NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

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

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the sponsor's submission of evidence and with the EAC report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Some potential key issues for consideration by the Committee are described in section 6, following the summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in [redacted].

This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: External Assessment Centre correspondence
- Appendix E: Sponsor's factual check of the assessment report and the External Assessment Centre's responses

1 The technology

The ReCell Spray-On Skin (Avita Medical Ltd) 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. The ReCell Spray-On Skin is prepared by taking a thin piece of split-thickness skin to harvest keratinocytes, melanocytes, fibroblasts and Langerhans cells. The cells are processed into a suspension, and delivered to the treatment area, using proprietary preparation and 'spray-on' processes. Cells from the suspension are able to rapidly proliferate and migrate in the wound bed. The regenerative nature of these skin cells is intended to promote the growth of healthy skin to facilitate rapid healing. It takes approximately 20–30 minutes in total to collect the tissue and prepare and apply the cell suspension. The procedure is designed to be carried out by clinicians, without input from specialised laboratory staff.

2 Proposed use of the technology

2.1 Disease or condition

Burns are relatively common and often extremely painful. Although most burns are minor, serious burns can result in disabling or disfiguring scarring, amputation or death. Recovery from a serious burn injury is associated with emotional and physical challenges and can have a significant effect on quality of life. A study of people hospitalised for burns found that around half changed job status as a result of their injury (Weichman and Patterson 2004). Burns can also lead to increased fear, grief, anxiety and depression and in some cases, post-traumatic stress disorder. Scarring can lead to negative body image, feelings of social isolation and social stigma.

The majority of burn injuries are caused by heat, with around 5% caused by chemical injury or electrocution. The main causes of severe burn injury are flame burns and liquid scalds.

2.2 Patient group

The ReCell Spray-On Skin can be in adults or children to treat partial thickness burns for which mesh grafts are not needed, or large area burns for which mesh grafts are needed. The ReCell Spray-On Skin should be used by burns experts in burns units or centres as suggested in the decision problem in the scope.

Around 250,000 people in the UK seek medical attention for burns each year. Of these, around 175,000 attend accident and emergency departments and the UK admission rate is 0.29 per 1000 cases of burns or smoke inhalation. In England in 2011/12 there were 12,213 hospital admissions for burns and corrosions (chemical burns), of which 9043 were emergency admissions. The average number of burns-related deaths in the UK each year is 300.

2.3 Current management

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

The first step in managing a burn injury is to assess the depth of the burn, the proportion of the body area involved and the site of injury. Burn depth is classified according to the level of skin or tissue affected. Epidermal and superficial dermal wounds tend to heal without scarring or surgical intervention within 21 days. Deep dermal or deep partial-thickness (where epidermis and dermis are both damaged) and full-thickness burns (epidermis, dermis and subcutis are damaged) may need surgical excision (to remove the burnt skin and tissues) and skin grafting to ensure rapid healing, to minimise scarring and reduce complications. It is usual for surgical excision to take place within a day or 2 of admission. For mixed-depth, partial-thickness scalds or burns, decision making to graft normally occurs over 14-21 days unless the

patient's condition deteriorates before this. If wounds are still unhealed after 14–21 days, skin grafts can be used to achieve a better cosmetic result.

Full-thickness burns more than 1 cm in diameter need skin grafts because the regenerative components of the skin have been lost. Healing can occur only from the edges of the wound; without a graft the skin contracts, leading to a poor cosmetic outcome and reduced mobility. Deep dermal burns are unlikely to heal within 3 weeks and will therefore often need grafting.

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 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. The donor site is itself a wound and needs treatment to ensure healing. If large grafts are needed for extensive wounds the donated skin can be perforated (or meshed) to increase the surface area. The pattern of meshing can be visible after healing, so sheet grafting is preferable to improve the cosmetic result.

Allografting (using skin from another person, often after death) and xenografting (using skin from animals) can also be used for temporary wound closure but these will ultimately be rejected by the body. Other alternatives to autologous grafts for deep partial-thickness and full-thickness wounds include artificial skin products.

2.4 Proposed management with new technology

For this assessment, the aim of the ReCell Spray-On Skin system is to treat partial thickness burns (for which a mesh grafting is not needed) and large area burns (for which mesh grafting may be needed) in adults and children in burns centres or units. Introducing this technology would not involve a significant change to current practice.

2.5 Equality issues

Two potential issues were identified at scoping:

- Skin grafting in people with darker skin can result in a poor colour match in the grafted area. The sponsor claimed that treatment with ReCell Spray-On Skin could result in better matching of skin colour. The evidence for this claim presented by the sponsor was in patients with hypopigmented scars and vitiligo lesions. However, the EAC considered that outcomes in these populations could not be extrapolated to patients with acute burns (see section 4.1). None of the included burns studies reported population ethnicity or any difference in outcomes according to skin colour. One expert adviser indicated that ReCell Spray-On Skin appears to produce better pigmentation outcomes than would otherwise have been expected (including in patients with darker skin).
- The trypsin enzyme used to disaggregate the skin cells from the biopsy during the ReCell process is derived from pigs. This means that the treatment may be unacceptable to people whose religious or cultural beliefs forbid contact with porcine material. The sponsor noted that the porcine origin of trypsin is well recognised and that Biobrane (a biosynthetic dressing which is currently used in the NHS to dress some burns) also contains material of porcine origin. Expert advice to the EAC indicated some variation in practice; either all patients are routinely informed about the nature of the product or only those patients who are suspected to object.

3 Decision problem

3.1 Sponsor's claimed benefits

The benefits to patients claimed by the sponsor are shorter wound healing time at the recipient site, leading to:

- improved aesthetic result with a lower likelihood of scarring of the burn wound and better match of skin colour
- repopulation of melanocytes to reduce hypopigmentation in healed wounds
- reduced dressing change frequency (weekly rather than daily)
- less need for dressing changes under anaesthetic
- a reduction in skin graft donor site size and depth

- fewer complications, reduced morbidity and shorter healing time at the donor site.

The benefits to the health system claimed by the sponsor are reductions in:

- length of stay in hospital, because weekly rather than daily dressing changes allow earlier discharge and outpatient management, thus reducing the costs of care
- re-dressings under anaesthetic, again reducing the costs of care
- the need for external technical laboratory support
- the likelihood of readmission for corrective surgery, because of improved aesthetic results.

The claimed benefits, together with the Committee's selection considerations, were used to develop the scope for the evaluation. Table 1 is a summary of the decision problem, on which the sponsor's submission was based. The decision problem generally contains a comprehensive list of the outcomes by which the technology's benefits could be realised. However the sponsor may choose to not submit evidence on all outcomes, either because none exists, or because there is no relevant evidence.

The sponsor did not vary the outcomes in the decision problem but the EAC highlighted an extra outcome included in the sponsor's submission: 'Graft loss or graft take following initial surgical and requirement for subsequent skin grafting' (page 16 of the assessment report).

Table 1 Summary of decision problem

	Scope issued by NICE
Population	Adults or children treated in burns units or centres for: • partial thickness burns, including scalds caused by hot water, for which mesh grafting is not needed • large area burns; full thickness or deep partial thickness burns, including those for which mesh grafting is needed
Intervention	For partial thickness burns, including scalds caused by hot water: • ReCell Spray-On Skin alone, or in combination with biosynthetic or standard dressings For large area burns and full or deep partial thickness burns for which mesh grafting is needed: • skin mesh graft in combination with ReCell Spray-On Skin
Comparator(s)	For partial thickness burns, including scalds caused by hot water: • Biosynthetic dressings (e.g. Biobrane) • Standard dressings For large area burns; full or deep partial thickness burns for which mesh grafting is needed: • Skin mesh graft alone • Skin mesh graft plus biosynthetic dressing
Outcomes (full details in scope)	The outcome measures to consider: • speed of healing • length of stay • degree of scarring • degree of pigmentation • device-related adverse events, such as wound infection rates
Special considerations, including issues related to equality	Skin grafting in people with darker skin can result in a poor colour match in the grafted area. The ReCell Spray-On Skin system may result in better colour matching of the resulting skin. The trypsin enzyme used to disaggregate the skin cells from the biopsy during the ReCell process is derived from pigs. This means that the treatment may be unacceptable to people whose religious or cultural beliefs forbid contact with porcine material.

4 The evidence

4.1 Summary of evidence of clinical benefit

The sponsor’s search identified 18 published references and 1 unpublished abstract relevant to the ReCell Spray-On Skin system. The sponsor excluded 7 references and presented the remaining 3 peer-reviewed journal papers and 8 conference abstracts. The EAC considered 2 of the conference abstracts (Echlin 2012b; Palombo 2012) to be outside the scope and identified an

additional 9 conference abstracts (of which 2 were unavailable and 5 contained data that overlapped with other references presented by the sponsor; section 3.3 page 21 of the assessment report). The EAC noted that the 9 additional references were identified by duplicating the sponsor's search strategy and that the sponsor provided no reasons for why they were excluded.

The sponsor also identified and presented 5 published studies in support of the degree of pigmentation outcome specified in the decision problem. The EAC considered all 5 to be outside the scope because the patient populations were people with scars or vitiligo and did not include people with burns. The EAC decided, on the basis of clinical expert advice, that evidence on the effect of the ReCell Spray-On Skin system in wounds created by dermabrasion and hypopigmentation lesions was not generalisable to the treatment of acute burns wounds.

Summaries of studies

A brief description of the relevant ReCell studies is given below and in table 2 (studies included by the sponsor) and table 3 (additional studies identified by the EAC). Full details of the methodologies and outcomes are provided in section 3.4 and 3.5 of the assessment report (pages 25–40). The EAC identified overlaps in the patient populations reported in multiple studies and contacted authors to obtain further information. Despite this, there is uncertainty about the degree of overlap between some studies.

Published studies

Full studies

Gravante et al. (2007) conducted a single centre randomised controlled non-inferiority trial in Italy to compare the ReCell Spray-On Skin system with skin grafting, for treating deep partial thickness burns in 82 adults. Aesthetic quality of the scars was measured using the Vancouver scar scale by 2 plastic surgeons, 1 of whom was blinded to the procedure. The functional quality of the scar was measured, based on the development of contractures (an area of skin that has undergone excessive scarring and can develop into

hypertrophic scars), after 1 month. Time to complete epithelialisation was 13±2 days (mean±standard deviation) for the ReCell group and 12±2 days for the comparator group (difference not significant). Despite being part of the study design, Vancouver Scar Scale values were not reported but were not different between the groups according to the judgment of 2 plastic surgeons. In the ReCell group 12 patients developed at least 1 contracture, as did 15 in the comparator group (difference not statistically significant). Postoperative pain in the ReCell group was statistically significantly reduced compared with pain in the comparator group (p=0.03). Postoperative analgesia was the same in both groups, although patients in the comparator group 'complained of an additional painful site (the area of harvesting)'. Procedure time (unreported) was significantly longer for the ReCell group than the comparator (p<0.001) group. The donor area harvested for the ReCell group was significantly smaller than that for the comparator group (p<0.001). A second procedure was needed for 7 patients in the ReCell group and 6 in the comparator group.

Park et al. (2013) carried out a retrospective multivariate analysis in Australia. The study included 767 patients who were admitted to the burns centre between January 2004 and December 2011 and who needed skin grafting or a skin replacement procedure. Patients were divided into 3 groups: the ReCell Spray-On Skin system alone, the ReCell Spray-On Skin system plus standard skin graft, or standard skin graft alone. The aim of the study was to determine whether infection, graft loss and length of stay were related to surgical intervention for burns. The study indicated that the type of surgical intervention did not influence the likelihood of the patient having a burn wound infection. The ReCell Spray-On Skin system alone was associated with a reduction in length of stay compared with standard skin graft alone (odds ratio [95% CI] 0.7 [0.57–0.82], p<0.01) but the ReCell Spray-On Skin system plus standard skin graft was not (0.98 [0.88–1.10], p=0.85). The authors concluded that the ReCell Spray-On Skin system reduced patients' length of stay by 30% (p<0.01) compared with standard skin graft. The EAC noted that the authors did state that the reduction of length of stay demonstrated by the ReCell Spray-On Skin system should be carefully interpreted because wound depth treated and surgery timing differed between the ReCell group and the

standard skin graft group. Burn depth and total burn surface area were taken into account to calculate the severity of the burn and the authors indicated that the reduction in donor skin harvesting for the ReCell technique may have reduced the length of stay.

