Cedar

Healthcare Technology Research Centre

External Assessment Centre Report:

The ReCell spray-on skin system for treating skin loss, scarring and depigmentation after burn injury

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The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Abbreviations

COD	Change of dressing
GA	General anaesthetic/anaesthesia
HRG	Health resource group
iBID	International Burn Injury Database
LOS	Length of (hospital) stay
PbR	Payment by Results
RCT	Randomised control trial
SSG	Split thickness skin graft
STDG	Split thickness dermal graft
TBSA	Total burn surface area (given as %)
VAS	Visual analogue scale
VSS	Vancouver scar scale - a multivariable scale that includes assessment of vascularity (0-3), pigmentation (0-2), pliability (0-5) and height (0-3). Normal skin would have a value of 0 and the maximum value is 13.

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1 Summary

Scope of the sponsor's submission

There are two groups of patient population, intervention and comparator defined in the Decision Problem corresponding to partial thickness burns and larger and/or deeper burn injuries. The sponsor did not address these two groups separately. They have collated evidence for the use of ReCell in all acute burns and described each study separately. This is an appropriate approach given the heterogeneity of burn injuries and treatment modalities and the difficulty of separating these into specific groups. There is difficulty with the multiple terms used to describe burn injuries and the ways in which these have been grouped, in the published evidence, the communication with advisers and the economic modelling. The sponsor has additionally included evidence for pigmentation outcomes following the use of ReCell in hypopigmented scars and vitiligo. This data has been excluded as outside the scope, as has additional data on the use of ReCell to treat skin graft donor sites.

Summary of clinical evidence submitted by the sponsor

The sponsor's summary of the clinical evidence is that ReCell is at least as effective as split thickness skin graft (SSG) in the treatment of partial thickness burns in terms of wound healing and scar outcomes. They further note no known device-related adverse events and no greater risk of wound infection or graft loss with respect to SSG. The sponsor also states that ReCell plus SSG or dermal grafts allows more rapid healing than SSG alone, and that ReCell plus Biobrane provides faster healing than SSG, along with reduced costs and shorter hospital stay. The sponsor notes that the use of ReCell plus Biobrane is not demonstrated to be superior to either ReCell alone or Biobrane alone.

Summary critique of clinical evidence submitted by the sponsor

The sponsor described an appropriate main search strategy and submitted 3 peer-reviewed journal articles and 8 conference abstracts. Two conference abstracts were deemed outside the scope by the EAC. The EAC additionally identified another 9 conference abstracts, 2 of which were unavailable and another 5 of which contained data that overlapped with references in the sponsor's submission. These additional references did not add substantially to the available clinical evidence due to low levels of detail in the available abstracts.

The EAC concurs with the sponsor's conclusion regarding the comparative clinical effectiveness between ReCell and SSG. We also agree that there is no evidence of additional clinical benefit from the addition of ReCell to Biobrane in comparison with Biobrane alone. The EAC do not agree that ReCell plus SSG has demonstrated more rapid healing than SSG alone as this comparison has only been examined in Park et al. (2013) who did not report any healing rate outcomes. ReCell plus dermal grafts have only been studied as case series and no comparative data are available. Further, there was only one study to support the claim that ReCell plus Biobrane provides faster healing or resource savings in comparison to SSG alone. This was a small comparative study with retrospective controls and no statistical testing, but this was reported in three conference abstracts (Rawlins

2011a; Rawlins et al. 2011a; Rawlins et al. 2011b – these three references will be cited as "Rawlins 2011a, etc" for brevity).

The EAC concludes that ReCell may be a clinically suitable alternative to the use of SSGs in mid-deep partial thickness burns. There is no clinical evidence examining the use of ReCell in partial thickness burns which are considered not to require skin grafting (Group A in the Decision Problem). There is also no evidence that demonstrates improved outcomes for the use of ReCell plus SSG in comparison to SSG alone (Group B in the Decision Problem).

Summary of economic evidence submitted by the sponsor

The sponsor's search for economic studies did not identify any comparative economic publications that included ReCell, but identified papers on general burns care that could be used for resource identification for standard care. The sponsor conducted a survey of expert opinion to supplement the limited published evidence. The sponsor's de novo model is the primary economic evidence regarding ReCell.

Summary critique of economic evidence submitted by the sponsor

The sponsor did not identify Wood et al. (2012) as a relevant comparative cost analysis of ReCell plus Biobrane and Biobrane alone compared with conventional dressings, although this was included in the clinical evidence. The sponsor did not include NHS Reference Costs (Department of Health 2012), either as a source of inputs for the model or to validate the model.

The model produced by the sponsor was robust and was supplemented by one-way sensitivity analysis and scenarios. The sponsor identified five underlying assumptions in the model, but the EAC described additional structural assumptions that the sponsor had made. The main weakness of the model is that the evidence underpinning the model is very limited.

External Assessment Centre commentary on the robustness of evidence submitted by the sponsor

The clinical evidence is sparse, generally of low quality and characterised by overlapping patient groups and brief descriptions in conference abstracts. The two highest quality studies are in non-UK settings and do not demonstrate improved healing, better scar outcomes or resource savings. Gravante et al. (2007) is a reasonably high quality randomised trial but is limited to small deep partial thickness wounds. They reported a reduction in the negative consequences of surgical intervention between ReCell and SSG (i.e. smaller donor site and post-operative pain) but an increase in operative time for ReCell. Park et al. (2013) report a reduced length of stay (LOS) for ReCell plus SSG in comparison to SSG alone, but the patient populations are not strictly comparable. The evidence cannot be generalised to patient populations outside those in the studies and does not strictly reflect the Decision Problem.

The relative outcomes of the treatment options in the sponsor's de novo economic model have been shown to be relatively robust using both sensitivity and scenario analysis. However, the drivers for

the cost saving are dependent on clinical benefits and resource savings that are supported by poor evidence and clinical opinion.

Summary of any additional work carried out by the External Assessment Centre

The EAC conducted an additional literature search for clinical evidence that we considered to be broader than that undertaken by the sponsor. The EAC attempted to contact several of the authors for clarification and additional data but obtained only a small amount of information. The EAC has examined the heterogeneity of the patient population, interventions and comparators and attempted to categorise the available evidence accordingly.

The EAC also conducted an additional literature search for economic evidence and conducted quality checks on the economic analysis reported in Wood et al. (2012) and for the sponsor's economic model. The model costs were validated using NHS Reference Costs and data from Wood et al. (2012).

