delivery system for treating skin loss and preventing scarring and depigmentation in adults and children with burns. ReCell Spray-On Skin is prepared by shaving a 0.15 mm to 0.20 mm-thick piece of skin, measuring up to 2 cm by 2 cm, from a donor site close to the burn. The donor skin is added to a proprietary enzyme solution (derived from pigs) in a processing unit and heated for 15 to 30 minutes to disaggregate the cells. The skin is then removed and scraped with a scalpel to develop a plume of cells. These cells are added to a buffer solution, aspirated and filtered to create a cell suspension that contains keratinocytes, melanocytes, fibroblasts and Langerhans cells. The suspension is delivered to the debrided burn using a spray applicator, or it can be dripped directly onto the site. It is designed so that cells from the suspension are able to proliferate rapidly and migrate in the wound bed. The regenerative nature of these skin cells is intended to promote the growth of healthy skin to achieve rapid healing. The procedure is designed to be carried out by clinicians, without input from specialised laboratory staff.

2.2 ReCell is supplied as a sterile pack containing all the components needed to create and apply a skin cell suspension sufficient to treat burn injuries up to 320 cm^2. The cost of ReCell stated in the sponsor's submission is £950 plus VAT per pack.

2.3 The claimed benefits of ReCell in the case for adoption presented by the sponsor are:

- A reduction in the size and depth of the skin graft donor site.
- Shorter healing time, fewer complications and reduced morbidity at the donor site.
- Shorter healing time at the recipient site, leading to:

  - improved aesthetic results for burn wounds, with a reduced likelihood of scarring
  - reduced likelihood of later readmission to hospital for corrective surgery as a result of improved aesthetic results.

- Repopulation of melanocytes to reduce hypopigmentation and improve skin colour match in healed wounds.
- Reduced frequency of dressing changes to weekly rather than daily, allowing for a shorter stay in hospital and outpatient management.
- Reduced need for dressing changes under anaesthetic.
- A reduction in the need for external technical laboratory support.

Current management

2.4 The treatment of burns can be considered in 2 phases: acute and reconstructive. The acute phase is the initial management of the burn wound, where the aim is to heal with minimal scarring and physical limitation. The reconstructive phase aims to improve the functional or visual effect of scarring, usually by surgical means, and may be done months or years after the initial injury.

2.5 The first step in managing a burn is to assess the site of the injury, the proportion of the body surface area involved and the burn depth. The extent of a burn is usually expressed as a proportion of the total body surface area affected. Burn depth is classified according to the layer of skin (epidermis, dermis or subcutaneous layer) affected. Burns can be classified as:

- epidermal or superficial, affecting the epidermis only, as in cases of sunburn
- partial thickness or dermal, affecting the dermis and stratified into superficial, mid-dermal or deep
- full thickness, where the epidermis, dermis and subcutaneous layer, and in some cases the underlying muscle or bone, are affected.

2.6 Superficial epidermal burns and full thickness burns are easily identifiable by experienced clinicians, but burn depth can be more difficult to assess accurately in partial-thickness burns and in children because they have thin skin. Burn depth is usually assessed by clinical evaluation using visual and tactile assessment. When burn depth is uncertain, NICE recommends assessing it using the moorLDI2 Burns Imager: a laser doppler blood flow imager for burn wound assessment in its medical technologies guidance. Burns can be of mixed depths within a single injury site and can be dynamic, becoming deeper over time, depending on the cause and initial treatment. Burns of uncertain depth are often classed as indeterminate or intermediate.

2.7 Epidermal and superficial partial thickness burns tend to heal without scarring or surgical intervention within 21 days. Mid-dermal or deep partial thickness burns and full thickness burns may need surgical excision or debridement to remove the burnt skin and tissues. It is usual for surgical excision to be done within 48 hours of admission to hospital. The burn wounds are then dressed with conventional or biosynthetic dressings or skin grafts in more serious burns. Skin grafting is used to promote rapid healing, to minimise scarring and to reduce complications. Healing can occur only from the edges of a burn wound, so without a skin graft the wound can contract. This contraction and formation of scar tissue can lead to a poor cosmetic outcome and reduced mobility. Skin grafting grafts is often used to treat mid-dermal or deep partial thickness burns. For mixed-depth burns, or if there is uncertainty over depth, a decision about whether to use skin grafting is based on assessment of burn healing and the patient's condition, between 10 and 21 days after the injury. Delayed healing (more than 21 days) increases the probability of hypertrophic scarring. Full thickness burns more than 1 cm in diameter will always need skin grafting because the regenerative components of the skin have been lost.

2.8 Skin grafts may be classified as partial or full thickness grafts, depending on how much of the dermis is harvested by the surgeon. The clinical 'gold standard' for skin grafting is an autologous (from the patient's own skin) split-thickness graft taken from an area of unburnt skin. Grafts should ideally be taken from donor sites adjacent to the injury to improve the match with the surrounding skin. However, the size and location of the burn injury can limit the choice of donor site, so grafts may be taken from other areas of the body. The donor site is itself a wound and needs treatment to ensure healing. If large grafts are needed for

extensive burns, the donated skin can be perforated (or meshed) to increase its surface area. The mesh ratio differs depending on the area needing coverage and is generally between 1:1.5 and 1:4 times the original skin size. The pattern of meshing can be visible after healing, so sheet (non-meshed) grafting is preferable for a good cosmetic result.