Wood et al. (2012) carried out a 3-armed randomised controlled pilot study at a burn centre in western Australia, evaluating the use of the ReCell Spray-On Skin system plus Biobrane, Biobrane alone, and local standard treatment dressings every 2–3 days with definitive surgery at 10–14 days post injury) in 13 children over a 12-month period. The aim of the study was to investigate using early interventions to prevent the need for surgery. None of the patients in the ReCell plus Biobrane group needed surgery 10 days after the burn; 1 patient in the Biobrane group needed surgery, and 3 out of 4 patients in the standard treatment group needed surgery. The median length of time for the ReCell group to reach complete healing 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 [11.5–18.0], 16.0 [14.25–23.0] and 36.5 [18.5–47.7] days respectively; no statistical analysis provided). The patients treated with the ReCell Spray-On Skin system plus Biobrane experienced greater wound healing, based on the outcome ‘speed of healing’ at both 10 and 21 days post burn compared with Biobrane alone and standard treatment (no statistical analysis provided).

Abstracts

Dunne and Rawlins (2012a) observed 40 children in the UK who had 1 of 3 procedures: the ReCell Spray-On Skin system plus Biobrane (mid and deep dermal burns, n=13), Biobrane (superficial dermal burns, n=20) or standard skin graft (full thickness burns, n=7). The aim of the study was to assess average hospital stay, scar appearance, wound healing, donor site morbidity, and analgesic and dressing costs. Hospital stay was shorter in the Biobrane group and the ReCell plus Biobrane group, and scar assessment was good or good to excellent in all groups.

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 the ReCell Spray-On Skin system plus non-adherent dressings because they were assessed 9–11 days after the burn and deemed unlikely to recover within 3 weeks. One further patient was assessed 23 days after injury and was treated with the ReCell Spray-On Skin system plus allograft dressing. Analgesia needed at the first dressing change and in total was measured. The authors concluded that the ReCell Spray-On Skin system increased the speed of wound healing and decreased the need for standard skin graft and therefore subsequent scar development. As a result, the burns service involved (Chelsea and Westminster) changed its practice to treat these wounds with the ReCell Spray-On Skin system rather than a skin graft.

Rawlins et al. (2011a) compared 15 adults with deep dermal flame burns treated with either the ReCell Spray-On Skin system plus Biobrane (n=5), or standard skin grafting (n=10) 48–72 hours after injury. The mean time to wound healing was 18 days in the ReCell plus Biobrane group and 48 days for the standard skin graft group. Less analgesia was used in the ReCell plus Biobrane group than the standard skin graft group and scar quality was better in the ReCell plus Biobrane group.

Rawlins (2013) observed 26 children with deep dermal burns who were treated with the ReCell Spray-On Skin system (n=11) or standard skin graft (n=15) in an unspecified location. The mean visual analogue scale score was very similar in the 2 groups (3.9; 95% CI 2.8 to 4.9 for ReCell, and CI 3.3 to 4.5 for standard skin graft; p=0.97). Operative time was longer for the ReCell Spray-On Skin system than the standard skin graft cohort (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).

Unpublished studies

[redacted]

[redacted]

Table 2 Summary of clinical evidence (adapted from table 2 and section 3.4 in the assessment report)

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Full, peer-reviewed articles					
Gravante et al. (2007)	Randomised controlled trial (Italy)	• Partial thickness burns <320 cm^2 • Adult (30–65 years) • Sample size 82	ReCell applied to burn wound and biopsy site vs Mesh SSG	• Time to complete epithelialisation (days; mean±sd) 13±2 for ReCell, 12±2 for SSG • Functional quality of scar (patients with contractures) 12/42 for ReCell, 15/40 for SSG • Postoperative pain (VAS) 3.3±1.6 for ReCell, 6.8±1.2 for SSG (p=0.03) • Procedure time (mins) 59±4 for ReCell, 20±6 for SSG (p<0.001) • Area harvested (cm^2) 2.2±1.0 for ReCell, 110±50 for SSG (p<0.001) • No intraoperative or postoperative adverse effects were observed	• Lack of clarity around the treatment allocation • Blinding difficult for some outcomes • The accuracy and precision of time to healing may be poor as patients were assessed weekly.

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Park et al. (2013)	Retrospective multivariate analysis (Australia)	• Burns treated with skin grafting or replacement • All patients • Sample size 767 (770, 3 excluded)	**Two intervention groups** • ReCell alone • ReCell plus SSG vs • SSG	• Presence of post-operative burn wound infection (odds ratio, CI) :ReCell vs SSG 0.78 (0.34-3.42); ReCell+SSG vs SSG 1.23 (0.45-4.52) • Graft loss (OR, CI): ReCell vsSSG 0.89 (0.45-2.32) (p<0.09); ReCell+ • SSG vs.SSG 1.56 (0.56-.21)(p=0.67) • Length of stay (OR, CI)ReCell vsSSG 0.7 (0.57-0.82) (p<0.01);ReCell+SSG vs SSG 0.98 (0.88-1.10) (p=0.85)	• Baselines results between intervention groups not provided • Number of patients in each surgical analysis unknown • Co-author is the inventor of ReCell and Director of Avita Medical

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Wood et al. (2012)	Three-arm randomised controlled pilot study (Australia)	• Scalds >2% TBSA, expected to need surgery • Paediatric (8 months – 9 years) • Sample size 13	**Two intervention groups** • ReCell plus Biobrane • Biobrane Vs. • Standard Care (SC) with silver (Acticoat) and hydrocolloid (Duoderm) dressings on alternate days	• Complete wound healing (days; median, IQR) 16.0 (11.5-18.0) for ReCell+Biobrane, 16.0 (14.25–23.0) for Biobrane, 36.5 (18.5–47.7) for SC • Wound healing (Visitrak): ReCell+Biobrane, Biobrane and SC after 10days 95%, 83.2%, 71.2% and after 21 days 100%, 97.7% and 90.1% respectively • Scar assessment (VSS) for ReCell+Biobrane (VSS 0,3,5,6), Biobrane (VSS 2,3,3,9) and SC (VSS 0,5,6,6) • Change in pain (VAS, pre-post randomisation) for ReCell+Biobrane −1.0, Biobrane −2.0 and SC +1.0 • Surgery needed at 10 days: Recell +Biobrane 0/5 (0%), Biobrane 1/4 (25%) and SC 3/4 (75%) • Number of dressing changes (median, IQR): ReCell+Biobrane 5.0 (4.0-6.0), Biobrane 7.0 (5.5–9.5) and SC 12.5 (8.0-15.0)	• Good randomisation was used but this provided small numbers and resulted in differences in the patient demographics. Burn area is only recorded as TBSA with the ReCell plus Biobrane patients having absolute burn areas that were significantly smaller than the other groups • There was also discrepancy in the reported number of days for assessment of surgery • Accuracy and precision of healing time is unknown • The main author Wood is the co-inventor of ReCell and Director of Avita Medical

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Abstracts					
Dunne and Rawlins (2012a)	Retrospective review (UK)	• Scalds of differing depth • Paediatric (9 months–15 years) • Sample size 40	• Biobrane (Superficial dermal) • ReCell plus Biobrane (Mid and deep dermal) • Early skin grafting (SSG)	• Frequency of secondary SSG for ReCell+Biobrane 5/13 (38%), Biobrane 6/20 (30%) and SSG alone 2/7 (29%) Qualitative outcomes included • hospital stay, scar assessment, wound healing, analgesic and dressing costs	• Non-comparative review of patients with different scald depths. The patients were treated 3 different ways therefore can be regarded as 3 different case studies
Echlin et al. (2012a)	Case series (UK)	• Mid to deep dermal facial burns • Age 10 months to 50 years) • Sample size 5	• Patients that were assessed at 9–11 days post injury and deemed would not heal in 3 weeks were treated with ReCell and non-adherent dressing	• Time to healing (days; mean)	• 1 patient treated at 23 days • There was very little numerical data • There was no data on the previous standard of care
Rawlins (2011a)	Comparative pilot study using matched controls (Not reported, probably Australia)	• Deep dermal burns • Adult (17–59 years) • Sample size 15	**Intervention** • ReCell plus Biobrane • Data from matched controls who received standard skin graft	• Length of time to wound healing (days; mean) for ReCell 18 and SSG 48 Qualitative outcomes including • Analgesia needs • Scar assessment at 6 months	• Overlap with Rawlins *et al.* (2011b) and Rawlins (2011a) • No report on how the controls were selected

Study	Study design (country)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Rawlins (2013)	Unclear if prospective or retrospective, comparative study (Not reported, probably UK)	• Deep dermal scalds • Paediatric • Sample size 26	• ReCell vs • SSG	• Scar quality (VAS, 95% CI) for ReCell 3.9 (2.8-4.9) and SSG 3.9 (3.3-4.5) (p=0.97) • Operative time (minutes) for ReCell 87 and SSG 58 (p=0.05) • Duration of physiotherapy (days; mean) for ReCell 21 and SSG 40 (p=0.29)	• Overlap with Dunne and Rawlins (2012b) • TBSA was greater in the ReCell group indicating the patient populations differ: TBSA (%) ReCell 6.5, and SSG 2.9 (p=0.04)
Unpublished studies					
Philp et al (2013)		Burns • Population unreported • Sample size 10	• ReCell and dressed with Telfa or Biobrane vs • SSG harvesting and STDG	• Time to healing for graft and donor site (days; mean) • Patient survival • Scarring	
Abbreviations: SC - standard care, SSG - standard skin graft, TBSA – total burn surface area; VAS – visual analogue scale, VSS – Vancouver Scar Scale					

Additional studies found by the External Assessment Centre

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

Dunne and Rawlins (2013) observed 11 children treated with the ReCell Spray-On Skin system plus Biobrane for scalds and 10 adults, 8 of whom were treated with the ReCell Spray-On Skin system plus Biobrane for flame burns and the other 2 were treated for scalds. This is a retrospective review with possible overlap with Rawlins (2013) and Dunne and Rawlins (2012a, 2012b). Outcomes measured included wound coverage, pigmentation, hypertrophic scarring and donor site morbidity. One patient needed a standard skin graft after treatment with the ReCell Spray-On Skin system but early wound coverage and good pigmentation were reported with minimal hypertrophic scarring or donor site morbidity.

Hiller et al. (2013) (possible overlap with Rennekampff et al. 2011) reported outcomes on 5 patients who had partial thickness facial burns and were treated with the ReCell Spray-On Skin. Only narrative outcomes were recorded.

Rawlins (2011a) and Rawlins et al. (2011b) (overlap with Rawlins et al. 2011a) observed 4 patients treated with the ReCell Spray-On Skin system plus Biobrane compared with 10 matched controls who received standard skin grafts. Time to healing, analgesia needs and length of hospital stay were all reduced in the ReCell group compared with standard skin graft group. After 6 months an assessment using the Vancouver Scar Scale demonstrated better results in the ReCell group than in the standard skin graft group.

Rennekampff et al. (2011) (possible overlap with Hiller et al. 2013) reported a case series of 5 patients with facial burns who were treated with the ReCell Spray-On Skin system. Epithelialisation took 7–9 days after surgery and skin pigmentation was slightly reduced compared with skin surrounding the area. There were no hypertrophic scars or severe contractions.