2 Background

2.1 Overview and critique of sponsor's description of clinical context

Current clinical management

The sponsor indicates the variety of treatment strategies in use depending on the individual injury and local burn service preferences. They state that patients with burn injuries are taken to theatre for wound cleaning and assessment within the first two days post injury. At this point superficial dermal burns are treated with debridement and conventional dressings and full thickness burns are debrided and have split thickness skin grafts (SSG) applied. Partial thickness and indeterminate thickness burns are debrided and dressed with either conventional or biosynthetic dressings (Biobrane) with a view to reassessment of the wound at 7-10 days. The sponsor indicates that patients will usually remain as an in-patient with a daily change of dressing (COD) which may be carried out under general anaesthetic (GA). If at the time of reassessment the wound has not healed sufficiently, delayed skin grafting will be used. If injuries are extensive this may take place in stages due to a scarcity of donor sites and the need to allow existing donor sites to heal before re-cropping.

ReCell in the clinical pathway

The sponsor indicates that ReCell could be introduced into this care pathway either at the initial treatment stage or at the delayed grafting stage. They state that the application of ReCell at initial treatment in partial or indeterminate thickness burns may promote better healing and may reduce the extent of later skin grafting. They also state that the dressings are not disturbed until the wound is reassessed at 7-10 days and that patients may be discharged and reassessed as an outpatient.

Additionally, ReCell may be used in conjunction with meshed SSG either initially or at a later stage. 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.

The sponsor states that following acute treatment for burn injuries there is a need for patient education regarding the nature of the wound healing and the potential need for additional dressings or skin grafts to protect wounds from re-injury. The treatment of healed scars is outside the scope of this evaluation and is not considered further.

EAC comments on the clinical pathway

The EAC agree that obviously superficial dermal and full thickness wounds would receive early treatment with conventional dressings and skin grafts respectively. However, expert advisers indicate that Biobrane is in common use in the UK and this is also used in early treatment of more superficial dermal burn injuries, particularly over approximately 5% total burns surface area (TBSA).

Patients with partial thickness or indeterminate burns may be treated with conventional or biosynthetic dressings and then reassessed at 7-10 days. However, the sponsor has not referred to the use of the moorLDI2 Burn Imager in their submission. Expert advisers indicate that this is in relatively common use in specialist burn services. It is used at around 2-5 days post-injury to aid determination of healing time in indeterminate burns and may enable earlier treatment and reduce the frequency and extent of skin graft operations (NICE 2011). The sponsor indicates that in such cases ReCell would be applied at 0-2 days post-injury.

Expert advisers and published evidence indicates that many patients do not remain as in-patients beyond the first COD post-surgery. Patients may remain as in-patients depending on the size and location of the burn, their level of pain, age of the patient and also practical considerations such as distance from home (Griffiths et al. 2006). Paediatric patients are more likely to require COD in theatre with GA. Following surgery, conventional dressings are usually changed no more frequently than every other day, either in theatre (for larger and more painful burns), on the ward or in outpatient dressing clinics. Alternatively Biobrane remains attached to the wound surface and only requires secondary dressings to be changed for wound inspection, for trimming the detaching dressing or when they are dirty. If ReCell is covered with conventional dressings the primary dressings should remain undisturbed for 5 days (manufacturer's instructions), but the outer dressings may be changed sooner so that the wound can be inspected for infection. Most COD occur every 2-3 days.

The EAC understands that ReCell is used in combination with SSGs, but the impact of this on the current patient pathway is unclear. An expert adviser indicated that burn wounds that have not healed as expected within two weeks may be treated with ReCell, presumably as an alternative to delayed skin grafting. Also, many of the studies included in the clinical evidence involve the use of ReCell (alone or with Biobrane) in mid-deep partial thickness burns in comparison to SSG. Expert advisers have indicated that this could be an appropriate use of the ReCell technology.

Epidemiology

The sponsor has used data from the Hospital Episode Statistics (HSCIC 2012) for England from 2011-2012 and data from the UK burn injury data from the International Burn Injury Database (iBID, NBCG 2008) to estimate the size of the appropriate patient population. Although not precise and prone to ambiguous definitions these are appropriate sources of UK incidence data. The iBID reports are difficult to interpret as data definitions and sources are not provided, however this does suggest that there are around 4000-7600 admissions to specialist burn services in England and Wales each year. A definition of burn severity categories is not provided but 'Minor' and 'Moderate' are identified as suitable for treatment at a Burn Facility, 'Moderate/Severe' and 'Severe' at a Burn Unit and 'Severe' and 'Severe/Complex' at a Burn Centre.

2.2 Overview of sponsor's description of ongoing studies

The sponsor identified a single ongoing study in their submission. This is a multicentre randomised within-patient controlled study investigating the use of ReCell in treating scars from skin grafts (NCT01476826). This US/Canadian study is out of scope as it is not treating the acute burn injury.

The EAC identified a single ongoing trial that is within the scope. This is a multicentre randomised, within-patient controlled feasibility study in the US in collaboration with the Department of Defence and is being conducted for an FDA license for ReCell (NCT01138917). Treatment with ReCell is being compared to split thickness meshed skin graft in second degree burns of at least 100cm^2 in adults. (Whether the comparator includes unmeshed skin graft is unclear from the information available.) The end date for data collection is July 2013 and the estimated completion date is March 2014 (www.clinicaltrials.gov, website accessed 20/09/13). However in an email the sponsor indicated that this trial has encountered recruitment problems and is not now expected to complete until 2015 at the earliest.

2.3 Critique of sponsor's definition of the decision problem

The sponsor has not altered the Decision Problem from that defined in the final Scope.

Population definition

There are two patient population groups defined in the Decision Problem. The EAC has labelled these as Group A and Group B for ease of reference throughout the Assessment Report:

- partial thickness burns including scalds caused by hot water where mesh grafting is not required (Group A)
- large area burns; full thickness or deep partial thickness burns including where mesh grafting is required (Group B)

The sponsor's search strategy did not distinguish between these, and their assessment of the clinical evidence is not separated into these groups. The EAC has closely examined the patient population definitions in the scope, the sponsor's submission, the available clinical evidence and information provided from clinical experts. We have determined that defining patient populations in burn injuries is a complex issue.