2.9 Alternatives to autologous skin grafts for deep partial thickness and extensive full thickness burns include bio-engineered skin substitutes, that may be cultured autologous skin cells (epithelial autografts), synthetic dermal substitutes or artificial membranes. Cultured epithelial autografts need cells (usually keratinocytes) from a donor site to be grown in vitro either as sheets or in a liquid suspension. Culturing can take days or weeks and cells are then applied directly to the wound or can be attached to synthetic or biological carriers such as silicone, collagen or fibrin glue. Cultured skin cells can also be used in conjunction with other dermal substitutes or autologous grafts in full thickness injuries.

3 Clinical evidence

Summary of clinical evidence

3.1 Full details of all clinical outcomes considered by the Committee are available in the assessment report overview in the supporting documentation.

3.2 The key clinical outcomes for the ReCell Spray-On Skin system ('ReCell') presented in the decision problem were:

- speed of healing
- length of stay in hospital
- degree of scarring
- degree of pigmentation
- number and size of donor sites
- device-related adverse events.

3.3 The sponsor presented 11 studies: 3 peer-reviewed articles (Gravante et al. 2007, Park et al. 2013 and Wood et al. 2012) and 8 conference abstracts. An abstract by Sen et al. (2012) reported findings from a case series that overlapped with a study by Philp et al. (2013), submitted as academic in confidence. The External Assessment Centre considered 2 of the conference abstracts (Echlin 2012b and Palombo 2012) to be outside the decision problem because these studies evaluated the treatment of donor site wounds and hypertrophic scars rather than acute burns. The External Assessment Centre identified a further 9 conference abstracts, of which 2 were unavailable (Rawlins 2010 and 2011b), 4 contained data that overlapped with references presented by the sponsor and 1 other may have contained overlapping data.

3.4 The sponsor also presented 5 additional published studies in support of the degree of pigmentation, which was an outcome included in the decision problem. The External Assessment Centre considered these studies to be outside the

scope of this guidance because they evaluated treatments for people with vitiligo or hypertrophic scars and not with burns.

Studies included in the sponsor's submission

3.5 Gravante et al. (2007) compared ReCell with skin grafting for treating deep partial thickness burns in a randomised controlled trial. Time to complete epithelialisation (completely healed), pain, aesthetic and functional scar quality and procedure time were assessed in 82 adults, 42 treated with ReCell alone and 40 with split thickness skin grafting. Time to complete epithelialisation was 13±2 days for the ReCell group and 12±2 days for the skin grafting group (difference not statistically significant). Postoperative pain (measured using a visual analogue score) in the ReCell group was statistically significantly lower than pain in the skin grafting group (3.3±1.6 in the ReCell group compared with 6.8±1.2 in the skin grafting group, p=0.03). Postoperative analgesia levels were the same in both groups, although patients in the skin grafting group 'complained of an additional painful site (the area of harvesting)'. The total donor site in the ReCell group was statistically significantly smaller than that in the skin grafting group (p<0.001). Aesthetic scar quality was measured using the Vancouver scar scale and the development of contractures after 1 month was also measured as an indication of function in the burned area. Quantitative Vancouver scar scale values were not reported but were described as not different between the groups according to the judgment of 2 plastic surgeons. In the ReCell Spray-On Skin system group, 12 patients (29%) developed at least 1 contracture, as did 15 patients (38%) in the skin grafting group (difference not statistically significant). Procedure time was significantly longer for the ReCell group than for the skin grafting group (59±4 minutes [mean ± standard deviation] for ReCell and 20±6 minutes for grafting, p<0.001). A second procedure was needed for 7 patients (17%) in the ReCell group and 6 (15%) in the comparator group.

3.6 Park et al. (2013) compared outcomes for 722 patients who were admitted to an Australian burns centre between January 2004 and December 2011 and who needed skin grafting or a skin replacement procedure. A total of 770 patients were enrolled in the study but 48 were later excluded from this analysis. The authors reported that 724 enrolled patients were divided into 3 groups: ReCell alone (n=73), ReCell plus standard skin graft (n=264), or standard skin graft

alone (n=387). It is assumed that 2 of these patients were later excluded but no information was given about their treatment group. The study reported that the type of surgical intervention did not influence the likelihood of the patient having a burn wound infection. ReCell alone was associated with a shorter hospital stay than standard skin grafting alone (actual values not reported, odds ratio 0.7, 95% confidence interval [CI] 0.57 to 0.82, p<0.01), but ReCell plus standard skin grafting was not associated with a shorter hospital stay (odds ratio 0.98, 95% CI 0.88 to 1.10, p=0.85). The authors concluded that patients treated with ReCell alone had a 30% shorter length of hospital stay (p<0.01) compared with standard skin grafting. The External Assessment Centre questioned the validity of the statistical analysis, but noted that the authors stated that the shorter hospital stay for those treated with ReCell alone should be interpreted carefully. This is because wound depth and surgery timing differed between the ReCell and standard skin grafting groups. The study authors also speculated that the reduction in donor skin harvesting associated with the ReCell technique may have reduced the length of hospital stay.

3.7 Wood et al. (2012) evaluated the use of ReCell and a biosynthetic dressing (Biobrane) compared to standard treatment (dressings every 2 to 3 days with definitive surgery at 10 to 14 days after the injury). A total of 13 children were included and followed up over 6 months; 5 received ReCell with Biobrane, 4 received Biobrane alone and 4 received standard treatment. At 10 days after the initial burn, none of the patients in the ReCell plus Biobrane group were assessed as needing surgery; 1 patient in the Biobrane group needed surgery, and 3 out of 4 patients in the standard treatment group needed surgery. The median time to complete healing for ReCell group was similar to the time for the Biobrane group and the median time was longer in the standard treatment group (median [interquartile range] 16.0 [11.5 to 18.0], 16.0 [14.25 to 23.0] and 36.5 [18.5 to 47.7] days respectively; no statistical analysis provided). The patients treated with ReCell plus Biobrane showed a higher proportion of wound area healing at both 10 and 21 days after the burn (95% and 100% respectively) compared with Biobrane alone (83.2% and 97.7%) or with standard treatment (71.2% and 90.1%) although no statistical analysis was reported.