Sood et al. (2009) reported an intra-patient comparative study in 10 patients with partial thickness burns. Patients were treated with the ReCell Spray-On Skin system in 1 area and meshed standard skin grafting in another. Graft take was the main outcome and results showed 100% take at both treatment sites in 8 patients; the other 2 patients had a lower take at the ReCell site (93.6%) than at the standard skin graft site (98.2%).

Table 3 Additional references identified by EAC

Study	Study design (country known)	Population	Intervention versus comparator	Outcomes considered	EAC comments on study
Dunne & Rawlins (2012b)	Comparative observational study	Burns Paediatric Sample size 21	• ReCell Vs. • SSG	• Scar quality (VAS) ReCell 4.6 vs SSG 4.7% (p=0.97) • Operative time (mins) for ReCell 87 vs SSG 64 (p=0.22) • Length of physiotherapy follow-up (days; mean) ReCell 21 vs SSG 25 days (p=0.29)	• Overlap with Rawlins (2013) • Population difference; TBSA (%) ReCell 6.5 vs SSG 4.3 (p=0.22)
Dunne & Rawlins (2013)	Non-comparative observational study	Deep dermal burns All patients Sample size 21	• ReCell and Biobrane	• Scar pigmentation • Degree of hypertrophy	• Retrospective review of cases, overlap with Rawlins (2013), Dunne and Rawlins (2012a,b) • No numerical results provided
Hiller et al. (2013)	Case series (Germany)	Partial thickness facial burns • Adult (27–81 years) • Sample size 5	• ReCell • ReCell plus grafting	• Author stated 'acceleration in epithelialization and healing time as well as improvement in scar quality'.	• Possible overlap with Rennekamff et al (2011)

Rawlins (2010)	RCT	Scalds Paediatric Sample size unknown	• Unknown	• Unknown	• *Abstract unobtainable*
Rawlins (2011a) Rawlins et al. (2011b)	Comparative pilot study with matched controls	Deep dermal burns to the legs • Adults (17–59 years) • Sample size 14	• ReCell plus Biobrane Vs. • SSG	• Time to healing (days) ReCell+ Biobrane 18 vs SSG 48 • Analgesia needs (mg Tramadol) ReCell+Biobrane 280 mg vs SSG 450 mg • Scar assessment (VSS) ReCell+ Biobrane 5.3 vs SSG 6.5	• Overlap with Rawlins et al. (2011a)
Rawlins (2011b)	Unknown	Scalds Paediatric Sample size unknown	• Unknown	• Unknown	• *Abstract unobtainable*
Rennekampff et al. (2011)	Case series (Germany)	Facial burns (assumed deep partial thickness) • Population unreported • Sample size 5	• ReCell	• Time to epithelialisation: ReCell 7–9days post-surgery • Scar quality and skin pigmentation (qualitative outcome)	• Timing of skin grafting not clear
Sood et al. (2009)	Intrapatient comparative study	Partial thickness burns • Population unreported • Sample size 10	• ReCell Vs. • Meshed SSG	• Graft take (% take) for ReCell 93.6% Vs SSG 98.2% (calculations by EAC)	• No description of graft take
Abbreviations: SC - standard care, SSG - standard skin graft, TBSA – total burn surface area; VAS – Visual Analogue Scale VSS – Vancouver Scar Scale					

Conclusions about the clinical evidence

The EAC noted that interpretation of the clinical evidence is limited by inconsistencies between the population, intervention and comparator groups in the studies and those defined in the scope. Despite this, the EAC considered that 2 studies (Gravante et al. 2007; Park et al. 2013) provided robust evidence and concluded that the evidence overall does appear to demonstrate that the ReCell Spray-On Skin system is at least as effective as other current treatments in the care of acute burns within a specialist burns service.

4.2 Advice from experts and patient organisations

Expert adviser questionnaires were completed by 5 experts at the briefing note stage (4 of whom also provided advice during the evaluation). No further questionnaires were completed during the evaluation stage. All questionnaires are summarised in appendix B.

NICE's Public Involvement Programme received no response from patient organisations about this technology during the evaluation stage. One patient organisation responded at the initial briefing note stage but the advice received referred to patients outside of the decision problem.

4.3 Summary of economic evidence

The sponsor's search was broader than the scope and identified 8 published studies and 1 unpublished audit and cost analysis (Rawlins 2011c) .The EAC excluded all the studies identified by the sponsor because they were outside the scope, although it did recognise that the studies contained useful cost information for standard care. The EAC 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. But after quality assessment, which showed several limitations (small number of patients, non-UK care pathway, heterogeneous population), the EAC judged that the evidence could not be generalised to support the sponsor's economic case.

De novo analysis

The sponsor submitted a de novo cost analysis model in TreeAge format comparing comparing the ReCell Spray-On Skin system plus conventional dressing, the ReCell Spray-On Skin system plus Biobrane, Biobrane alone, and conventional dressing alone, for treatment of a partial thickness 640 cm^2 burn. Costs were modelled from an NHS and personal social services perspective. The population included in the model was limited to patients treated for partial thickness burns including scalds, for which mesh grafting was not needed. Patients needing a meshed skin graft were not included in the model.

The model consisted of a decision tree with 4 primary branches: 2 intervention branches (1 ReCell plus Biobrane, 1 ReCell plus conventional dressing (referred to as ReCell alone here); and 2 comparator branches (1 Biobrane and 1 conventional dressing). The model covered a 21-day period. The EAC considered this was an appropriate length of time for an acute episode. The key assumptions are included in section 9.1.5, pages 134–5, of the sponsor's submission and in the costs section below.

Model parameters

In the base-case the sponsor assumed a time to healing of 15 days (based on the mean 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), which the EAC judged was appropriate. The sponsor then used a percentage reduction in healing times 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 Ethlin (2012b) and were 30% for Biobrane or ReCell alone and 40% for the combination (see table 4). The EAC were concerned by the use of this data and noted that the only study that that provided any evidence of reduced healing times for ReCell alone was a small case series (Rennekampff et al. 2011). However, the EAC acknowledged that the sponsor took account of the uncertainty in the sensitivity analyses by varying the healing time reductions

for all interventions from 0 to 50%, giving a healing time range of 7.5 to 15 days.

The estimates of the proportion of patients treated as inpatients (page 53 of assessment report) for the different interventions were based on clinical opinion only, although none of the experts could directly answer the questions. The EAC commented that the resulting assumptions are subject to particular uncertainty because of the lack of evidence and direct clinical opinion.

The EAC questioned the value used by the sponsor for the proportion of patients needing a standard skin graft with conventional dressings (30%). It considered that the parameter based on clinical studies (Caruso et al. 2006; Cuttle et al. 2007; Ostlie et al. 2012; Silverstein et al. 2011) may be overestimated because the patient populations were heterogeneous and included severe cases, and clinical opinion suggested a 5–10% standard skin graft rate. The sponsor used clinical opinion to inform this parameter for the other interventions (table 12, page 154 of the assessment report). The EAC noted that the sponsor's values (see table 4) seemed to be higher than those suggested by clinical experts but that there was agreement between experts that the ReCell Spray-On Skin system alone and in combination with Biobrane reduced the number of patients needing a standard skin graft compared with Biobrane alone.

Table 4 Parameters used by sponsor in the model

	Proportion of patients treated as inpatients	Proportion of patients progressing to standard skin graft	Healing time
Conventional dressing	50%	30%	15 days
ReCell	25%	10%	10.5 days
Biobrane	25%	30%	10.5 days
ReCell plus Biobrane	25%	10%	9 days

Costs in the model

The costs included in the de novo analysis are described on pages 55–7 of the assessment report. The EAC noted that the sponsor did not include NHS reference costs as input data or for validating the model.

The cost of each treatment in the model was based on the technology costs and hospital costs; this included staff and dressing costs, together with theatre and bed costs if needed. The general hospital costs in the model were based on data from an unpublished cost analysis ([redacted]). In the base case for a partial thickness burn treated with a conventional dressing, costs per patient varied from £4291 to £14,863 depending on the treatment options received, that is inpatient or outpatient care and graft or no graft needed. Taking into account the proportions of patients in each treatment arm, the average cost per patient was £9543 (including hospital costs of £8422 and technology costs of £1121). If the ReCell Spray-On Skin system plus Biobrane were used for treating a partial thickness burn the costs varied from £6082 to £17,082, with an average cost per patient of £7787 (including hospital costs of £5652 and technology costs of £2135). Figure 1 illustrates the overall costs for all the possible treatment pathways in the model and the average patient cost for each intervention.

The EAC highlighted several concerns about the costs used in the model for secondary dressing of wounds. It considered there was uncertainty as to whether the

[redacted]

[redacted]. The cost of secondary dressings was also an area of uncertainty, with little consensus among experts about whether general anaesthesia was needed when changing dressings. Despite initial concerns, the EAC was able to verify the costs used by using an alternative method to derive them (table 13, page 56 in the assessment report).

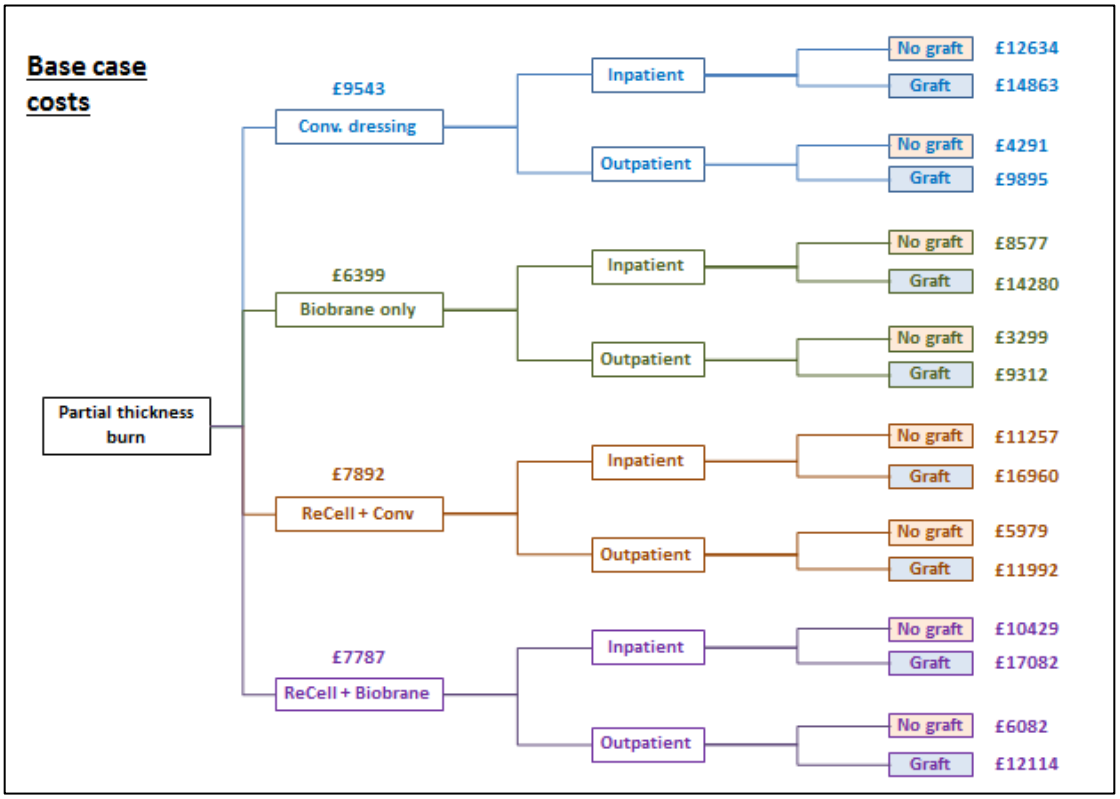

Figure 1 Base case costs used in sponsor's model (supplied by EAC)

The cost of the ReCell Spray-On Skin system was given by the sponsor and confirmed by the EAC as £950 per 320 cm^2 (the base-case model was based on 2 packs) and the cost of Biobrane used was £60.80 per 320 cm^2. Costs for consumables, training and maintenance were not included in the model but the EAC considered this to be reasonable because the device is single use and the manufacturer provides training. The only additional cost the sponsor had included for ReCell was an additional 10 minutes in theatre for debridement and dressing of the initial wound.