Heterogeneity of patient condition

Firstly, burn injuries are highly individual; their treatment depends on size, location and depth, and a single burn wound may vary in depth and require multiple treatment modalities. There are differences between adults and paediatric patients, as indicated in the referral guidelines.

Definition using referral criteria for specialised burn services

Secondly, both groups are defined as involving patients who are treated in Burns Units or Centres. Specialised services for burns in England and Wales are organised into a three-tiered level of service provision – Facility, Unit and Centre (as recommended in the National Burn Care Review 2001). The full referral guidelines for these are described in the National Burn Care Referral Guidance (National Network for Burn Care 2012). This indicates that the minimum TBSA for the populations considered in the Decision Problem would be 1-5% in paediatric patients and 5-10% in adults (depending on burn depth).

Table 1: UK specialist burn services referral guidelines (NNBC, 2012)

		Facility	Unit	Centre
Paediatric	TBSA	≥ 2% and < 5%	≥ 5% and < 30% ≥ 5% and < 15% (<1 yr)	≥ 30% ≥ 15% (< 1 yr)
	Depth	All full thickness burns	≥ 2% full thickness (< 10 yrs) ≥ 1% full thickness (< 6 mths)	≥ 20% TBSA if full thickness
Adult	TBSA	≥ 3% and < 10%	≥ 10% and < 40%	≥ 40%
	Depth	Any full thickness burns	≥ 5% and < 40% (if no blanching)	

However, amongst the four regional Burn Care Networks in England and Wales, two currently use an interim service designation (NHS Specialised Services 2011) and therefore these services are not fully defined. Also, patients who live locally to a specialist burns services but who have a burn injury severity below the minimum referral criteria would also be treated there. So an adult burn Centre will treat patients with burns from 3% TBSA upwards, but accept patients with very large burns from a wide geographical area. This indicates that defining a patient population by the type of service in which they are treated will not necessarily be consistent. The body surface area of a typical UK adult is approximately 1.7-1.9 m^2 (Sacco et al. 2010), so that a single ReCell kit covering a wound area of 320 cm^2 is equivalent to around 1.5-2% TBSA. Therefore an adult treated in a Burn Facility for a 9% TBSA partial thickness burn (for example) would be suitable for treatment with up to 4 or 5 ReCell kits. By strictly following the patient population definition in the Decision Problem this evaluation may exclude appropriate burn injuries that are treated in burn services not designated as Units or Centres.

Definition using burn depth and requirement for meshed grafts

Thirdly, the distinction between the Decision Problem groups is intended to separate less serious and more serious burn wounds. No mention of indeterminate thickness burns is made in the Decision Problem, suggesting that the intention in the scope was that the 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). The groups are partly defined by the requirement for meshed graft. Full thickness burns require skin grafting as the regenerative capacity of the skin has been lost. Deep partial thickness burns, and partial thickness burns that do not heal within around 10-14 days, also require skin grafting to speed up the healing process as long healing times are associated with poor scar outcomes. Both the scope and Briefing Note for this evaluation state that meshed grafts are used only in “extensive wounds” (undefined) suggesting that Group B should be restricted to large area burns. However, information from expert advisers indicates that meshing is commonly applied to all skin grafts except for those used on the face, hands and groin.

Heterogeneity of patient populations in the clinical evidence

Fourthly, in the studies included in the clinical evidence burn injury depth is described and grouped in various ways. For example:

- partial, deep partial and full thickness considered separately (Park et al. 2013),
- deep partial or full thickness burns considered as a group (Sen et al. 2012),
- mid-deep dermal burns considered as a group (Rawlins 2013; Echlin et al. 2012a),
- partial thickness scalds anticipated to benefit from surgery and therefore would not heal within 10 days (Wood et al. 2012),
- scalds and flame burns considered combined (Dunne and Rawlins 2013; Park et al. 2013) or separately (Rawlins et al. 2011a; Wood et al. 2012).

EAC interpretation of the patient population in the Decision Problem

A strict interpretation of the Group A population would include all partial thickness burns and scalds, including those that may require sheet skin grafts. However, the comparator for this group does not include skin grafting, suggesting that this group was not intended to include patients who would require skin grafts (meshed or unmeshed) and therefore restricting this to the more superficial dermal wounds that are expected to heal without skin replacement. This is reinforced by the 'Reasons for developing guidance' in Section 2 of the scope that defines partial thickness as burns where 'only ReCell is used' rather than 'as an adjunct to skin grafting'. The EAC therefore interprets the Group A population as:

> *partial thickness burns or scalds where skin grafting (meshed or unmeshed) is not required.*

The definition of the Group B population is ambiguous and varies between the population, intervention and comparator sections of the Decision Problem. It is unclear whether this represents:

- only large area burns, which are full or deep partial thickness (and may require meshed grafts), or
- all large area burns, and all full or deep partial thickness burns that require meshed grafts, or
- only large area burns, which are full or deep partial thickness and require meshed grafts.

Meshed skin grafting is included in this group as part of the intervention or comparator but not unmeshed grafting. As the scope reserves meshed grafts for use only in extensive wounds this suggests that only larger burns should be included in this group. However, this interpretation would exclude smaller deep partial and full thickness burns from this evaluation of ReCell. (The difference between 'smaller' and 'larger' being defined possibly by the need to mesh grafts at a higher ratio due to a lack of suitable donor sites.) The statements in Section 2 of the scope indicate that the effect of using ReCell in any full or deep partial thickness burn should be included in the evaluation. The EAC therefore interprets the Group B population as:

> *full thickness or deep partial thickness burns where skin grafting (including meshed grafting in larger burns) is required.*

Clinical evidence appropriate to the patient populations

For the reasons described above it is difficult to separate the clinical evidence into the two Decision Problem patient populations. Both the sponsor and the EAC have included all the studies they have identified in which ReCell has been used to treat acute burn wounds; i.e. no clinical evidence was excluded on the basis that it did not exactly match one or other of the patient populations. The EAC has further attempted to classify each study according to its patient population, intervention and comparator. This is shown in Table 10 in section 3.5.

Decision Problem Group A patient population

Wood et al. (2012) compared scalds treated with ReCell plus Biobrane versus Biobrane alone or standard dressings. This is consistent with Group A. However, the patient population was defined as wounds which were "anticipated to benefit from surgery and therefore would not heal within 10 days". This is more consistent with the Group B population but this study has been retained in Group A as it is the only study that compares ReCell with standard dressings. Rennekampff et al. (2011) and Hiller et al. (2013) described the injuries in their case series as "partial thickness", and without additional information the EAC has assumed that these also correspond to Group A.