3.8 Dunne and Rawlins (2012a) observed 40 children in the UK who were treated either by ReCell plus Biobrane (mid and deep dermal burns, n=13), or Biobrane (superficial dermal burns, n=20), or standard skin grafting (full thickness burns,

n=7). The authors reported that hospital stay was shorter and scar assessment was better in the ReCell plus Biobrane and the Biobrane groups, although neither numbers nor statistical significance were reported. The External Assessment Centre noted that this was a non-comparative review of treatments in burns of different depths and could be considered as 3 separate case series.

3.9 Echlin et al. (2012a) observed 5 patients with mid to deep dermal facial burns (3 scalds and 2 flame burns) in the UK. Four patients were treated with ReCell plus non-adherent dressings because they were assessed 9 to 11 days after the burn and their burns were deemed unlikely to heal within 3 weeks. One further patient was assessed 23 days after injury and was treated with ReCell plus an allograft. The authors concluded that ReCell increased the speed of wound healing (mean healing time 5 days for those treated 9 to 11 days after the burn, maximum healing time 7 days) and decreased the rate of standard skin grafting and subsequent scar formation, but no comparative data or statistical analyses were reported. The authors reported that as a result of this study the burns service involved changed its practice to treat these wounds with ReCell rather than a skin graft.

3.10 Rawlins et al. (2011a) compared the outcomes for 15 adults with deep dermal flame burns treated 48 to 72 hours after injury with either ReCell plus Biobrane (n=5), or standard skin grafting (n=10). The mean time to wound healing (no healing measurement defined) was 18 days in the ReCell plus Biobrane group and 48 days for the standard skin grafting group. No statistical analyses were reported. The authors reported that less analgesia was needed in the ReCell plus Biobrane group than in the standard skin graft group and that scar quality was better in the ReCell plus Biobrane group, but values were not reported.

3.11 Rawlins (2013) described the outcomes for 26 children with deep dermal burns who were treated with ReCell (n=11) or a standard skin graft (n=15). The mean visual analogue scale score for scar quality, assessed by independent clinicians, was very similar in the 2 groups (3.9, 95% CI 2.8 to 4.9 for ReCell and 3.9, 95% CI 3.3 to 4.5 for standard skin graft; p=0.97). Operative time was longer for ReCell than for standard skin grafting (mean 87 minutes compared with 58 minutes; p=0.05), although the total burn surface area was greater for the ReCell group than the standard skin graft group (mean total burn surface area of 6.5% compared with 2.9%; p=0.04).

3.12 Sen et al. (2012) reported data from a case series. The data from this case series overlap with a study by Philp et al. (2013), a report on which was available in full to the Committee as academic in confidence. Sen et al. reported narrative findings from a case series of 5 patients with deep partial or full thickness burns over more than 50% of their total body surface area. Burns were covered with split thickness skin grafts and split thickness dermal grafts. The split thickness dermal grafts and donor sites were treated with ReCell. The graft and donor sites were assessed by 2 independent observers. Graft take was reported as being complete for all patients and healing was reported to be similar to that for patients treated with split thickness skin grafting alone.

Additional studies identified by the External Assessment Centre

3.13 Dunne and Rawlins (2012b) reported early results from the same study as Rawlins (2013).

3.14 Dunne and Rawlins (2013) reported outcomes for 11 children treated with ReCell plus Biobrane for scalds and 10 adults, 8 of whom were treated with ReCell plus Biobrane for flame burns. The nature of the burns in the other 2 adults was unclear. This was a retrospective review with possible overlap with Rawlins (2011a, 2013), Rawlins et al (2011a and 2011b) and Dunne and Rawlins (2012b). Wound coverage, pigmentation, hypertrophic scarring and donor site morbidity were assessed. One child needed a standard skin graft after treatment with ReCell but early wound coverage and good pigmentation were reported with minimal hypertrophic scarring or donor site morbidity.

3.15 Hiller et al. (2013) (possible overlap with Rennekampff et al. 2011, see section 3.17) described the outcomes for 5 patients who had partial thickness facial burns and who were treated with ReCell. Only narrative outcomes were reported, with the authors reporting accelerated healing time and an improvement in scar quality.

3.16 Rawlins (2011a) and Rawlins et al. (2011b) (overlap with Rawlins et al. 2011a, see section 3.10) described outcomes for 4 patients treated with ReCell plus Biobrane compared with 10 matched controls who received standard skin grafts. Time to healing (healing measurement not defined) was 18 days in the ReCell plus

Biobrane group and 48 days in the standard skin grafting group. Analgesia needs and length of hospital stay were reported as being reduced in the ReCell group compared with standard skin grafting, but no statistical analyses were reported. After 6 months, an assessment using the Vancouver scar scale indicated better scar outcomes in the ReCell group (5.3) than in the standard skin graft group (6.5).

3.17 Rennekampff et al. (2011) (possible overlap with Hiller et al. 2013, see section 3.15) reported outcomes in a case series of 5 patients with facial burns who were treated with ReCell. The depth of the burns was not clearly reported, although the authors' discussion implied that partial and full thickness burns were included. The authors reported that the full thickness burns needed skin grafting, however they did not state clearly that these burns were also treated with ReCell. Time to epithelialisation was reported as being 7 to 9 days after surgery and skin pigmentation was described as being slightly reduced compared with skin surrounding the area. No hypertrophic scars or severe contractions occurred.