Results

The sponsor's base-case analysis showed Biobrane to be the lowest cost treatment (£6398), followed by the ReCell Spray-On Skin system plus Biobrane (£7787), the ReCell Spray-On Skin system (£7892) alone and then conventional dressings (£9543). Biobrane was the lowest cost treatment because of its lower acquisition cost, reduced number of dressing changes and reduced healing time. 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.

The sponsor carried out sensitivity analyses to explore the impact of the uncertainty in various parameters and costs. Results are described for each intervention separately in table C13 on pages 159–62 of the sponsor's submission. The EAC corrected some minor errors in these results (assessment report page 58) with no change in the rank order of cost saving interventions: Biobrane, the ReCell Spray-On Skin system plus Biobrane, the Recell Spray-On Skin system alone, and conventional dressings.

Table 5 Incremental costs from EAC scenario analysis (negative values indicate a cost saving for the ReCell Spray-On Skin system)

Scenario	ReCell vs conventional dressing	ReCell+Biobrane vs conventional dressing	ReCell vs Biobrane	ReCell+Biobrane vs Biobrane
Base-case (TBSA 640 cm^2)	**−£1,651**	**−£1,756**	£1,494	£1,389
TBSA 320 cm^2	£23	£20	£1,146	£1,143
TBSA 1280 cm^2	**−£1,148**	**−£1,680**	£3,718	£3,186
Benefits reduced by 50%	**−231**	**−£265**	£1,076	£1,042
Hospital costs reduced by 25%	**−£1,052**	**−£1,104**	£1,523	£1,471
Hospital costs increased by 25%	**−£2,250**	**−£2,407**	£1,463	£1,306
Abbreviations: TBSA total burn surface area				

The sponsor investigated several scenario analyses that included varying the total burn surface area (320 to 1280 cm^2) and the in-hospital costs (section 4.3 of the assessment report). The EAC corrected some errors and re-ran these scenario analyses (see table 5) and showed that the ReCell Spray-On Skin system was cost saving compared with conventional dressings except when treating a smaller wound site of 340 cm^2. In this case both the ReCell Spray-On Skin system and ReCell plus Biobrane were more expensive than conventional dressings. The EAC concluded that the sensitivity and scenario analyses findings demonstrated the robustness of the sponsor's model.

Additional work presented by the EAC

The EAC used NHS reference costs to validate costs used in the model and found that overall results were consistent with the sponsor's model.

For completeness, the EAC compared the model results with those reported in the cost analysis by Wood et al. (2012). This found standard dressings were the lowest cost intervention followed by the ReCell Spray-On Skin system plus Biobrane, and that Biobrane alone was the most costly intervention. The EAC identified as factors that may have contributed to these different results the differences in clinical practice between Australia and UK, differences in patient population and the small number of patients (n=13) in the study.

The EAC could not find any evidence that the ReCell Spray-On Skin system reduced the number of patients who progressed to having a standard skin graft. It therefore expanded the range of the sensitivity analysis from 5–20% to 5–30%. Although this increased the total cost of the ReCell Spray-On Skin (£9079) it still remained cost saving compared with conventional dressings (£9543). The EAC also expanded the range of costs for changing dressings but the results showed the ReCell Spray-On Skin system was still cost saving compared with conventional dressings (see tables 18–21 in the assessment report, p60).

Conclusions about the economic evidence

The EAC considered there were some limitations to the model. The sponsor used data provided by 4 experts to populate the model but the information and description provided to the experts when describing burn type differed from those in the population being considered. The expert opinions differed about the proportion of patients needing standard skin grafts (see table 12 in the assessment report for details). The EAC agreed that 3 of the experts were likely to be familiar with UK practice but they considered that the fourth expert, who had experience working in Australia, was less pertinent. This expert was also one of the ReCell inventors and may therefore have a conflict of interest. The model also relied on unpublished cost data

[redacted]

The EAC concluded that the sponsor's model was robust in the 1-way sensitivity analysis and scenarios modelled except for the treatment of smaller burns (320 cm^2: 2.5–5% total burn surface area).

5 Ongoing research

The EAC identified 1 ongoing multicentre randomised, within-patient controlled feasibility study that fitted the decision problem. The trial is being carried out in the USA in collaboration with the Department of Defence in order to gain an FDA licence for the ReCell Spray-On Skin system.

The sponsor also identified a second trial but this was outside the scope because it investigated the use of the ReCell Spray-On Skin system in treating scars from skin grafts.

6 Issues for consideration by the Committee

6.1 Clinical evidence

Efficacy of the ReCell Spray-On Skin system for burns that do not need grafting

There was limited clinical evidence in this patient group. The EAC considered that Woods et al. (2012) was the most relevant study. This reported results from a small trial in children who had a scald injury greater than 2% total burn surface area that was expected not to heal within 10 days and therefore likely to benefit from surgery. The results suggested that the ReCell Spray-On Skin system plus Biobrane may reduce healing time and reduce the number of patients who need subsequent grafting compared with both Biobrane alone and standard dressings. The EAC noted there is no evidence comparing the use of the ReCell Spray-On Skin system alone with the use of Biobrane alone.

Efficacy of the ReCell Spray-On Skin system for burns that need grafting

The EAC agreed with the sponsor's conclusion that the ReCell Spray-On Skin system is at least as effective as standard skin grafting in the treatment of partial thickness burns in terms of wound healing and scar outcomes. It disagreed with the sponsor's claim that the ReCell Spray-On Skin system plus standard skin graft demonstrated more rapid healing than a standard skin graft alone. This comparison has been investigated only in the study by Park et al. (2013), which did not report healing rate outcomes. The EAC also

highlighted that the claim that the ReCell Spray-On Skin system plus Biobrane provides more rapid healing, lower costs and shorter length of hospital stay than a standard skin graft is weak because it was based on only 1 study of 15 patients (Rawlins et al. 2011a). The EAC stated that the evidence also suggested that the use of the ReCell Spray-On Skin system is associated with an increase in operative time, and there was no evidence to demonstrate that the ReCell Spray-On Skin system added any additional clinical benefit to Biobrane.

6.2 Additional evidence identified by the External Assessment Centre

The EAC identified 9 additional conference abstracts that were not presented by the sponsor. The EAC reported that 6 of these abstracts presented data from studies that were the same as or overlapped with those presented in the sponsor's evidence. Where possible the EAC contacted authors to confirm the duplication or overlap but they received few responses. Three of the abstracts provided new information, although 2 may have reported the same study. The EAC commented that these additional references did not add substantially to the evidence because of the low levels of detail in the abstracts.

Hypopigmentation

The EAC excluded 2 conference abstracts (Echlin 2012b; Palombo 2012) identified by the sponsor in their main literature search, because the EAC did not consider them relevant to the decision problem. The EAC also excluded all evidence the sponsor collated identifying pigmentation outcomes in people with hypopigmentation (scars and vitiligo) because the patient groups and wound types were outside the decision problem. The EAC confirmed with experts that these outcomes in these populations could not be extrapolated to acute burns patients. Several of the studies reported scar quality outcomes using numerical scales but pigmentation is not reported separately.

6.3 Economic evidence

Limited availability of evidence to support modelling assumptions

The EAC considered that the evidence underpinning the model is very limited and some of it is of questionable suitability, given the heterogeneity of the patient population, the multiple ways of grouping burn injuries and the variable nomenclature used. The EAC recognised that it was a challenge for the sponsor to ensure that all the model inputs were based on the chosen patient population. The evidence was taken from a small number of published and unpublished studies, often with different populations. Expert opinion was used to bridge gaps in the evidence but the advice obtained was varied. The EAC also noted that the model relied quite significantly on an unpublished study for cost data [redacted] for which little information about data acquisition and cost derivation is known.

Robustness of the results

Despite the paucity of data, the EAC considered that the sponsor had produced a model for 1 of the population groups specified in the scope: those with partial burns that do not need grafting. The EAC considered the model fit for purpose and was able to validate it using NHS reference costs. Results from the model were shown to be robust in 1-way sensitivity analysis and in scenario analysis conducted by the sponsor and expanded by the EAC, except for a scenario analysis that involved smaller burns (320 cm^2: 2.5–5% total burn surface area).

The sponsor considered that the lower costs for Biobrane alone reflect an inappropriate comparison. It noted that Biobrane is mostly used in patients with smaller or more superficial burns, and it considered that it would not be used in isolation for the types of burns for which the ReCell Spray-On Skin system might be considered.

The EAC noted that the important factors in the ReCell Spray-On Skin system being cost saving compared with conventional dressings are the reduction in the proportion of patients needing a standard skin graft and the shorter healing time. The EAC also highlighted there was little evidence for the

parameters used in the model for these clinical outcomes, especially for the ReCell Spray-On Skin system plus conventional dressings intervention, for which there was only 1 small case series study. (Rennekampff et al. 2011).

No cost analysis for large area burns

The sponsor did not provide an economic model for the patient group specified in the scope: ‘large area burns; full thickness or deep partial thickness burns including where mesh grafting is required’ because of insufficient evidence to provide input parameters. The EAC did not disagree with this. There is some clinical evidence that suggests that the ReCell Spray-On Skin system can be used instead of standard skin grafting for certain burn types and this is likely to have potential cost saving implications.

7 Authors

Caroline Hall, Technical Analyst
Bernice Dillon, Technical Adviser
NICE Medical Technologies Evaluation Programme
November 2013

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

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

B Submissions from the following sponsors:

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

C Related NICE guidance

Published

- moorLDI2-BI: a laser doppler blood flow imager for burn wound assessment. NICE medical technology guidance 2 (2011)

Under development

- Trauma services: service delivery of trauma services, NICE clinical guideline. Publication expected October 2014
- Major trauma: assessment and management of major trauma, NICE clinical guideline. Publication expected June 2015

D References

Dunne J, Rawlins J (2012a) Early Paediatric Scald surgery - developing a (cost effective) dermal preserving surgical protocol for all childhood scalds [abstract]. In: Proceedings of the 16th Congress of the International Society for Burn Injuries, 9th – 13th September 2012, Edinburgh, Scotland. Abstract 716

Dunne J, Rawlins J (2012b) A comparison of ReCell and split thickness skin grafts in management of paediatric burns [abstract]. In: Proceedings of the 16th Congress of the International Society for Burn Injuries, 9th – 13th September 2012, Edinburgh, Scotland. Abstract 718

Dunne J, Rawlins J (2013) How we do it. Early dermal salvage with Biobrane and ReCell in the management of deep dermal burn wounds [abstract]. In: Proceedings of 15th Congress of the European Burns Association, 28th-31st August 2013, Vienna, Austria. Abstract number 172, page number 196.

Echlin K, Way B, Jones I (2012) Autologous non-cultured epidermal cell suspension to improve healing in deeper partial thickness facial burns. In International Society for Burns Injuries meeting [abstract]. In: Proceedings of the 16th Congress of the International Society for Burn Injuries, 9th – 13th September 2012, Edinburgh, Scotland. Abstract number 709

Gravante G, Di Fede MC, Araco A et al. (2007) A randomized trial comparing ReCell system of epidermal cells delivery versus classic skin grafts for the treatment of deep partial thickness burns. Burns 33: 966–72

Hiller M, Limbourg A, Branski L et al. (2013) Improving aesthetic outcome – therapy for facial burns with ReCell [abstract]. In: Proceedings of 15th Congress of the European Burns Association, 28th-31st August 2013, Vienna, Austria. Abstract number 170, page number 193.