Decision Problem Group B patient population

The remaining studies investigated the use of ReCell in mid or deep partial thickness or full-thickness burns in which surgical intervention (grafting) would (otherwise) be required. In two studies (3 references; Park et al. 2013; Sen et al. 2012 [redacted]) ReCell was used in combination with grafting. In the remaining studies ReCell was applied either alone or with Biobrane and where a comparator was used this was meshed or unmeshed skin graft. In these patients with mid to deep partial thickness burn wounds (where a dermal component was still retained) ReCell was being used as an alternative to split thickness skin grafting (SSG). This represents a different intervention in a Group B patient population than that described in the Decision Problem. The EAC considered whether this use of ReCell was appropriate in a UK context. The provenance of several of the conference abstracts is unclear but at least two of these studies were conducted in the UK (Dunne and Rawlins 2012a; Echlin et al. 2012a). An expert adviser also indicated that this was an appropriate treatment. Therefore we assume that this practice is appropriate to the UK.

Adult and paediatric populations

Several of the studies included in the clinical evidence include only adult patients, or only paediatric patients with scald injuries. (Scalds are the most common source of burn injury in children.) Neither the sponsor nor the EAC have separated the evidence into age groups and there was no suggestion in the clinical evidence or the sponsor's submission of differential outcomes between adults and children treated with ReCell. An expert adviser indicated that paediatric patients may be given general anaesthesia during dressing changes more frequently than adults, but this outcome was not included in any of the clinical evidence studies.

ReCell in hypopigmentation populations

The sponsor also separately collated evidence in a population of patients with hypopigmentation (scars and vitiligo) in order to identify pigmentation outcomes which may not have been included in the acute burn studies. Such patients are outside the scope of this evaluation. Additionally expert advisers did not think that outcomes from these indications could be extrapolated to acute burns wounds. These studies have been excluded by the EAC.

Intervention

The technology in the sponsor's submission matches that in the Scope. ReCell is a stand-alone, battery-operated kit for the processing of a thin split thickness skin biopsy (up to 4 cm^2). The device heats a Trypsin solution into which the skin biopsy is placed. After 20-30 minutes the epidermal cells can be scraped off the biopsy and mixed with a buffer solution for application by spraying or dripping onto the wound. The suspension includes a mixed cell population of fibroblasts, keratinocytes, melanocytes and Langerhans cells. These are intended to attach to the wound and proliferate thus accelerating healing.

The device obtained a CE mark in March 2005. ReCell is a Class III medical device and the sponsor has provided the EAC with a copy of their revised Declaration of Conformity dated January 2012. The sponsor has satisfied the regulatory requirements and supplied the EAC with all necessary documentation.

In their submission the sponsor claims that ReCell is in wide use in the NHS, including at least eight specialist burns services.

Comparator(s)

Only one study includes standard or biosynthetic dressings as a comparator as defined in Group A in the Decision Problem (Wood et al. 2012). The sponsor did not provide any additional evidence in the clinical submission. However, in the economic submission they included four questionnaires from burn surgeons regarding their experience of using ReCell in comparison to conventional dressings and Biobrane. Two of these respondents are also NICE MTEP expert advisers.

As described above, unmeshed split thickness skin grafting was not explicitly included in the comparators for Group B. The sponsor and the EAC have included studies where the skin grafts were not meshed, where there was a mixture of meshed and unmeshed grafts and where there was insufficient information to determine whether the graft was meshed.

There is only one study in which ReCell plus split thickness skin grafting is compared to skin grafting alone, although in this study the patient groups are not identical (Park et al. 2013). In another study ReCell is used in a case series in combination with split thickness dermal grafts (Philp et al. 2013; Sen et al. 2012). The expert questionnaires referred to above also included questions regarding the comparison between ReCell plus skin graft versus skin graft alone.

Outcomes

Most of the outcomes listed in the Decision Problem have been addressed by one or more clinical studies included in the sponsor's clinical evidence submission. Additional evidence identified by the EAC supplemented this information. Those outcomes described in the Decision Problem that are not included in the clinical evidence are:

- Re-admission to hospital for management of scarring
- Transfusion rates during skin grafts
- Number of donor sites
- Growth rate in children

Scar outcomes are reported as multidimensional scales (Vancouver scar scale and visual analogue scale), but pigmentation is not reported separately. Scar outcomes were assessed up to 6 months following treatment (where time of assessment is reported) and do not necessarily represent long term responses. The sponsor included a subsidiary literature search for pigmentation outcomes following the treatment of hypopigmented lesions (scars and vitiligo) but these papers were determined to be outside the scope of the evaluation.

Additional outcomes that were reported in the clinical evidence were graft loss or graft take following the initial surgical treatment and the requirement for subsequent skin grafting. Graft loss or take following initial SSG is understood to refer to how much of the graft has integrated to the wound surface. Graft loss or take following treatment with ReCell is understood to refer to the extent of epithelial regrowth over the wound. Subsequent grafting could occur where early treatment (including SSG) has failed to achieve the intended complete wound healing or where early treatment (not including SSG) is intended to reduce the number or extent of skin grafts required at 10-21 days post-injury.

Cost analysis

The sponsor stated that there was insufficient data to model the inputs for the Group B cost analysis and has therefore only provided a cost analysis for Group A. Their de novo model compares the cost of treatment between ReCell (with and without Biobrane) and conventional dressings or Biobrane alone. The burn wound in the base case model was defined as partial thickness with no definite areas of deep involvement and an area of 640cm^2 (the maximum treatment area for two ReCell kits). In adults this corresponds to approximately 3-4% TBSA and for a 2 year old child this would be approximately 10-12% TBSA. This is appropriate for inclusion in Group A. However, there may be substantial differences in the treatment protocols for an adult with a 4% partial thickness burn and a young child with a 10% partial thickness burn.

Subgroups

No subgroups were identified in the Decision Problem.

Special considerations, including issues related to equality

In the Decision Problem special consideration was given to pigmentation outcomes in patients with darker skin and to the use of porcine-derived trypsin in the ReCell kit.