3.18 Sood et al. (2009) reported findings from an intra-patient comparative study in 10 patients with partial thickness burns. Each patient was treated with ReCell in 1 area and meshed skin grafting in another. Skin graft take was the main outcome reported, but the method of measurement was not reported. Results showed the overall graft take was 93.6% at the ReCell sites and 98.2% at the standard skin graft sites. Eight patients had 100% graft take in the ReCell group. In the standard skin grafting group, 9 patients had 100% graft take.

3.19 The External Assessment Centre identified 1 ongoing multicentre randomised, within-patient controlled feasibility study that fitted the decision problem, but no findings were available.

Additional work requested by the Committee

3.20 The Committee requested additional information on the potential effect of the use of ReCell on improving skin colour match in burn scars. The External Assessment Centre gathered this information from an additional literature search and a survey of clinical experts, in conjunction with further work requested by the Committee to enable revision of the sponsor's cost modelling (see sections 5.7

to 5.9).

3.21 The External Assessment Centre identified 3 comparative studies examining the effect of using ReCell on the repigmentation of stable vitiligo lesions.

3.22 Daniel et al. (2011) reported interim results in a conference abstract from an intra-patient randomised comparison of ReCell compared with mini-grafting in 14 patients with stable vitiligo. Repigmentation at 3 months was 27% for the ReCell-treated areas compared with 11% for mini-grafting, but at 12 months the proportions were 15% and 12% respectively (not statistically tested).

3.23 Venugopal et al. (2009) reported results in a conference abstract from an intrapatient randomised comparison of ReCell compared with mini-grafting in 12 patients with stable vitiligo who completed a 6-month follow-up. Pigmentation results were 'highly variable' with no difference between treatments, although ReCell produced a more uniform repigmentation in some cases.

3.24 Mulekar et al. (2007) conducted an intrapatient comparison of ReCell against melanocyte-keratinocyte transplantation in 5 patients with stable vitiligo. At 4 months postoperatively results were comparable, with 100% repigmentation in both sites in 2 patients, no repigmentation in either site in 1 patient, 65% for ReCell compared with 100% for melanocyte-keratinocyte transplantation in 1 patient and 40% for ReCell compared with 30% for melanocyte-keratinocyte transplantation in 1 patient.

3.25 The External Assessment Centre stated that results from the comparative studies were inconclusive. The clinical experts surveyed by the External Assessment Centre pointed out that there were physiological differences between burns and surgically created wounds, such as debrided vitiligo lesions prepared for treatment. The opinion of the experts about whether outcomes from the treatment of vitiligo could be transferable to burns was divided. Most experts stated that they might consider using ReCell for acute burns if it could be shown to have benefit in hypopigmentation conditions.

Additional evidence

3.26 During consultation, 4 additional unpublished clinical studies were identified. These included interim findings from an ongoing clinical trial comparing ReCell with split thickness skin grafts for healing burn wounds and with standard care for healing donor sites; 2 comparative studies (Komen et al., Aust et al.) using ReCell in vitiligo and healed burn scars; and 1 case study from the United States (Holmes et al.) describing the use of ReCell to treat a large area burn, comparing outcomes with an institutional average. These studies were presented to the Committee in full (1 as commercial in confidence and 3 as academic in confidence) and were reviewed by the External Assessment Centre. The External Assessment Centre was of the opinion that the interim findings from the ongoing trial agreed with data presented in the sponsor's submission and the assessment report. The External Assessment Centre advised the Committee that the information submitted on the 2 comparative studies was not sufficiently detailed to draw robust conclusions, and that the findings did not suggest that outcomes for these indications would be transferable to acute burn wounds. The External Assessment Centre described the single case study as not being representative of the NHS care pathway and providing limited comparative data.

Adverse events

3.27 No adverse event reports relating to ReCell were found in a search of the Manufacturer and User Facility Device Experience (MAUDE) database operated by the US Food and Drug Administration.

Committee considerations

3.28 The Committee heard clinical expert advice that a key motive for using ReCell would be to reduce burn healing time, which could reduce the risk of infection and the degree of scarring, as well as shortening length of hospital stay. It also noted the potential benefits associated with using ReCell for treating burns by generating viable skin cells from a small donor site. However, the Committee judged that there was insufficient evidence to quantify any improvements in burn healing time, shorter hospital stays and improvements in pigmentation in healed

burns to make a recommendation for routine adoption.

3.29 The Committee heard expert advice that small (up to 10% total body surface area) partial thickness burns usually heal with conventional dressings or a biosynthetic dressing such as Biobrane, without the use of skin grafting. The Committee considered the clinical evidence taken together with the clinical expert advice gathered by the External Assessment Centre (see sections 5.7 to 5.9). It accepted the views of the majority of clinical experts obtained by the External Assessment Centre, who agreed that these burns would heal without the use of skin substitutes. The Committee concluded that ReCell was unlikely to be beneficial in treating patients with small partial thickness burns.

3.30 The Committee noted that the available clinical evidence suggested that ReCell may be an effective alternative to skin grafting for mid-dermal to deep dermal partial thickness burns and the need for a smaller donor site may offer advantages. The Committee was aware that most of these studies were conducted outside the UK, and it accepted that current clinical opinion would not favour the use of ReCell as an alternative to skin grafting in these burns in NHS practice.

3.31 The Committee heard clinical expert advice that ReCell might be used alone on mid to deep dermal or indeterminate depth burns where the need for grafting is initially unclear. The External Assessment Centre confirmed that there was some support for this scenario in the clinical expert views obtained (see section 5.15). The Committee concluded that ReCell may offer some benefit in this group from avoiding skin grafting and better scar outcomes, but that further evidence about these outcomes was needed.