Park JH, Heggie KM, Edgar DW et al. (2013) Does the type of skin replacement surgery influence the rate of infection in acute burn injured patients? Burns 39: 1386–90

Philp B, Dziewulski P, El-Muttardi N et al. (2013) [redacted] (Submitted for presentation)

Rawlins J (2010) A prospective randomised clinical trial to investigate and evaluate patient outcomes of Biobrane biosynthetic wound dressings with and without ReCell autologous cell suspension in paediatric scald injuries [abstract]. In: Proceedings of the 15th Congress of the International Society for Burn Injuries, 21st – 25th June 2010, Istanbul, Turkey.

Rawlins J (2011a) Treatment of deep dermal burns to the legs – a comparative pilot study [abstract]. In: Proceedings of British Burns Association Annual meeting, 22nd-25th March 2011, Salisbury District Hospital, UK.

Rawlins J (2011b) Early surgery for ALL paediatric scalds – developing a dermal preserving protocol for the benefit of patients and healthcare providers [abstract]. In: Proceedings of the American Burns Association 43rd Annual Meeting American Burns Association, 29th March – 1st April, Chicago, Illinois.

[redacted]

Rawlins JM (2013) ReCell versus split-thickness skin grafts in the management of deep dermal paediatric Scalds. In Chinese Burns Association

Rennekampff H, Herold C, Vogt M (2011) Keratinocyte suspension for the treatment of facial burns. European Burns Association. Burns 37 (September): S17

Sen S, Ives M, Philp B et al. (2012) Use of split thickness dermal grafts in combination with sprayed keratinocytes in burns [abstract]. In: Proceedings of the 16th Congress of the International Society for Burn Injuries, 9th – 13th September 2012, Edinburgh, Scotland. Abstract number 693

Sood S, Roggy D, Zieger M (2009) Preliminary results with the use of spray keratinocytes in the treatment of partial thickness burns. European Burns Association Congress. Burns 35 (September): S20

Wood F, Martin L, Lewis D et al. (2012) A prospective randomised clinical pilot study to compare the effectiveness of Biobrane synthetic wound dressing, with or without autologous cell suspension, to the local standard treatment regimen in paediatric scald injuries. Burns 38: 830–9

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Miss Isabel Jones
Burns Consultant, British Association of Plastic, Reconstructive and Aesthetic Surgeons

Dr Rebecca Martin
Lead Anaesthetist & Intensivist, Association of Burns & Reconstructive Anaesthetists

Dr Sarah Pape
Consultant Plastic Surgeon, British Association of Plastic, Reconstructive and Aesthetic Surgeons and British Burn Association

Mr Bruce Philp
Consultant Plastic Surgeon, British Burn Association

Dr Amber Young
Lead Paediatric Burns Anaesthetist and Paediatric Burns Network Lead Title, Association of Burns & Reconstructive Anaesthetists

- Of the 5 experts who responded, 3 have had direct experience of ReCell, 1 has managed patients in whom it has been used and 1 would like to use the technology. One expert has conducted research on the technology
- Three experts felt that the technology was thoroughly novel, 1 that it was a significant modification of existing technology and 1 that it was a significant modification of an existing technology
- All 5 experts said that the technology would be used to aid wound healing in burns patients, particularly in partial thickness burn injuries; 1 expert also felt it could be used in superficial burns. Two experts were of the opinion that that ReCell would be particularly useful for those with larger or difficult-

to-heal wounds and another felt that this could reduce the need for skin grafting. If ReCell were used in conjunction with skin grafting, 2 experts thought that it could improve the healing time and aesthetic appearance of meshed grafts. One expert considered ReCell would be useful for resurfacing of mid to deep-dermal burns for quicker healing and less scarring, repigmentation of depigmented skin in scars and vitiligo.

- The comparators were stated as split thickness skin grafts, biological dressing, cultured autologous keratinocytes (although the expert did comment these were rarely used and 2 experts explained that ReCell was quite different to cultured autologous keratinocytes) and camouflage make-up.
- No similar competing technologies were identified.
- Four experts were of the opinion that ReCell could aid wound healing, improving speed and quality for burn injuries including large burn areas, meshed grafts, or partial thickness scalds as well as donor sites. Two experts specifically mentioned the potential for ReCell to improve pigmentation in burn injuries and 3, a reduction in scarring. Two experts felt that the improvements in healing could reduce length of stay, and 1 that this could therefore facilitate a faster return to normal activities of daily living. One expert suggested ReCell could improve the appearance of scars.
- The main obstacles to realising the benefits in practice were thought to be cost, with 1 expert also mentioning technical ease of use and another suggesting the use of anaesthesia may be a barrier.
- Four experts thought that the technology would benefit the healthcare system by reducing resource use, such as dressings, analgesia (as a result of a reduction in pain), antibiotics or other therapy, and associated costs. Three experts said that the device could reduce the length of hospital stay. A reduction in scar appearance and improved functionality, as a result of using ReCell, could also reduce the need for future scar management interventions. One expert considered that fewer patients may have long-term psychological distress from scars and skin depigmentation.

- Four experts felt that some training would be needed to use the device, although 2 commented that the technology was easy to learn and use subsequently. One expert suggested appropriate storage would need to be provided.
- Three experts thought that the potential for ReCell to promote faster and better wound healing would reduce overall management costs and would offset the cost of the device. Another expert felt that cost savings would be achieved by the immediate accessibility of the ReCell-prepared suspension when compared against cultured cell suspension techniques. One expert didn't know how the introduction of the technology would affect costs but thought the cost of training and the technology would have to be taken into account.
- All the experts felt that guidance on the device would be useful.

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations. The following patient and carer organisations responded at briefing note stage:

- The Vitiligo Society

This society and patients were outside the scope of the Decision Problem.

No further societies responded during the evaluation stage.

Appendix D: External Assessment Centre correspondence

National Institute for Health and Care Excellence
External Assessment Centre correspondence

The ReCell Spray-On Skin system

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	**Question / Request** *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	**Response** *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	**Action / Impact / Other comments**
Section 7.1 Appendix 1	Sponsor (J Belsey) – requested detailed search strategy appendix missing from the Clinical Evidence submission (19/08/13)	Appendix 1 received by email on 20/08/13	
(1-3) Section 7.1 (4) Section 5 (5) Section 4	Sponsor (JB) to request additional information: (1) Manufacturer's list of studies (2) Search platform used for reference databases (3) Explanation of search terms (4) Ongoing study clarification (5) Declaration of Conformity (22/08/13)	Response received by email on 22/08/13 with requested information attached (Declaration of Conformity and manufacturer's list of studies). Email response included in Appendix 1.	
Section 7	Author (Gravante) – email requesting additional information regarding the method of randomisation in their study (Gravante et al, 2007), on 23/08/13 and again on 03/09/13	No response.	
Section 7	MTEP clinical expert advisors were asked their opinion regarding the generalisability of the evidence regarding hypopigmentation. (10/09/13).	One advisor responded by email but had misinterpreted the question. The email was resent with clarification. They responded with the opinion that hypopigmentation evidence was not generalisable.	

Submission Document Section/Sub-section number	**Question / Request** *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	**Response** *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	**Action / Impact / Other comments**
		Two advisors responded but felt unable to answer the question. One adviser did not respond. Emails attached as Appendix 2.	
Section 7	The sponsor (JB) was contacted regarding how they had obtained the conference proceedings, which were not available on the Web. (13/09/13)	Sponsor (JB) replied stating that manufacturer supplied the conference abstracts and he will forward missing ones to the EAC. Attached as Appendix 3	
Section 9.2.5	Sent email to sponsor (JB) requesting the questionnaire and responses used in the economic evidence. Also email address for J Rawlins. (18/09/13)	JB sent questionnaire and 4 responses, plus J Rawlins email address. Also information regarding ISBI 2012 conference abstracts. Attached as Appendix 4.	
Section 7	Sent email to J Rawlins with questions about conference abstracts. (19/09/13). Reminder sent on 25/09/13).	Response on 27/09/13 stating that all publications without F Wood's name on	

Submission Document Section/Sub-section number	**Question / Request** *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	**Response** *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	**Action / Impact / Other comments**
		were conducted in Wakefield, UK. Attached as Appendix 5.	
Section 5.1	Sent email to JB requesting clarification on the ongoing trials. (20/09/13)	Received email clarifying the trial identifiers. (20/09/13). Attached as Appendix 6.	
Section 7	Sent email to J Dunne regarding conference presentations. (25/09/13)	Got response on 26/09/13 asking J Rawlins to be included. Returned email with specific questions. Got response on 30/09/13 indicating study overlap & locations. Attached in Appendix 7.	
[redacted]	[redacted]	[redacted]	
Section 3 Section 9	Sent email to expert advisers requesting information about clinical pathway (27/09/13)	Got email response from 1 adviser and telephone conversation (followed up with email) with another adviser. Attached in Appendix 9	

Submission Document Section/Sub-section number	**Question / Request** *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	**Response** *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	**Action / Impact / Other comments**
Section 7	Sent email to B Philp regarding overlap between Sen et al. (2012) and Philp et al. (2013). (30/09/13)	Received information that Sen et al. (2012) was a feasibility study for Philp et al. (2013). Attached in Appendix 10	
	Sent email to expert advisers regarding the use of meshing in skin grafts. (07/10/13)	Got response from three advisers indicating that meshing is quite common Attached in Appendix 11	
Section 7.7.2 - 7.7.4	Sent email to expert advisers regarding advice to patients regarding tryspin and sodium lactate. (09/10/13)	Got response from three advisers indicating routine advice to patients about trypsin and safety of lactate. Attached as Appendix 12.	
	Sent email to expert advisers regarding the use of ReCell in combination with SSG. (10/10/13)	Two advisers indicate that ReCell would be used with higher mesh grafting in larger burns. Attached as Appendix 13.	
2.1	Sent email to sponsor to clarify the use of the word ‘thinness’ when describing meshed grafts. (16/09/13)	Advised that ‘thinness’ related to the thickness of	

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
		the graft and not the mesh ratio. Report wording amended as per Sponsor's Fact Check. Attached as Appendix 14.	

Appendix 1

From: Susan Peirce
Sent: 22 August 2013 11:12
Hi Jonathon

Nice to speak with you this morning. Here are my initial queries, mainly regarding the search strategy:

1. Please send us the list of studies that were in the 'Manufacturer's database of known studies'.
2. What platform did you use to access the literature databases? We use OVID and NEAR is not an operator defined on this platform (we use 'adjacent' with a number to stipulate how many words distance). Please can you let us know how NEAR is defined?
3. What was the rationale for using the search phrase 'autologous NEAR cell NEAR harvest*'? Did you have any information from the manufacturer that this was the preferred alternative if authors didn't use the brand name?
4. Please can you confirm the national clinical trials identifier for the study identified in the Ongoing Studies section (5.1, p21). This has similarities to NCT01476826 (http://clinicaltrials.gov/ct2/show/NCT01476826). Also, do you have additional information regarding study NCT01138917 (http://clinicaltrials.gov/ct2/show/NCT01138917), intended to complete in March

2014? Maybe the manufacturer has more up-to-date information that this study information will not be available within 12 months.

5. Please send us a Declaration of Conformity for the CE mark? We have three certificates for the manufacturer's quality systems, but there should also be a certificate declaring ReCell's conformity with the Medical Devices Directive and stating its classification.

I'll be in the office until about 3:15pm today. I can phone you or you can call me direct on the number below.