The sponsor also described improved pigmentation outcomes as a key claimed benefit of ReCell and that its use may result in better colour matching in patients with darker skin. The sponsor conducted a subsidiary literature search to identify studies specifically addressing ReCell use in hypopigmented scars and vitiligo lesions. However the outcomes in this population cannot be extrapolated to the treatment of acute burns and these studies have been excluded from the EAC's analysis. Pigmentation is included in qualitative scar scale assessments in the clinical evidence but is not reported separately. In Gravante et al. (2007) the scar assessment specifically only included pigmentation and vascularity. None of the included studies report skin colour or ethnicity of their patient population or report any difference in outcomes with reference to skin colour. One expert adviser indicated that ReCell appears to produce better pigmentation outcomes than would otherwise have been expected (including in patients with darker skin), but that this was anecdotal.

The sponsor notes that the porcine origin of trypsin is 'well-recognised' and that Biobrane also contains material of porcine origin. They state that advice from clinicians is that patients and their families are comfortable making a decision about the use of both products according to their beliefs. The expert advisers indicated that either all patients are routinely informed about the nature of the product or only patients who may be suspected to object.

No additional equality issues have been identified by the sponsor or the EAC.

3 Clinical evidence

3.1 Critique of the sponsor's search strategy

The sponsor conducted a single search for both populations from the scope. This is sensible considering the small number of studies likely to be found, the difficulty of categorising burn types and the indexing methods of the databases.

The sponsor searched the four reference databases stipulated in the instructions. Their search strategy was relatively simple, combining terms for burns and scalds with terms to describe ReCell. This latter consisted of 'ReCell' as a textword or the combination of 'autologous', 'cell' and 'harvest' within 3 words proximity. In an email the sponsor states that the last three search terms were taken from the description of the technology - "non-cultured autologous cell harvesting" – and that studies using cultured cells were excluded after the search. The sponsor further indicated that no studies were identified solely on the basis of these three combined terms.

The EAC considered this strategy to be somewhat restrictive and redundant. The term 'harvest' relates to the detail of the ReCell process and may not appear in an abstract. Also, we considered that 'autologous' and 'harvest' were unlikely to be found in proximity as only autologous cells are harvested during a surgical procedure. The EAC therefore conducted an additional search using a similar strategy to that of the sponsor, but replacing the combination of 'autologous', 'cell' and 'harvest' with 'cell' in combination with 'spray' or 'suspension' (see Figure 1 for a comparison of search strategies and section 3.9 and Appendix 1 for details of the additional work done). The EAC considered this strategy to be more generic, however all relevant studies identified by the EAC included 'ReCell' in the title and/or abstract and therefore these additional search terms were redundant.

Sponsor:	burn OR scald	AND	ReCell OR autologous AND cell AND harvest
EAC:	burn OR scald	AND	ReCell OR cell AND (spray OR suspension)

Figure 1: Comparison of sponsor's & EAC's database search strategies

The sponsor additionally used a list of known projects. This was not included in the clinical submission but was provided to the EAC on request. They also hand searched the abstracts for four burns-related conferences for the past 5 years: British Burn Association, European Burn Association,

American Burn Association and the International Society for Burn Injuries. The rationale for limiting this search to 5 years was not provided. The EAC additionally identified the Birmingham Burns Association as a suitable conference and searched the available proceedings for the years 2013 and 2010. (These were the only years identified. It is believed that this conference only meets every three years.)

The sponsor's search strategy was effective and reasonably thorough. It is unlikely that suitable studies would be unknown to the sponsor and all studies identified by the EAC have used the brand name in the title or abstract of the reference. Therefore all additional studies identified by the EAC should have been identified by the sponsor.

3.2 Critique of the sponsor's study selection

The inclusion criteria deviated from the scope slightly:

- **Population:** The sponsor defines the indication as 'flame burns and scalds', whereas the Scope does not specify flame burns. This may have excluded other types of burn, e.g. chemical burns.
- **Intervention:** The sponsor defines the intervention as ReCell 'alone or in combination with other treatments', thus combining the two population groups. The Decision Problem restricts the intervention to ReCell plus biosynthetic or standard dressings, and ReCell plus skin mesh graft. This may result in the inclusion of additional types of combined interventions.
- **Comparator:** This was not defined in the selection criteria.
- **Outcomes:** Outcomes are as specified in the Decision Problem with three additions – analgesic/anaesthetic resource, and other resource or patient-relevant outcomes not otherwise specified. The Decision Problem outcomes were not exhaustive so the addition of other outcomes is consistent and appropriate.
- **Study design:** Systematic reviews with quantitative outcomes, controlled trials, observational studies and case studies were included. Narrative reviews without patient effectiveness data, single case reports, animal studies and in vitro studies were excluded. Although single case studies cannot provide comparative data they may contain information on adverse events, so these should have been examined for any data relating to this.
- **Language:** no restrictions were applied. This is appropriate as ReCell originates in Australia and has regulatory approval in multiple non-English speaking countries.
- **Date:** The sponsor's search was limited to studies published from 1995 onwards. This is appropriate as the technology was developed during the 1990's and the ReCell device was launched in 2005.

3.3 Included and excluded studies

According to the PRISMA diagram in Figure 1 of the sponsor's submission 61 records were identified from their literature search of which 50 were excluded:

- 22 were for indications other than thermal burns,
- 13 were not evaluations of ReCell,

- 10 were narrative reviews,
- 3 were basic science/animal studies
- In 2 ReCell use was incidental to the study objectives

A list of excluded studies is not provided. Non-thermal burns (e.g. chemical) are not excluded in the Scope, however the EAC did not identify any relevant studies of ReCell in non-thermal burns. Other criteria for excluding the studies appear to be appropriate (but see below for additional studies included by the EAC). One study (included in the 61 studies above) was initially included but then excluded by the sponsor on the basis of insufficient data (De Angelis B. et al. 2009).

The sponsor therefore included eleven references: 3 peer-reviewed journal papers and 8 conference abstracts. Two of the journal papers were randomised controlled trials (Gravante et al. 2007; Wood et al. 2012) and the third was a retrospective multiple regression study (Park et al. 2013). One journal paper (Park et al. 2013) and 1 conference abstract [redacted] were unpublished at the time of submission.

- Gravante et al. (2007) conducted a randomised controlled trial in adult patients with deep partial thickness burns up to 320cm^2 comparing ReCell alone (n=42) with meshed and unmeshed SSG (n=40).

- Wood et al. (2012) conducted a three-arm randomised controlled pilot study in paediatric patients with partial thickness scalds anticipated to require surgery, comparing ReCell plus Biobrane (n=5), Biobrane only (n=4) and standard care (silver and hydrocolloid dressings, n=4).