3.32 The Committee was advised by experts that the patients most likely to benefit from the use of ReCell were those with large full thickness or deep partial thickness burns that need meshed skin grafting. It was advised that potential applications also include the use of ReCell on skin graft donor sites to reduce healing time and allow further grafts to be taken sooner from the same site to treat very large burns. The Committee was aware that there was little published evidence on these outcomes. The Committee considered additional clinical expert advice subsequently gathered by the External Assessment Centre and concluded that use of ReCell in conjunction with meshed skin grafts in these

burns and donor sites showed promise, but the evidence was inconclusive.

3.33 The Committee considered the possibility that ReCell might reduce the occurrence of hypopigmentation in healed burns, as a result of the retention of melanocytes in the cell suspension. It noted that scar skin colour match was an important consideration for burns patients, but that primary evidence for pigmentation outcomes when using ReCell in burns was scarce. At its first meeting, the Committee noted a difference in clinical expert opinion on the relevance of data on using ReCell for treating hypertrophic scars or for non-burn indications such as vitiligo. It therefore asked the External Assessment Centre to include questions about skin colour match in burns scars in its additional work, as well as reviewing any relevant evidence. The Committee accepted the External Assessment Centre's conclusion from its additional work that both the study evidence and expert opinion on pigmentation outcomes when using ReCell were inconclusive.

3.34 The Committee judged that further evidence should be gathered from additional research to investigate the clinical utility of using ReCell in:

- full thickness or deep partial thickness burns that need skin grafting (see section 3.32) and
- partial thickness or indeterminate depth burns where the need for grafting is unclear (see section 3.31).

The Committee was advised that observational data, such as those collected in the International Burn Injury Database or from well-designed clinical audits, could be useful in helping to resolve some of the clinical uncertainties in these patient groups.

3.35 For larger burns needing wide-meshed skin grafting, the Committee heard advice from clinical experts that cultured cells are sometimes used in the NHS to promote healing. Their advice concurred with the findings in the External Assessment Centre's additional report, that the choice of whether to use cultured cells or ReCell was based on the availability of cultured cells and the personal preferences of clinicians because of a lack of good comparative evidence. The Committee was advised by clinical experts that using cultured cells has the advantage of the availability of large volumes of viable cells, but may be

associated with a fragile epithelium and problems with skin loss in the healed burn. The External Assessment Centre confirmed that there was currently no evidence comparing ReCell with cultured cells. The Committee concluded that data from further research comparing these treatments would be useful.

3.36 The Committee was advised by clinical experts that multicentre research into the effectiveness of ReCell in treating burns would be possible, but difficult, particularly for large full-thickness burns that occur in only a small number of people each year. The Committee was also advised that it might be hard to determine the effect of the use of ReCell or other treatment strategies on length of hospital stay because many other factors influence this in patients with large, deep burns. Careful selection of patients would be necessary to minimise the confounding effect of comorbidities.

3.37 The Committee heard expert clinical advice that time to 95% healing is a standard measure and would be an appropriate endpoint to include in any research, in addition to length of hospital stay, cosmetic appearance of scars (assessed using a validated scale) and a measure of function in the burned area.

3.38 At its meeting to discuss the comments received during consultation, the Committee considered the additional evidence obtained by the External Assessment Centre, described in section 3.26. The Committee concluded that these studies did not provide sufficient clinical evidence to alter its recommendations. However, the Committee considered that findings from these studies could be useful to inform further research.

4 NHS considerations

System impact

4.1 Claimed system benefits in the case for adoption presented by the sponsor included a statement that the ReCell Spray-On Skin system ('ReCell') may lead to a reduction in:

- the length of hospital stay because weekly rather than daily dressing changes are needed, allowing earlier discharge and outpatient management
- the need for re-dressings under anaesthetic.

Committee considerations

4.2 The Committee was advised by clinical experts that in large full or deep partial thickness burns, length of stay in hospital is influenced by many factors in addition to wound healing time. These factors include other injuries sustained at the time of the burn such as inhalation injuries, existing comorbidities and psychosocial factors. The Committee concluded that further research would be necessary in a carefully selected group of patients to determine the effect of using ReCell on length of hospital stay, because the resource implications were unclear.

4.3 The Committee accepted the findings from the External Assessment Centre's report that there was variation in practice in the frequency and nature of dressing changes, types of dressing used and use of anaesthesia. The Committee considered that evidence about the possible effect of using ReCell on the resources used in dressing changes could be gathered in further research.

5 Cost considerations

Cost evidence

Published evidence

5.1 The External Assessment Centre excluded all the studies identified by the sponsor because they were outside the scope of the evaluation, although it did recognise that the studies contained useful cost information for standard care. The External Assessment Centre initially considered that the study by Wood et al. (2012) (not presented by the sponsor as part of its economic evidence) may provide some relevant evidence on costs. However, quality assessment showed several limitations (small number of patients, non-UK care pathway, heterogeneous population), so the External Assessment Centre concluded that the evidence could not be generalised to support the sponsor's economic case.

Sponsor's cost model

5.2 The sponsor submitted a de novo cost analysis comparing the ReCell Spray-On Skin system ('ReCell') plus conventional dressings, ReCell plus Biobrane, Biobrane alone, and conventional dressings alone, for treatment of a partial thickness 640 cm^2 burn. Full details of all cost evidence and modelling considered by the Committee are available in the assessment report overview in the supporting documentation.