Sue Peirce (Dr)
Research Associate
School of Engineering
Cardiff University

Hi Sue

1. I have attached the list of studies provided by the manufacturer
2. I carried out my searches using the search engine on the Royal Society of Medicine members system. The platform that they use is ProQuest Dialog. The NEAR function is the same as the ADJACENT function in Ovid – in this case I used the default setting of within 3 words, although it can be specified otherwise
3. The manufacturers advised me that the description of the technology is "non-cultured autologous cell harvesting", although the full term would not necessarily be used as it stands in an article. Because we applied an exclusion of cultured cell harvesting studies after the search, I used only the last three words of the term. In order to capture all possible instances of this (eg a statement in the abstract that "an autologous cell sample was harvested from near the wound site" I adopted the NEAR function and based it on text words. In the event, no study was identified purely on this basis.
4. Yes, the ongoing study mentioned is NCT01138917, which has now finished recruiting although not all patients have yet completed 6 months follow-up. Study NCT01138917 is being carried out to provide data for a US FDA submission. As I understand it there have been issues with slow recruitment so that the time frame has been extended and it is now not expected to report until 2015 at the earliest and is hence outside the twelve month window.
5. Declaration of conformity attached

I will ring you to confirm that these answer your queries
Kind regards

Jonathan

Appendix 2

From: Susan Peirce (Cardiff and Vale UHB - Cedar)
Sent: 10 September 2013 16:26

Hello

I'm writing to ask your expert advice with regards to the current NICE evaluation of ReCell for burn injury. The Scope defines this as an evaluation of the evidence for ReCell in partial to full thickness burns in comparison to standard care (dressings or grafts, as appropriate).

Particular mention was made in the Scope about the effect of ReCell treatment on pigmentation of the burn scar, especially with reference to patients with darker skin. To address this the sponsor has included studies that evaluate ReCell for the treatment of hypopigmentation; the indications are essentially scar revision and vitiligo. My initial reaction is that data relating to repigmentation of these lesions following treatment with ReCell would not be generalisable to pigmentation outcome from treatment of an acute burn wound with ReCell. However, I'd like your clinical opinion as to the similarity between these indications (acute burns versus hypopigmentation), i.e. how transferable are outcomes reported in hypopigmentation patients to outcomes expected in patients with burns?

Thank you.
Sue

Sue Peirce (Dr)

Dear Sue
Thank you for the conversation. I hope it helped. I have a few changes to the content below as regards our conversation. Please do get back in touch again if I can help.

Best wishes
Amber

- Your expertise is the in treatment of acute burns and the affects of acute treatements on outcomes including scar formation. You have no clinical experience of repigmentation treatments for burn scars or vitiligo.
- You are not an expert in the long-term outcomes for burns relating to de-pigmentation
- Although scar quality is an important outcome for burns treatment there is little mention of comparative methods of treating burns acutely and the effect this has on pigmentation of burn scars at clinical conferences or research journals.
- You suspect that outcomes from using ReCell in repigmentation treatments for non-burn cases cannot be extrapolated to its use in burns.
- It may be worth asking the other clinical advisors if they have any data/information regarding pigmentation outcomes in burns managed using different strategies including ReCell.

Dr AER Young
Consultant Paediatric Anaesthetist, Lead Specialist Paediatrics

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Sue

Thank you for the email and sorry for delayed response.
This is not really an area of expertise for me as I feel my surgical colleagues would be best placed to answer on this point.
I work with Bruce Philp, who I think you emailed, and believe his response would be more valid then mine.
From what I have witnessed in clinical practice I would agree with Isabel Jones's statement.
Sorry not to be more helpful on this point, please let mw know if there is any other way in which I can help.
Kind regards
Rebecca

Dr Rebecca Martin
Consultant in Burns Anaesthesia and Intensive Care & College Tutor

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Yes, happy with this thank you.

Isabel Jones MBBS MD FRCS(Plas)
Consultant Burns and Plastic Surgery

From: Susan Peirce
Sent: 23 September 2013 09:52
Isabel

Thank you for calling this morning. I've summarised the content of our conversation – please alter anything that I've mis-represented/misunderstood or add anything that you have thought of in the meantime. This email will be included in our report to NICE.

- In your experience treatment of burn wounds with ReCell (including in patients with darker skin) appears to produce better skin pigmentation than would have otherwise been expected, but this is anecdotal and there is no published evidence to support this.
- Pigmentation outcomes following the treatment of old scars and vitiligo with ReCell cannot be extrapolated to treatment of acute burns. An acute burn wound is more complex than a surgical wound created by debridement of scars or vitiligo lesions.

Thank you,

Sue

Appendix 3

Hello Sue

Sorry about the NEAR issue - thankfully the economics search doesn't use any of these terms, so it should be simpler.

I got hold of the conference listings (and the abstracts) from the manufacturer - they tend to be at all the meetings and collect them. There is a great deal of duplication involved here, with the same work being presented at several conferences - often with different authors listed just to confuse things further.

I am out of the country now until Wednesday morning now, with only limited access to my files. I will have a look through your list and see if I have any of these with me. If not, I will sort it out when I return next week. Hope this is OK

Kind regards
Jonathan

On Fri, Sep 13, 2013 at 3:11 PM, Susan Peirce wrote:
Hello Jonathon

Regarding the clinical evidence, I've attempted to replicate your search strategy using Ovid and retrieved 32 records. I don't think we need to worry about the extra 2 records – I found that using the operator 'AJD3' (Ovid) didn't produce the same results as the operator 'NEAR' (ProQuest Dialog) so in the end I just used 'AND'.

I've reviewed the literature search you conducted and have a question.
How were you able to access the conference proceedings? I've located all three of the EBA conferences, two each of the BBA and one of the ISBI (either online or hardcopies that I already had). In particular Avita press releases indicate eight relevant presentations at the 2012 IBSI/BBA meeting in Edinburgh, of which five are included in your clinical evidence submission. However,

the website for this conference has expired. Did you manage to obtain the proceedings from the organisations? If you have electronic copies of the programmes/abstracts please could you forward them to me? I've attached a summary of additional references that I've located and the conferences I've checked so far.

This was rather confusing due to the number of similar references – I suspect a lot of overlap.

Sue Peirce (Dr)
Research Associate

Appendix 4

Hi Sue

1. I have attached the questionnaire and responses

2. Jeremy Rawlins e-mail address is: [*text removed*]

3. Regarding last weeks request – I will forward the ISBI 2012 abstract file to you. Unfortunately it is very large (100Mb+) so I will have to send it on a disk. At the moment I can only track down a hard copy version of the BBA 2013 abstracts. I am trying to find it electronically, to avoid a lot of photocopying. As it happens, there were no ReCell abstracts at this meeting.

4. I have also tracked down the issue that explains why sections A+B were different between the original and subsequent submissions – the manufacturer had inserted some new references into the file between my finishing it and it being submitted. I have now forwarded the correct file to Caroline, which she will presumably forward on to you. Unfortunately this has changed the reference numbering, so I will also forward to you a new disk with the revised numbering. Sorry for the mix-up.

Kind regards

Jonathan

Appendix 5

From: Jeremy Rawlins
Sent: 27 September 2013 15:17

Sorry, have been overwhelmed with rather a busy stint of on-call and then interstate travel (and catching-up with emails). Will follow-up on this as I can, but to answer your question on studies - all of my stuff without Fiona Woods' name on have come from my UK Cons practice in Wakefield. Hope this is helpful.

J

Appendix 6

From: Jonathan Belsey
Sent: 20 September 2013 12:20

Hi Sue

Sorry – typo in the first sentence of my reply. I should have said:

4. Yes, the ongoing study mentioned is NCT01476826, which has now finished recruiting although not all patients have yet completed 6 months follow-up. Study NCT01138917 is being carried out to provide data for a US FDA submission. As I understand it there have been issues with slow recruitment so that the time frame has been extended and it is now not expected to report until 2015 at the earliest and is hence outside the twelve month window.

Kind regards

Jonathan

From: Susan Peirce
Sent: 20 September 2013 12:04

Hi Jonathon

I've just gone back to this email in writing up my report and I've noticed that the answer to Q4 is a bit confused. Did you mean to say that the ongoing study mentioned is NCT01476826?

Sue

Appendix 7

From: Jonathan Dunne
Sent: 30 September 2013 19:21
Dear Sue,

Study 4 was conducted at Pinderfields and Royal Perth Hospital, Australia. It will be my affiliation that you may have seen as different elsewhere, but all procedures have been undertaken by Mr Rawlins at Pinderfields or Royal Perth. Abstract 4 is a retrospective review of Mr Rawlins' cases, and an update on previous presentations so there is some overlap with abstracts 1 and 3, and a small amount of overlap with 2, although that did include predominantly non-recell patients. Abstracts 3 and 4 had patients in with adequate follow-up photographs, and as they were retrospective studies there was some loss to follow-up. Abstract 1 includes patients with different follow-up timings and therefore scar assessments, which is where the differences arise from.

I haven't been through the patient data that Mr Rawlins has produced with other authors, but I believe there will be a degree of overlap with reference 4.

Hope this helps.
Kind regards,
Jonathan

On Fri, Sep 27, 2013 at 11:02 AM, Susan Peirce wrote:
>
> Thanks Jonathan
>
> I have emailed Jeremy Rawlins, but I've had no response and am on a short timescale.
> The references that I thought you might be able to help me with are:
>
> Rawlins (2013):

> (1) ReCell versus Split-Thickness Skin grafts in the Management of Deep Dermal Paediatric Scalds. Chinese Burns Association
>
> Dunne & Rawlins (2012)
> (2) "Early Paediatric Scald surgery – Developing a (cost effective) dermal preserving surgical protocol for all childhood scalds." – ISBI, Edinburgh
> (3) "A comparison of ReCell and split thickness skin grafts in management of paediatric burns" - ISBI, Edinburgh
>
> Dunne & Rawlins (2013)
> (4) "How we do it. Early dermal salvage with Biobrane and ReCell in the management of Deep Dermal Burn Wounds" - European Burn Association, Vienna
>
> I have copies of the abstracts.
>
> 1. (3) and (1) appear to be the same patient population, but with an extra 5 patients in the 2013 presentation. Was this study retrospective? Was it conducted at Pinderfields? There appears to be a marked difference in the scar assessments that isn't explained by the additional patients – do you know why this is?
>
> 2. Where was (4) conducted? Are the 11 paediatric scald patients the same as those included in (3) and (1)?
>
> 3. Can you confirm that (3) was conducted at Pinderfields? Is there some overlap with the other studies.
> I also have 3 references for Jeremy Rawlins (solo & in combination with 3 other authors) on a series of deep flame burns (mostly legs) – I thought these were conducted in Australia, but it's unclear. I just wondered whether these patients might also be include in reference (4).

> I know that both you and Jeremy have moved about a bit and when presenting it's most likely that the affiliation at the top is your current one rather than the place where the study took place. If you have any other information about these studies that you can provide (e.g. the slides) I would also be grateful for that.
> Sue

Appendix 8

From: Jonathan Belsey
Sent: 26 September 2013 14:27

Sorry – missed your second question. From what I understand, they carried out a prospective audit of resource utilisation, documenting all elements of care for 22 successive patients. They then sourced unit costs for each element from the Trust administration and applied these to the documented resources.