- Park et al. (2013) conducted a retrospective analysis of patients with burns requiring surgery over an 8 year period. Multiple regression was used to assess the association between surgical modality and outcomes (infection, graft loss and length of stay). Treatment with ReCell alone (n=73) and ReCell plus SSG (n=264) were compared to SSG (n=387).

- Dunne and Rawlins (2012a) conducted a non-comparative retrospective review of paediatric patients with scalds (n=40). Different levels of burn injury have separate treatments, with ReCell (plus Biobrane) used only in mid-deep dermal burns (n=13).

- Rawlins (2013) conducted a retrospective observational comparative study in paediatric patients with deep dermal scalds treated with ReCell (n=11) or with SSG (15).

- Rawlins et al. (2011a) conducted a mixed method pilot study in adults with deep dermal burns comparing treatment with ReCell plus Biobrane (prospectively recruited, n=5) against matched controls treated with standard SSG (assumed to be retrospective, n=10).

- Echlin et al. (2012a) reported a case series of patients with mid to deep dermal facial burns treated with ReCell (n=5).

- Echlin et al. (2012b) reported a case series of patients with donor site wounds (at risk of delayed healing or requiring recropping) treated with ReCell (n=9).

- Palombo et al. (2012) reported a case series of paediatric patients with scars from scalds treated with ReCell (n=6).

- Sen et al. (2012) reported a case series of adult patients with deep partial or full thickness burns treated with split thickness dermal grafts (STDG)[1] and ReCell (n=5). (Feasibility study for [redacted].)

- [redacted].

Studies included by the EAC

Nine additional references were identified by the EAC in our literature search (detailed in section 3.9). Three were included in the Briefing Note for this technology (Dunne and Rawlins 2012b; Rawlins et al. 2011b; Sood et al. 2009) and three studies (4 references) were included in the sponsor's list of known studies (Rawlins et al. 2011b; Sood et al. 2009; Dunne & Rawlins 2012b; Rawlins 2011a). Others were identified from database searches or conference listings. All should have been identified by the sponsor's search strategy. The reasons for exclusion are not known although there is some overlap with studies included by the sponsor.

- Sood et al. (2009) conducted an intrapatient comparison in patients with partial thickness burns, treating one area with ReCell and another other with SSG (n=10).

- Rawlins (2010) – *abstract unobtainable.*

- Rawlins et al. (2011b) & Rawlins (2011a) conducted a comparison between prospectively recruited patients treated for deep dermal burns treated with ReCell plus Biobrane (n=4) and a matched control group treated with SSG (n=10). (These overlap with Rawlins et al. 2011a.)

- Rawlins (2011b) – *abstract unobtainable.*

- Rennekampff et al. (2011) described a case series of patients with facial burns treated with ReCell (n=5).

- Dunne & Rawlins (2012b) – conducted an observational comparison between paediatric patients with scalds treated with ReCell (n=11) or SSG (n=10). (Overlap with (Rawlins 2013).)

- Dunne and Rawlins (2013) reported a case series of patients with mid-deep dermal burns treated with ReCell plus Biobrane (n=21).

- Hiller et al. (2013) reported a case series of patients with partial thickness facial burns treated with ReCell (n=5). (Possible overlap with (Rennekampff et al. 2011).)

[1] Split thickness dermal grafts consist of recropping an SSG donor site to produce a thin layer of dermal tissue for grafting purposes.

Studies excluded by the EAC

Two conference abstracts identified by the sponsor in their main literature search were excluded by the EAC.

- Echlin et al. (2012b) treated the skin graft donor sites of 9 patients where there was a risk of delayed healing or where donor sites would need to be reused.
- Palombo et al. (2012) treated 6 children with hypertrophic scarring following scalds.

Both studies are out of scope as the intervention and comparator treatments in the Decision Problem are limited to burn wounds.

Table 2: Studies included by the sponsor and the EAC

Study	Patient population	Country	Age	Study design	Time of intervention	Notes	Sample size
Gravante et al. (2007)	Deep partial thickness burns <320 cm^2	Italy	Adult (30-65 years)	Randomised controlled trial	Day 3-5		82
Wood et al. (2012)	Scalds >2% TBSA, expected to require surgery	Australia	Paediatric (8 months – 9 years)	Three-arm randomised controlled pilot study	Day 2	Assessment of early intervention protocol	13
Park et al. (2011)	Burns treated with skin grafting or replacement	Australia	All	Retrospective multivariate analysis	Not reported		722 (770, 48 excluded)
Dunne & Rawlins (2012a)	Scalds of differing depth	UK	Paediatric (9 months-15 years)	Non-comparative retrospective review	Day 1-2		40
Rawlins (2013)	Deep dermal scalds	UK (email from author)	Paediatric	Retrospective comparative observational study	Not reported	Overlap with Dunne and Rawlins (2012b).	26
Rawlins (2011a)	Deep dermal burns	Probably Australia	Adult (17-59 years in the intervention group)	Comparative pilot study using matched controls	Day 2-3	Overlap with Rawlins et al. (2011b) and Rawlins (2011a)	15
Echlin et al. (2012a)	Mid to deep dermal facial burns	UK	All (10 months-50 years)	Case series	Day 9-11 (n=4)	1 patient treated at day 23	5

Study	Patient population	Country	Age	Study design	Time of intervention	Notes	Sample size
Sen et al. (2012)	Deep partial or full thickness burns and donor sites, >50% TBSA	UK, USA, Australia	Adult	Case series	Not reported	Overlap with Philp et al. (2013)	5
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Additional studies identified by the EAC							
Sood et al. (2009)	Partial thickness burns	USA	Unreported	Intrapatient comparative study	Not reported	Sponsored by Avita but not included in their spreadsheet.	10
Rawlins (2010)	*Scald*	*UK (email from author)*	*Paediatric*	*RCT*		*Abstract unobtainable*	
Rawlins et al. (2011b) Rawlins (2011a)	Deep dermal burns to the legs	Australia (email from author)	Adults (17-59 years)	Comparative pilot study with matched controls	Day 2-4 Day 2-3	Overlap with Rawlins et al. (2011a)	14
Rawlins (2011b)	*Scalds*	*UK (email from author)*	*Paediatric*			*Abstract unobtainable*	
Rennekampff et al. (2011)	Facial burns (assumed to be deep partial thickness)	Germany	Unreported	Case series	Not reported	Overlap with Hiller et al. (2013)?	5

Study	Patient population	Country	Age	Study design	Time of intervention	Notes	Sample size
Dunne & Rawlins (2012b)	Burns	UK (email from author)	Paediatric	Retrospective comparative observational study	Not reported	Overlap with Rawlins (2013).	21
Dunne & Rawlins (2013)	Deep dermal burns	UK (email from author)	All	Non-comparative observational study	Day 2	Retrospective review of cases, overlap with Rawlins (2013), Dunne and Rawlins (2012a,b)	21
Hiller et al. (2013)	Partial thickness facial burns	Germany	Adult (27-81 years)	Case series	Not reported	Overlap with Rennekampff et al. (2011)?	5

3.4 Overview of all included studies

The methodology, critical appraisal and results for each study included by the EAC in the clinical evidence are presented below.