5.3 The sponsor submitted a base case analysis modelling patients treated for partial thickness burns including scalds, for which meshed grafting was not needed. The model covered a 21-day period. The extent of healing was observed after the first 10 days, assessing whether wounds had 100% epithelialisation (completely healed) or incomplete healing. This determined whether a patient's wound was likely to heal without intervention within the 21-day timescale or whether skin grafting would be needed. Other clinical parameters in the model included length of time as an inpatient and need for a skin graft.

5.4 In the base case, the sponsor assumed a time to healing of 15 days (based on the time to 100% epithelialisation) for the conventional dressing treatment arm. This was based on the median from 3 studies observing conventional topical burn treatments (Caruso et al. 2006; Cuttle et al. 2007; Silverstein et al. 2011). The sponsor then used a percentage reduction in healing time for the conventional dressings to calculate healing times for the other 3 interventions. The estimated reductions were based on results from Wood et al. (2012) and Echlin et al. (2012b) and were 30% for Biobrane or ReCell alone and 40% for the combination. The estimates of the number of people who were treated as inpatients were based on clinical opinion obtained by the sponsor. The proportion of patients having a standard skin graft was based on clinical studies (Caruso et al. 2006; Cuttle et al. 2007; Ostlie et al. 2012; Silverstein et al. 2011) which may have overestimated the proportion because of the included populations. Clinical opinion also suggested this figure may be lower (5% to 10%). The sponsor used clinical opinion to inform this parameter for the other interventions.

5.5 The sponsor's base case included several key assumptions:

- A burn size of 640 cm^2 (5% to 10% total body surface area depending on the age and size of the patient).
- The burn was considered to be partial thickness with no definite areas of deep involvement.
- Burns were considered sufficiently severe to warrant initial debridement in theatre. Patients having conventional and Biobrane treatment were assumed to need 20 minutes theatre time at the start of treatment. Those treated with ReCell would need 30 minutes theatre time (based on clinical opinion).
- All patients would remain as inpatients until day 2. Those who were discharged at this point would have re-dressing either as outpatients or as day visitors to the ward (based on clinical opinion).
- All patients were assumed to have their burn managed on a general burns ward (or in an outpatient clinic if discharged). The sponsor excluded intensive care unit costs because it considered these costs would obscure other treatment cost differences.

5.6 The sponsor's base case analysis showed Biobrane to be the lowest cost

treatment (£6,398), followed by the ReCell Spray-On Skin system plus Biobrane (£7,787), the ReCell Spray-On Skin system (£7,892) alone and then conventional dressings (£9,543). Biobrane was the lowest cost treatment because of its lower acquisition cost compared with the alternative treatments, fewer dressing changes needed and reduced healing time compared with conventional dressings. Cost savings for the ReCell Spray-On Skin system were driven by a reduced proportion of patients needing a standard skin graft and shorter healing times compared with conventional dressings. The sponsor explored the uncertainty around the model parameters and the effect this had on the incremental cost of ReCell using a one-way sensitivity analysis. The results of the sensitivity analysis showed that in all of the scenarios presented, ReCell was cost saving compared with conventional dressings, except for the smaller wound size of 320 cm^2, when ReCell and ReCell plus Biobrane were more costly than conventional dressings. In all of the other scenarios Biobrane was the lowest cost option followed by ReCell plus Biobrane, ReCell alone and conventional dressings.

5.7 After reviewing the available economic evidence, the Committee asked for additional information on the cost consequences of using ReCell to treat full or deep partial thickness burns in conjunction with grafting, in the form of a revised economic model (see section 5.18). The Committee also requested further information on 3 parameters used in the sponsor's existing model for partial thickness burns not needing grafting that it considered to be particularly uncertain, which were length of hospital stay, time to epithelialisation and need for a skin graft. The External Assessment Centre gathered additional information from clinical experts working in NHS burns units and centres to further inform the revisions to the sponsor's model.

5.8 The External Assessment Centre was asked to consider full or deep partial thickness burns in 2 subgroups:

- Patients with full or deep partial thickness burns judged to need skin grafting and likely to need 1 operation with inpatient stay on a burns ward. The interventions for this group were skin grafting in conjunction with ReCell and ReCell alone. The comparator was skin grafting alone.
- Patients with large area full or deep partial thickness burns judged to need wide meshed skin grafting and likely to need multiple operations and grafting and time in an intensive care or high dependency unit. The intervention for

this group was meshed grafting with ReCell and ReCell alone at the donor site. The comparator was meshed skin grafting alone and standard donor site treatment.

The External Assessment Centre further classified these 2 groups as patients with burns covering 10% and 40% of the total body surface area respectively, based on referral thresholds to burns services. The External Assessment Centre intended to use these parameters as the base case for the model and to vary them in sensitivity analyses. It also classified the partial thickness burns not needing grafting as those covering 10% of the total body surface area for the purposes of gathering information about the uncertainties in the sponsor's model. Adults and children were considered separately within the burn groups.

5.9 In order to find further information to inform the analysis of full or deep partial thickness burns in the 2 subgroups, the External Assessment Centre carried out an initial literature search around burn care in the UK. Results from this search, the sponsor's model and previously identified literature were used to create a list of parameters for which information was needed. The External Assessment Centre devised a questionnaire to gather data on these parameters, with the help of the lead clinical experts from the evaluation. The questionnaire was aimed at capturing quantitative information for the revised modelling and also for the 3 uncertain parameters from the sponsor's model. It also included questions to gather qualitative data on the cosmetic outcomes of using ReCell in burns and vitiligo. The questionnaire was administered as a semi-structured interview with optional email follow-up because of the volume of questions included and the opportunity to gain additional insight from the clinicians.

5.10 The External Assessment Centre tried to obtain data from the International and National Burn Injury Databases (iBID and NBID) but was unable to gain access within the timeframe for the additional work.