J

Appendix 9

From: Jones, Isabel
Sent: 01 October 2013 13:44

Response in blue below. (Itallic & underlined for clarity – EAC)
I will be away on leave from the 3rd-6th October.
Kind regards

Isabel Jones MBBS MD FRCS(Plas)
Consultant Burns and Plastic Surgery

From: Susan Peirce
Sent: 27 September 2013 18:16

Hello Isabel
I have some more questions. Please also correct any incorrect assumptions below.
This is the way the patient population/intervention/comparator combinations are split in the scope for this evaluation:

	Population	Intervention	Comparator
Group A	Partial thickness burns including scalds caused by hot water where mesh grafting is not required	ReCell alone, or in combination with biosynthetic or standard dressings	Biosynthetic dressings OR standard dressings
Group B	Large area burns; full thickness or deep partial thickness burns including where mesh grafting is required	Skin mesh graft in combination with ReCell	Skin mesh graft alone OR skin mesh graft plus biosynthetic dressing

1. For burns that are dressed with conventional (not biosynthetic) dressings – where does this happen *Usually on the ward, unless too large to tolerate pain, between 5 & 10% TBSA.* Do these patients need to remain as inpatients *because* dressing changes are done in theatre *No, only if they cannot manage at home because of size/ site of burn or pain*? How many and what grade of staff are needed for this? How long would it take? Does this depend on TBSA? *Theatre change of dressing (COD) are done by doctors, ward COD by nurses. Theatre staff is 6+, ward is 1-2 nurses. Time to do dressing change depends on size of burn, site of burn and psychology of patient*
2. For burns that are treated with ReCell and covered with conventional dressings I understand that ReCell should not be disturbed for 5 days. Do the secondary dressings on top get changed in this time? Are the dressing changes after this conducted in the same way as for question 1? *We change the secondary dressing at 48 hours to check for infection, then every 3 – 4 days. Subsequent dressings are generally far quicker and more pain free than with conventional dressings. See note below**
3. For burns that are treated with Biobrane (with or without ReCell) I understand that the Biobrane is left undisturbed (unless infection etc. occurs) until it lifts of its own accord, but that it would have a secondary dressing on top. Where & how would this dressing be changed, and by whom? *The secondary dressing is changed by a nurse, generally in OP after the first review.*
4. Would you use ReCell on partial thickness burns that you expect to heal without surgery, i.e. burns that you would dress with conventional or biosynthetic dressings (Group A)? We haven't identified any studies in this group. *Yes. Jeremy Rawlins and Fiona Wood have presented this work internationally, predominantly in paediatric scalds.*
5. How widely used is Biobrane? Is this standard care for certain burn injuries? *Yes*
6. Do you use the moorLDI burns imager? Is this widely used to assess burn depth? *Yes*
7. Most of the published evidence available compares ReCell (alone or with Biobrane) to SSG in partial thickness burns, but this doesn't fit the groups defined above. It appears that ReCell (without graft) is being used in mid-deep dermal burns as an alternative to SSG and that ReCell plus SSG would only be used in deep/full thickness burns. Does this seem correct to you? Would this be a more appropriate division of the population/treatment groups? *Yes*
8. The sponsor indicates that partial thickness/indeterminate burns would be dressed and then reassessed about a week later. Several of the clinical studies examine the use of 'early' surgical intervention, i.e. treating with ReCell, Biobrane or SSG at around day 2-3 post injury. Please could you indicate what the standard practice is at your centre? Can you estimate how widely used each protocol (early intervention versus wait-and-see) is in the UK? *Both are standard, depending on the scenario, but the earlier approach more often the case: The gold standard is to excise and definitively treat the burn on the next available routine list (24-72 hours usually, aiming for day 1 rather than day 2-3). Unfortunately the laser Doppler is most accurate 2-5 days post burn, so in some cases the intervention may be indicated by the laser Doppler several days after the burn, and*

Recell may be used later. Occaisionally a burn that was expected to come through by 2 weeks is seen to be struggling at 2 weeks and application of Recell at this time may successfully heal it within 3 weeks. Rarely a partial thickness would develops into a chronic wound over a number of weeks (eg a donor site in the elderly population) and use of Recell in these chronic wounds appears to kick start the wound to heal.

Thank you. The deadline for this assessment report is Friday 11th October and I will have more questions for you before then as we try to model the care pathway for the economic assessment. Your input is vital to the assessment in order to make sure the evaluation and model reflect current UK practice.

**If the same size burn can be initially treated in either conventional dressings or biosynthetic (Biobrane/suprathel), the subsequent dressings are more likely to be done with simple analgesia on the ward rather than in theatre. The larger the size of the burn (approaching or > 10%) the more likely the conventional dressings would go to theatre for COD. By definition these are burns that should be healed within 21 days, so we are looking at a maximum of 7 dressings if changed every 3 days.*

Sue

Sue Peirce (Dr)
Research Associate
School of Engineering
Cardiff University

From: Young Amber
Sent: 03 October 2013 16:34

Hi Sue
Comments are as per the below.
Please email if you need more info.
best wishes and thanks

Amber

Dr AER Young
Consultant Paediatric Anaesthetist, Lead Specialist Paediatrics

_____

From: Susan Peirce
Sent: 30 September 2013 11:54
Amber

Thanks very much for talking through your answers with me. Here is a summary of your information – please correct or augment this as appropriate. I've added a couple of clarification questions in a different colour

(1) Conventional dressings: In a specialist burns service adult inpatients would be dressed on a ward and outpatients would be changed in dressing clinics by nurses, paediatric patients (especially with larger burns, >10%) would be dressed in theatre and would therefore require a burns surgeon (not necessarily a consultant). These are painful procedures. A surgeon would review the wound at each dressing change. The time to complete the changes would depend on the burn size, age of the patient, complexity of the wound (e.g. difficult location) and healing stage (new grafts would take longer as more care is needed). Large burns could take a couple of hours to change, smaller burns around 30 mins. *Yes.*

(2) Secondary dressings for ReCell: Not sure of answer. Generally conventional primary dressing are not transparent so the wound can't be inspected until this is removed. *They are generally changed every 48 hrs. If Recell requires no disturbance for 5 days then I am unsure what 'conventional dressing would be used?*

(3) Biobrane secondary dressings: Biobrane sticks to the wound; it lifts as healing occurs and is trimmed at dressing changes. Changing the secondary dressing (probably dry gauze and bandage) is simple and quick. The wound would be reviewed by a surgeon at the first change (~48hrs) but later dressing changes only require nurses (unless these is a problem – Biobrane is lifting prematurely, wound is pustulant or the patient is ill). Yes

(4) Burns expected to heal: There is no published evidence *for use of ReCell* in this group of patients (Group A) *that I know of*. ReCell is not *currently* used in these wounds *esp if small in area*; such burns would be dressed with a biosynthetic dressing *if > 2-5% TBSA.*

(5) Biobrane is widely used in the UK, depending on the size of burn. On wounds that are expected to heal, for areas >5% it would be used commonly. For >5% partial thickness scalds (and some burns) that you hope would heal without surgery it improves the speed of healing. (Is there a difference between treating scalds and treating burns?). *Yes - scalds are generally treated conservatively (ie without debridement with an attempt to get healing in less than 2-3 weeks without scarring unless very large area or deep PT or FT.*

(6) moorLDI: This is used *relatively* commonly – it assesses the expected time to heal (not burn depth) and is used at 48 hrs post-injury.*Yes*

(7) Division of burn groups: It is very difficult to be clear about this. The extremes of the patient groups are more straightforward; superficial burns (no graft) and deep partial or full thickness burns (definitely graft). Using grafts in the mid-dermal group is controversial. ReCell plus graft may be used, especially on larger burns.*Yes*

(8) Early intervention: There is controversy about the management of partial thickness burns (as (7)), especially the smaller ones. In wounds where there is uncertainty about their potential to heal early grafting would not be used unless the burn is very large or the patient very unwell. Generally the burn would be dressed *(with standard dressings or biosynthetic esp if > 2-5% TBSA?*) and inspected at 2 and 3 weeks to assess likelihood of healing *or earlier if patient unwell*. Some surgeons would be more aggressive with early intervention, but would use Biobrane not grafts at this stage.

Additional question: Can you define a size range in which ReCell would or would not be used?
<10% - Largest patient group, wide variation in practice, little evidence, ReCell unlikely to be used.
10-20% - Difficult patient group, more likely to use ReCell and grafts.
>20% - Major burn, complex patients, long hospital stay, will use grafts with or without ReCell.
>40% - High risk of death, use everything possible to help patient survive, cosmetic considerations are less important, use grafts and maybe ReCell. *Yes*

Sue

Appendix 10

From: Philp Bruce
Sent: 30 September 2013 16:11

Dear Susan
the first paper was on the first 5 patients and was presented as a paper at ISBI/BBA 2012. It was indeed a feasibility study. We are putting together an ethics application to do a proper prospective trial.

The second paper is the first 10 patients but has not yet been presented.

best wishes
Bruce

From: Susan Peirce
Sent: 30 September 2013 13:22

Apologies Bruce, I meant to include this question last Friday. This is a question about presentations that you are an author on. Please could you let me know if there is any overlap of patients between these two confererence papers. Was Sen et al. a feasability study or maybe just the first few patients? Thanks

Sen, S., Ives, M., Philp, B., Dziewulski, P., Herndon, D., & Wood, F. 2012, Use of Split thickness dermal grafts in combination with sprayed keratinocytes in burns. In International Society for Burns Injuries Meeting, Edinburgh, Scotland.

Philp, B., Dziewulski, P., El-Muttardi, N., Shelley, O., Mazurek, M., Barnes, D., Ives, M., Sen, S., Lloyd-Hughes, A., Myers, S., Herndon, D., & Wood, F. Dermal grafts combined with ReCell - preliminary clinical results. (Abstract submitted for presentation).

Sue

Appendix 11

From: Young Amber
Sent: 07 October 2013 17:36

Hi Sue.

In general that is right re meshing. You would do a non-meshed graft on 'special' areas. SSGs will be more widely meshed for larger area burns when you have less skin available ie you trade a poorer cosmetic result for a larger area of cover. Re specific numbers and ratios for meshing, you will need to contact one of the surgeons I think. I am not sure that there is a 'rule' though.

best wishes and hope that is OK
Amber

Dr AER Young
Consultant Paediatric Anaesthetist, Lead Specialist Paediatrics

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From: Susan Peirce
Sent: 07 October 2013 14:20

Hello Amber

Just a quick question. When split thickness skin grafting is used to treat burns, is it always meshed (except maybe for areas such as hands, face and groin)? Can you provide a rough estimate of what the ratios would be for different size burns?
Thanks

Sue Peirce (Dr)
Research Associate

From: Jones, Isabel
Sent: 09 October 2013 12:06

Hi Sue
I would tend to consider sheet grafts in burns <10% particularly in children and special sites such as the hands and face. 10% is very much the upper limit, with up to 5% being grafted with a sheet graft more usual in reality. However the majority of patients with any size of burn will have a meshed graft (1:1 – 2:1) as generally these take better (but long term look worse…)
The patients are only advised the trypsin is porcine derived if we suspect they will object to this on religious grounds. I have not yet met with an objection & suspect this will happen but only infrequently.
I can't think of a feasible way to test for sensitivity, certainly not in the urgent cases.
The trypsin is rinsed off, as prolonged contact affects keratinocytes viability deleteriously, so there should be minimal if any in contact with the patient.
Sodium lactate is a physiological solution, I am not aware of any reports of sensitivity to this, but have not done a literature search specifically to check.
Hope this helps
Isabel

Isabel Jones MBBS MD FRCS(Plas)
Consultant Burns and Plastic Surgery

From: Susan Peirce
Sent: 09 October 2013 10:14

Thanks for that Isabel,
So, 'smaller burns' would be below about 10%? You would tend to use sheet grafts on this sort of size?
(This is important because of the way that the patient populations have been defined in the scope for this assessment).

Also are patients (or their family) routinely advised about the use of porcine-derived trypsin in ReCell before use? Would there be some way to test for sensitivity to trypsin or sodium lactate before use (this is in the contraindications for the device)?

Sue

From: Jones, Isabel
Sent: 07 October 2013 20:14

Dear Sue
Unfortunately there is not a simple answer!
We use sheet skin on smaller burns for improved cosmesis & potentially function, as in the cases you refer to. In adition it is always a consideration for use in burns up to 10-20% TBSA, when improved aestheics and pliability have to be weighed up against the larger donor site and potential increases risk of graft loss from seroma under the graft.
The mesh size used varies from surgeon to surgeon and patient to patient, rather than being prescriptive. There are many factors that influence a surgeon's decision, for instance with the elderly with much thinner skin and poor donor site healing, I generally use a wider mesh on a smaller burn to minimise donor morbidity. There is a lot of variability in the use of 1:1 mesh - 3:1 mesh. As a rule in our service once the burn is >40% it is common to use the wider mesh, eg 4:1, and at >55-60% TBSA we use meek micromeshing at 9:1
Regards
Isabel

From: Martin Rebecca
Sent: 09 October 2013 11:00

Dear Sue

Yes -the graft is nearly always meshed with the exception of sheet grafts which are usually reserved for special areas eg hand/ face but occasionally are used elsewhere.