Note that the EAC attempted to contact some authors but was unable to obtain sufficient information to unequivocally define patient overlap between some of the references.

Overview and critique of the sponsor's critical appraisal

The sponsor used the tables provided in the template for their critical appraisal of randomised controlled trials and observational studies. These tables are used for the three journal papers and one conference abstract of a randomised controlled trial (Daniel B et al. 2011 – excluded by the EAC as outside the scope). Other conference abstracts have not been analysed for quality by the sponsor as they are case series and therefore unsuited to critical appraisal. However, Rawlins (2013) and Rawlins et al. (2011a) are comparative studies not case series.

Gravante et al. (2007)

Methodology

The authors conducted a single centre randomised controlled trial in Italy to compare ReCell with skin grafting. Adults (30-65 years) admitted to a burns centre over a 2 year period were eligible if they had deep partial thickness burns of up to 320 cm^2 that required debridement and epithelial replacement. Exclusion criteria included existing infections, comorbidities or medications that could interfere with wound healing, renal failure and a high anaesthesia risk. Patients were enrolled using a 'sampling chart' to produce homogeneous groups and were treated 3-5 days following the burn. The intervention was ReCell applied to the burn wound and biopsy site. The comparator was split-thickness skin graft meshed to a 1:2 ratio or sheet grafts on the face, hands, feet and genital areas. Follow-up was weekly visits during the first month and then at 3 and 6 months.

Primary outcomes were time to complete epithelialisation and aesthetic and functional quality of the scar. Aesthetic outcomes were assessed using a simplified Vancouver scar scale (pigmentation and vascularity – time not reported) by two plastic surgeons, including one blinded to the procedure. Range of motion was assessed 'with the help of' a physical therapist at 1 and 6 months (blinding not reported). Secondary outcomes were infections, adverse events, medications and post-operative pain (visual analogue score - VAS). The authors also reported procedure time, area harvested and the number of patients requiring a second procedure. Data were tested for normal distribution. Continuous variable were tested using Student's t-test and Mann-Whitney test (for area harvested) and nominal variables using the χ^2-test and Fisher's exact test.

Critical appraisal

The sponsor correctly identifies the lack of clarity regarding the treatment allocation method. The study is described as randomised and groups were matched for age, gender, burn type and TBSA. No additional information was reported. The EAC attempted to contact the authors for clarification but received no response. The treatment groups are comparable with regards to reported demographic

and burn injury data. Although no age criteria are described in the Methods, in the Results section the authors report that 18 patients were excluded as 'not homogeneous for age' (i.e. below 30 years or above 65 years). The suggestion is that this occurred before treatment allocation, but it is unclear. If patients were removed from the analysis after treatment (e.g. because the 'sampling chart' did not adequately control for age) then this could have biased the results.

The sponsor states that the nature of the treatments made blinding of patients and assessors impossible – the EAC does not consider this to be true for all outcomes. However, several outcomes are unlikely to have been affected by bias (operation time, area harvested, area treated). The sponsor notes that pain could have been affected by bias and the EAC considers that time to complete healing could also have been affected. The accuracy and precision of time to healing is likely to be poor as the patients were described as being assessed at weekly intervals. The sponsor correctly notes that scar assessment was carried out by one blinded and one unblinded assessor and that the blinding status of the physical therapist who assessed functional status was unknown.

Results

A total of 82 patients were treated; 42 in the ReCell group (ReCell only) and 40 in the comparator group (SSG). There were no significant differences in baseline patient characteristics. Follow up was weekly for the first month and then at 3 and 6 months, unless otherwise described. Time to complete epithelialisation was 13±2 days (mean ± standard deviation) for the ReCell group and 12±2 days for the comparator group (not significant). VSS values were not reported but were not significantly different between the groups. Functional quality of the scar at one month is indicated by the development of contractures. Twelve out of forty-two patients in the ReCell group and 15/40 patients in the comparator group had developed at least one contracture (not significant).

The authors reported no adverse events and no results are given for infections. Post-operative pain was 3.3±1.6 for the ReCell group and 6.8±1.2 for the comparator group (VAS, p=0.03). Post-operative analgesia was the same in both groups although patients in the comparator group "complained of an additional painful site (the area of harvesting)". It is not reported whether this information (in the Discussion) was collected as standard or is anecdotal. Procedure time (undefined) was 59±4 minutes for ReCell and 20±6 minutes for the comparator (p<0.001) despite the authors attempt to "optimize operating times" in the ReCell procedure. Donor area harvested was 2.2±1 cm^2 in the ReCell group and 110±50 cm^2 in the comparator (p<0.001). Seven out of 42 (17%) patients in the ReCell group and 6/40 (15%) patients in the comparator group required a second procedure to "complete few remaining areas that did not heal". It is unknown whether these procedures were limited to the burn areas included in the study as it is unclear whether patients may have had additional burn areas.

Wood et al. (2012)

Methodology

This is a three-arm randomised controlled pilot study in Australia to compare early surgical interventions with standard care. Paediatric patients presenting or referred to a burn centre over a 12 month period were eligible if they had a scald injury greater than 2% TBSA anticipated not to heal

within 10 days and therefore likely to benefit from surgery. Sample size was intended to be 45 patients. Exclusion criteria included inappropriate initial dressings (not Acticoat and Duoderm), late presentations and unsuitability for general anaesthesia at 48 hours post injury. Clinical assessment of the injury at 48 hours post-injury included laser Doppler scan (moorLDI2), wound measurement (Visitrak) and clinical photographs. Suitable patients were then randomised to equal sized groups using independently prepared sealed envelopes so that the study team were unaware of the next allocation.