5.11 The External Assessment Centre contacted lead clinicians from all specialist burns units and centres identified in England and Wales (adult and paediatric; 18 in total). Interviews were conducted with 10 clinicians, 9 consultant burns surgeons and 1 specialist burns nurse. Another burns surgeon provided comments on a summary of the data. Of those interviewed, 3 had not used

ReCell but all respondents were familiar with it.

5.12 The data collected for each of the 3 groups are summarised in tables 5 to 7 of the External Assessment Centre's additional report (pages 14 to 17). For the 10% total body surface area partial thickness burns not needing grafting, the External Assessment Centre found that many adults would be treated with conventional dressings rather than Biobrane and would not be taken to an operating theatre. Children would be more likely to be treated with Biobrane, which would need a general anaesthetic in an operating theatre. The External Assessment Centre found some variation between sites in terms of the care pathway and little quantitative data. Most respondents indicated that this type of burn would usually heal within 2 weeks without the need for alternative treatments such as ReCell. Those using ReCell in this group indicated that it would need additional theatre time and could not provide any quantifiable data about reduced healing time, subsequent need for grafting or scar outcome.

5.13 For the 10% total body surface area full or partial thickness burns needing grafting, the External Assessment Centre found that unmeshed sheet rather than meshed skin grafting was more likely to be used. Most respondents indicated that ReCell would not be used alone or with Biobrane in patients who were treated with sheet skin grafts.

5.14 For the 40% total body surface area full or partial thickness burns likely to need meshed grafting, the External Assessment Centre found considerable variation in practice between sites. Available data from the International Burn Injury Database indicated that there would be around 8 or 9 patients treated in each burns centre each year making generalisable estimates of the treatment pathway difficult. Many respondents described using autologous cultured cells in conjunction with meshed skin grafts to improve the speed of healing and to improve the appearance of the healed burn. Autologous cultured cells are available from 1 NHS laboratory and 1 commercial provider and take around 2 weeks to produce. ReCell was generally considered for use when cultured cells were not available. The respondents expected healing time to decrease and cosmetic outcome to improve with the addition of autologous cells but were unable to provide quantitative data.

5.15 The External Assessment Centre asked all interviewees what they considered the

role of ReCell in treating acute burns to be. All interviewees thought that ReCell might have some benefit, particularly in large burns needing skin grafting. The immediate availability of cells produced using ReCell was considered to be an advantage over the use of cultured cells needing a 2-week wait. However, some clinicians expressed a preference for cultured cells as a result of available volume and cell viability. Another advantage of ReCell identified was the potential for its use with left-over pieces of donor skin from grafting, which would otherwise be discarded. However, the External Assessment Centre noted that this type of use may extend theatre time. The respondents identified 2 other scenarios for the use of ReCell. In mid-dermal, mixed depth, intermediate or indeterminate burns ReCell could be used with the aim of reducing healing time and the need for later skin grafting. The other option identified was its use in deep facial burns as an additional treatment when the burn had not healed well after 2 weeks.

5.16 The External Assessment Centre summarised the available evidence from the assessment report, the additional literature search and the findings from the interviews with experts for 9 main parameters in section 3.3 of its additional report (pages 18 to 23). The External Assessment Centre stated that the lack of quantitative data for the clinical benefits or resource impact of using ReCell meant that it was unable to develop economic modelling for burns needing skin grafting.

5.17 The External Assessment Centre concluded that the uncertainties in the parameters used in the sponsor's model (length of hospital stay, time to healing and proportion of patients needing skin grafts) could not be verified. The findings from the interviews with experts indicated that ReCell was unlikely to be used in the NHS to treat the population included in the sponsor's model, because these burns are likely to heal without the need for skin substitutes and so there would be no additional benefit from its use.

Committee considerations

5.18 The Committee noted that the sponsor's economic model did not include the treatment of large area full or deep partial thickness burns needing skin grafting, as identified in the decision problem for the evaluation. The Committee heard expert clinical advice that the use of ReCell in this patient group might have

substantial clinical benefits. Therefore, the Committee asked the External Assessment Centre to produce economic analysis for the treatment of these burns to aid its decision-making in developing recommendations for ReCell. The Committee was aware of the lack of published data for this patient group but it considered that parameters for the economic analysis could reasonably be obtained by expert opinion from a broad range of clinicians working across NHS burns units and centres. The Committee also suggested that hospital-based audit data might be available to inform the model.

5.19 The Committee was unconvinced about the validity of some of the assumptions in the sponsor's model for partial thickness burns, in particular the length of hospital stay, time to healing and the proportion of patients needing skin grafts. The Committee accepted the conclusions of the External Assessment Centre's additional work that several parameters in the sponsor's model for smaller partial thickness burns not needing grafting could not be validated (see section 5.17). It also accepted the advice that ReCell is unlikely to be used by clinicians in the NHS for this group of patients because their burns would usually be treated with conventional or biosynthetic dressings without skin substitutes.

5.20 The Committee considered the External Assessment Centre's conclusion that there were insufficient data to inform the cost modelling to include the use of ReCell in full or deep partial thickness burns needing grafting. The Committee queried the effect of potential reductions in healing time on length of hospital stay for these burns in the NHS. In the light of expert clinical advice that treating these burn injuries has a high cost to the NHS and that a reduced stay could have a relatively large effect on resource use, the Committee considered that further research on use of ReCell should include evaluation of its cost and resource impact.

6 Conclusions

6.1 The Committee concluded that the ReCell Spray-On Skin system ('ReCell') is a promising technology with potential to improve healing in acute burns, especially for patients with burns that need skin grafting. However, the Committee judged that there was insufficient evidence about the most appropriate patient population and therefore, the clinical and cost benefits of using ReCell to support the case for routine adoption at the present time.