Mesh can be micro/ mini or 1: 1 up to 1:4 , with the larger meshes reserved for the major burns where there are a shortage of donor sites.

There is not a clear and fast rule but the smaller injuries will have less meshing but depends on site of body, whether infected injury and if primary graft procedure or redo following failed graft.

Larger mesh grafts are more fragile and take longer to heal so are usually used with additional allograft to protect them and stop the underlying tissue drying out. They tend to be reserved for when large surface areas of the body need covering.

Kind regards

Becky

Dr Rebecca Martin
Consultant in Burns Anaesthesia and Intensive Care

Appendix 12

From: Martin Rebecca
Sent: 09 October 2013 11:09

Hi

No testing that I am aware of - I expect just an allergy question as per normal.
We use sodium lactate solutions a lot in anaesthesia too.

Our practice would usually be to inform patients if porcine derived products of any nature are used as part of consent process.

Thanks

Becky

Dr Rebecca Martin
Consultant in Burns Anaesthesia and Intensive Care

From: Susan Peirce
Sent: 09 October 2013 11:06

Thanks for that Becky.

Also are patients (or their family) routinely advised about the use of porcine-derived trypsin in ReCell before use? Would there be some way to test for sensitivity to trypsin or sodium lactate before use (this is in the contraindications for the device)?

Sue

From: Jones, Isabel
Sent: 09 October 2013 12:06

Hi Sue
I would tend to consider sheet grafts in burns <10% particularly in children and special sites such as the hands and face. 10% is very much the upper limit, with up to 5% being grafted with a sheet graft more usual in reality. However the majority of patients with any size of burn will have a meshed graft (1:1 – 2:1) as generally these take better (but long term look worse…)
The patients are only advised the trypsin is porcine derived if we suspect they will object to this on religious grounds. I have not yet met with an objection & suspect this will happen but only infrequently.
I can't think of a feasible way to test for sensitivity, certainly not in the urgent cases.
The trypsin is rinsed off, as prolonged contact affects keratinocytes viability deleteriously, so there should be minimal if any in contact with the patient.
Sodium lactate is a physiological solution, I am not aware of any reports of sensitivity to this, but have not done a literature search specifically to check.
Hope this helps
Isabel

Isabel Jones MBBS MD FRCS(Plas)
Consultant Burns and Plastic Surgery

From: Young Amber
Sent: 09 October 2013 10:54

Thanks Sue. Patients should and would routinely be told about porcine-related products of all types during the formal consent procedure. This would be very important for certain religious groups.

Sodium lactate is commonly used in fluids and I have never heard of sensitivity to it. We all have lactate in our blood. I would imagine there is a way to test for sensitivity to both but that would complicate the use of ReCell hugely. I have never heard of this being done.

Best wishes
Amber

Appendix 13

From: Young Amber
Sent: 10 October 2013 12:21

Thanks Sue

I think there is no formal agreement on this as far as I understand.

My understanding is that if the graft needs to be meshed with a high ratio ie the holes in the graft are larger than normal (to be clear!) which would occur when there is a large area of skin loss to cover with little skin available then ReCell would be considered to improve both healing (main aim) and possibly cosmesis. Is that OK?

Best wishes
Amber

On 10 Oct 2013, at 12:14, Susan Peircewrote:
Hello Amber

We have very little information regarding the use of ReCell with skin grafts. Can you summarise when and why you would use ReCell in addition to skin grafting (meshed or sheet)?
Thank you. (The report is nearly finished, just trying to fill in the last few holes.)

Sue

Sue Peirce (Dr)

Research Associate

From: Jones, Isabel
Sent: 10 October 2013 17:29

There is no indication to use Recell in conjunction with a sheet graft (only if it is being used on the donor, ie indicated for the donor site healing not used in conjunction with the sheet graft).
It is currently used with meshed grafts of >/= 4:1 to reduce time to healing

Isabel Jones MBBS MD FRCS(Plas)
Consultant Burns and Plastic Surgery

Appendix 14

From: Susan Peirce (Cardiff and Vale UHB - Cedar)
Sent: 16 October 2013 13:30

Hi Jonathan

Thanks for getting back to me quickly. Just to ensure that we have a written record of our telephone conversation, you stated that the section in the sponsor's submission did refer to the thinness/thickness of the skin graft and not the proportion of meshing. This was to reflect the sponsor's claim that thinner and more widely meshed grafts are at higher risk of graft loss and that the use of ReCell with either of these can reduce this risk.
I will reword that part of the Assessment Report accordingly.

Sue

From: Jonathan Belsey
Sent: 16 October 2013 12:21

Hi Sue

I will be free for a call after about 12.30 – would that be OK for you?

J

From: Susan Peirce
Sent: 16 October 2013 11:56
Hi Jonathan

There have been a couple of additional factual corrections to our report suggested by Avita. (I don't know whether you have had a copy so I've attached one.)

Can you provide some very quick clarification regarding their Issue 1 please? In section 3.5 of the sponsor's submission, 3rd paragraph (starting "ReCell can..."). The penultimate sentence states:
"By using ReCell to spray harvested autologous epithelial cells over the mesh network at the time of application, a thinner graft may be taken without incurring the usual additional risk of graft failure."
This is the first time that the use of thinner skin grafts has been mentioned – the previous text in that paragraph is about meshing of skin grafts. Also the use of a thinner graft is suggested to increase the risk of graft loss, as is a wider meshed graft. I therefore took 'thinner' to indicate a more widely meshed graft. Please can you clarify whether this is what you meant or whether this was actually about the thickness of meshed skin grafts.

Thanks. I have a teleconference with NICE this afternoon and must respond to these points by tomorrow, so I would be very grateful for a rapid response from you. A telephone call may be more appropriate – I could call you if you're available.

Sue Peirce (Dr)
Research Associate
School of Engineering
Cardiff University

Appendix E: Sponsor's factual check of the assessment report and the External Assessment Centre's responses

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
On page 9 in the second paragraph under the heading 'ReCell in the clinical pathway' the EAC states: "*The EAC therefore considers that by 'thinner' the sponsor means 'widely meshed'.*" This is a misunderstanding of the terminology.	We would suggest deleting the two sentences starting from *"The EAC therefore considers…"*	Grafts can either have a narrow or wide mesh, or alternatively a thinner or thicker depth of skin can be used. In either situation, the wider mesh and thinner graft has an increased risk of graft loss, which the use of ReCell diminishes	The EAC thanks the sponsor for their clarification (see EAC's correspondence table). The paragraph has been altered as follows: From: "*The sponsor states that the addition of ReCell to a meshed graft enables thinner grafts to be used. No other reference is made to the thickness of the skin graft elsewhere in the submission. Also*

			the sponsor states that widely meshed grafts have increased risk of graft loss and that 'thinner' grafts have an additional risk of graft loss. The EAC therefore considers that by 'thinner' the sponsor means 'widely meshed'. In this way they suggest that the additional application of ReCell to a widely meshed graft will reduce the persistence of the mesh pattern in the healed skin, reduce the risk of graft failure and therefore allow wider meshing to be used more routinely which will reduce the donor site areas required." To: "*The sponsor states that the use of thinner or more widely*

			meshed grafts incurs an increased risk of graft loss but that the addition of ReCell mitigates this increased risk.They suggest that the additional application of ReCell to a thin meshed graft will reduce the persistence of the mesh pattern in the healed skin, reduce the risk of graft failure and therefore allow wider meshing to be used more routinely which will reduce the donor site areas required.”

Description of factual inaccuracy	**Description of proposed amendment**	**Justification for amendment**	**EAC response**
In lines 4-6 of the final paragraph on page 16 (Cost	Reword sentence as: *The burn wound in the base case model was defined as*	Simple factual error. Each kit can process a biopsy of up to	This was a typographical error. The text will be changed as

analysis) the EAC states that the base-case wound size of 640cm2 represents the maximum treatment area for a single ReCell kit. In fact it represents the maximum treatment area for two ReCell kits	*partial thickness with no definite areas of deep involvement and an area of 640cm^2 (the maximum treatment area for two ReCell kits)*	4cm2 and cover an area of 80 times this amount = 320cm2	requested. The EAC thanks the sponsor for noting this.

Description of factual inaccuracy	**Description of proposed amendment**	**Justification for amendment**	**EAC response**
In the last paragraph on page 12, the second sentence states: *"No mention of indeterminate thickness burns is made, suggesting that the use of ReCell should be delayed*	Delete this sentence	In paragraph 3.3 the care pathway states that step 1 is the clinical assessment of depth at 0-2 days. Further on in this section, in paragraph 5, we then state: *"For patients with partial thickness burns,*	This section refers soley to the Decision Problem in the final scope, where no mention of indeterminate burns is made. The text will be altered to make this clearer.

until definitive wound assessment is possible, either following several days wait or using the moorLDI2 Burns imager (NICE 2011)" In fact there is clear discussion of the role of ReCell in indeterminate depth burns – indeed this is one of its key indications		*or those of indeterminate depth, harvested cells can be applied using ReCell at step 1, in order to maximise the chances of a wound re-epithelialising."* This assumption then goes on to form the basis of the economic modelling.	*"No mention of indeterminate thickness burns is made in the Decision Problem, suggesting that the intention in the scope was that use of ReCell should be delayed until definitive wound assessment is possible, either following several days wait or using the moorLDI2 Burns imager (NICE 2011)"* Note that in sections 9.1.3 and 9.1.5 of the sponsor's submission the indication for the economic model is not described as an indeterminate depth burn. This is discused in the 'Patients' section of 4.2 in the Assessment Report (p48).

Description of factual inaccuracy	**Description of proposed amendment**	**Justification for amendment**	**EAC response**
Related to the previous point (Issue 3) in the first paragraph on page 10, the EAC discuss that we have not mentioned the use of a burn depth imager at day 2-5. As ReCell will be used from day 0-2, this is not relevant	Change the sentence that reads: *"However, the sponsor has not referred to the use of the moorLDI2 Burn Imager in their submission*" to read: "*The sponsor has not referred to the use of the moorLDI2 Burn Imager in their submission, as it falls outside the timescale envisaged for the use of ReCell at step 1"*	See rationale for Issue 3 above	The moorLDI2 Burns Imager is recommended by NICE for use in indeterminate depth burns (MTG2) and should be used between 2-5 days post-injury. Indeterminate burns are not mentioned in the ReCell scope. If the sponsor wants ReCell to be evaluated in the context of indeterminate burns they should explain how this fits in with existing guidelines. If the use of ReCell in these injuries is incompatible with the use of moorLDI2 then MTAC should be made aware of this.

			The suggesed sentence indicates that the EAC knows why the moorLDI2 was not referred to, which is not the case. The existing text has been retained and an additional sentence appended to the paragraph: "*The sponsor indicates that in such cases ReCell would be applied at 0-2 days post-injury*."

Description of factual inaccuracy	**Description of proposed amendment**	**Justification for amendment**	**EAC response**
On page 67, under "Claimed benefits for the patient" the EAC states that benefits relating to donor site healing fall outside the scope and	There needs to be an acknowledgement that this can legitimately be considered to be within scope, albeit one not assessed by the	Discussion between Caroline Hall, Bernice Dillon, Jonathan Belsey and Sue Pierce on 22/8/13	This is not a factual inaccuracy because it is an interpretation of the scope arrived at jointly between the EAC and the MTEP team. Discussions at the

have therefore not been considered. In our joint teleconference on 22nd August 2013, this issue was discussed and it was the opinion of NICE that a broad interpretation should be given and that data on donor site healing should be considered to be within the scope.	EAC		teleconference cannot be used to justify a factual amendment.