6.2 The Committee decided that further research into clinical outcomes of using ReCell for treating burns would be beneficial. It considered that further research could determine the benefits of treatment with ReCell in patients with larger full thickness or deep partial thickness burns, or mid-dermal partial thickness or indeterminate depth burns. The Committee considered that evidence about the relative benefits and costs of ReCell compared with cultured cells in treating large burns in combination with meshed skin grafts would be useful in making decisions about the use of ReCell for these patients.

6.3 The Committee concluded that research could reasonably involve the use of data from existing sources such as the International Burn Injury Database, as a supplement to other methods. The Committee considered that time to 95% healing, length of hospital stay, cosmetic appearance of scars and a measure of function of the burned area would be important outcomes in any research or data analysis.

7 Committee members and NICE lead team

Medical Technologies Advisory Committee members

The Medical Technologies Advisory Committee is a standing advisory committee of NICE. A list of the Committee members who took part in the discussions for this guidance appears below.

Committee members are asked to declare any interests in the technology to be evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each Medical Technologies Advisory Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Bruce Campbell (Chair)
Consultant Vascular Surgeon, Exeter

Dr Peter Groves (Vice Chair)
Consultant Cardiologist, Cardiff and Vale NHS Trust

Professor Dilly Anumba
Chair of Obstetrics and Gynaecology/Honorary Consultant Obstetrician and Gynaecologist, University of Sheffield

Ms Susan Bennett
Lay member

Dr Keith Blanshard
Consultant Interventional Radiologist, University Hospitals of Leicester NHS Trust

Professor Nigel Brunskill

Professor of Renal Medicine, University of Leicester

Mr Matthew Campbell-Hill
Lay member

Mr Andrew Chukwuemeka
Consultant Cardiothoracic Surgeon, Imperial College Healthcare NHS Trust

Professor Daniel Clark
Head of Clinical Engineering, Nottingham University Hospitals NHS Trust

Professor Tony Freemont
Professor of Osteoarticular Pathology, University of Manchester

Professor Shaheen Hamdy
Professor of Neurogastroenterology, University of Manchester

Dr Jerry Hutchinson
Independent Medical Technology Adviser

Dr Cynthia Iglesias
Health Economist, University of York

Professor Mohammad Ilyas
Professor of Pathology, University of Nottingham

Dr Greg Irving
GP, University of Liverpool

Dr Eva Kaltenthaler
Reader in Health Technology Assessment, ScHARR, University of Sheffield

Dr Paul Knox
Reader in Vision Science, University of Liverpool

Mrs Karen Partington
Chief Executive, Lancashire Teaching Hospitals NHS Foundation Trust

Mr Brian Selman
Managing Director, Selman and Co

Professor Wendy Tindale
Scientific Director, Sheffield Teaching Hospitals NHS Foundation Trust

Professor Allan Wailoo
Professor of Health Economics, ScHARR, University of Sheffield

Mr John Wilkinson
Director of Devices, Medicines and Healthcare Products Regulatory Agency

Dr Amber Young
Consultant Paediatric Anaesthetist, North Bristol NHS Trust

Dr Janelle Yorke
Lecturer and Researcher in Nursing, University of Manchester

NICE lead team

Each medical technology assessment is assigned a lead team of a NICE technical analyst and technical adviser, 2 clinical expert advisers, a patient expert (where appropriate), a non-expert member of the Medical Technologies Advisory Committee and representative of the External Assessment Centre.

Joanne Higgins
Technical Analyst

Bernice Dillon
Technical Adviser

Amber Young and **Bruce Philp**
Lead Expert Advisers

Cynthia Iglesias
Non-Expert MTAC Member

Sue Peirce and **Grace Carolan-Rees**

External Assessment Centre Representatives

8 Sources of evidence considered by the Committee

The External Assessment Centre report for this assessment was prepared by Cedar:

- Peirce S, Carolan-Rees G. The ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury. October 2013. Cedar
- Peirce S, Carolan-Rees G. The ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury – additional report. November 2013. Cedar

Submissions from the following sponsors:

- Avita Medical Ltd. (manufacturer)
- JB Medical Ltd. (sponsor)

The following individuals gave their expert personal view on the ReCell Spray-On Skin system by providing their expert comments on the draft scope and assessment report.

- Miss Isabel Jones, ratified by the British Association of Plastic, Reconstructive and Aesthetic Surgeons - clinical expert
- Dr Rebecca Martin, nominated by the Association of Burns and Reconstructive Anaesthetists - clinical expert
- Dr Sarah Pape, ratified by the British Association of Plastic, Reconstructive and Aesthetic Surgeons - clinical expert
- Mr Bruce Philp, ratified by the British Burn Association - clinical expert
- Dr Amber Young, nominated by the Association of Burns and Reconstructive Anaesthetists - clinical expert

The following individuals gave their expert personal view on the ReCell Spray-On Skin system in writing by completing a patient questionnaire or expert adviser questionnaire provided to the Committee.

- Miss Isabel Jones, ratified by the British Association of Plastic, Reconstructive and Aesthetic Surgeons - clinical expert
- Dr Rebecca Martin, nominated by the Association of Burns and Reconstructive Anaesthetists - clinical expert
- Dr Sarah Pape, ratified by the British Association of Plastic, Reconstructive and Aesthetic Surgeons - clinical expert
- Mr Bruce Philp, ratified by the British Burn Association - clinical expert
- Dr Amber Young, nominated by the Association of Burns and Reconstructive Anaesthetists - clinical expert

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