The two intervention groups were treated surgically following randomisation. These received debridement and either Biobrane only or ReCell plus Biobrane. The standard care group received continued treatment with silver (Acticoat) and hydrocolloid (Duoderm) dressings on alternate days. The injury was reassessed at 7 or 10 days post injury (inconsistently reported) and patients who were unhealed were treated surgically on day 10. The aim of the study was to investigate early interventions as a means to reduce surgical intervention; primary outcome was therefore surgery at 10 days post injury (yes/no). Additional outcomes were time to healing, pain and analgesia for dressing changes, length of stay, number and duration of dressing changes, complication rates and scar outcomes. Resource use and costs were also reported. Due to small patient numbers only descriptive statistics were used and no statistical tests were used.

Critical appraisal

A very large proportion of the patients screened for eligibility did not meet the inclusion criteria; 112 out of 123 who were excluded did not have burn injuries that were judged to require surgery. The sponsor correctly notes the good randomisation technique but that very small sample numbers resulted in differences in the patient demographics. Of note is the much younger age range in the ReCell plus Biobrane group; patients in this group were under 2 years whereas those in the other groups ranged from approximately 1.5 years to 9 years. The EAC additionally notes that burn area is only reported as TBSA and appears to be slightly reduced in the ReCell plus Biobrane group so the absolute burn area on these patients is likely to be significantly smaller. There was also discrepancy in the reported time of assessment for surgery between the text (10 days) and Figure 1 (7 days).

The sponsor incorrectly states that healing was validated by an independent assessor. An independent clinician was provided with photographs from the recruitment in order to verify the *selection* of patients for inclusion in the trial. As no results of this verification process are reported we assume that the independent clinician agreed with the recruitment choices made by the study team. No blinding of any assessors is reported in this study. The sponsor states that objective outcomes would not be affected by assessor bias, however the EAC does not agree that requirement for surgery is not subject to bias as it is a clinical judgement. The protocol for dressing changes and assessment following the assessment at day 7 or 10 is not described, so the accuracy and precision of the time to healing is unknown. One patient in the ReCell plus Biobrane group was lost to follow-up at 6 weeks. The main author (F Wood) is the co-inventor of ReCell and a director of Avita Medical.

Results

A total of 13 patients were included; 5 in the ReCell plus Biobrane group, 4 in the Biobrane only group and 4 in the standard care (dressings only) group. Data are presented as medians and interquartile range (unless otherwise stated) in the order ReCell plus Biobrane versus Biobrane only and standard care. Patient age was 1.3 (0.8-1.8) years versus 5.5 (1.5-8.8) years and 5.4 (2.5-7.1) years. TBSA was 3.0 (3.0-8.5) versus 6.5 (4.0-13.5) and 4.5 (4.0-5.0).

Surgery at 10 days was 0/5 (0%) versus 1/4 (25%) and 3/4 (75%) patients. Time to complete healing (defined as dressings no longer required) was 16.0 (11.5-18.0) days versus 16.0 (14.25-23.0) days and 36.5 (18.5-47.7) days. Healing assessed by wound measurement at 10 and 21 days was 95% and 100% versus 83.2% and 97.7%, and 71.2% and 90.1%. Slower healing in the standard care group was partially attributed to complications in 2/4 patients in this group. VSS was assessed at 6 months and indicates the score for the worst part of the scar. Scores were 0, 3, 5, 6 versus 2, 3, 3, 9 and 0, 5, 6, 6 (1 patient in the ReCell plus Biobrane group was lost to follow-up before this assessment).

Pain during dressing changes was assessed using three age-appropriate tools; clinician assessment for those under 7 years (CHIPPS for 0-23 months, FLACC for 2-7 years) and the Revised Faces Pain Scale for older children. All these report pain on a scale of 0-10. The pain score at the initial dressing change (pre-randomisation) was compared to the highest pain score following randomisation. The median pain scores were 4.0 to 3.0 (difference of −1.0) versus 4.0 to 2.0 (−2.0) and 4.5 to 5.5 (+1.0). The authors note that the reduction in pain scores in the two intervention groups was potentially related to the longer delay to the first post-randomisation dressing change and therefore more advanced healing. The increase in the pain score for the standard care group may reflect increased anxiety in these children. The number of dressing changes was 5.0 (4.0-6.0) versus 7.0 (5.5-9.5) and 12.5 (8.0-15.0). Fewer dressing changes in the intervention groups were partially attributed to faster healing and fewer changes in the acute phase (Biobrane dressings were not changed between the intervention and reassessment at day 7 or 10).

There were 2 complications in the ReCell plus Biobrane group (wound infection and sepsis), 1 in the Biobrane only group (wound infection) and 2 in the standard care group (overgranulation and graft loss following surgery at day 10). These two patients in the standard care group and another patient in the Biobrane group had poor scar outcome and were treated with steroid injection.

Park et al. (2013)

Methodology

The authors conducted a retrospective multivariate analysis in Australia to determine whether surgical intervention modalities were associated with infection, graft loss and length of stay. All patients admitted to a burn centre who required skin grafting or a skin replacement procedure between January 2004 and December 2011 were eligible. Data were obtained from the hospital's Burns Minimum Dataset linked to laboratory records (iSoft). Exclusion criteria included the presence of burn wound infection or community-acquired infection on admission and positive sputum, urine or blood microbiology culture.

Descriptive statistics, χ^2 two-tailed test and Fisher exact test were used along with univariate and multivariate logistic regression. The outcomes used for the regression models were the presence of burn wound infection (post-operative), graft loss and length of stay. Input variables tested were surgical technique, age category, TBSA, burn depth, inhalational injuries and comorbidity (diabetes – other conditions were too rare). Where the univariate associations were significant at $p<0.05$ these variables were included in the multivariate analysis. Surgical techniques were SSG, ReCell alone, ReCell plus SSG and CellSpray plus SSG. (CellSpray is a cell suspension produced by the same manufacturer as ReCell, but using laboratory cultured cells). Three patients treated with CellSpray alone were excluded due to low numbers. SSG, alone or in combination with ReCell, was used for burns extending to the deep reticular dermis whereas ReCell alone was used for "deeper" mid-dermal burns.

Critical appraisal

Baseline differences between the surgical intervention groups are not reported. The sponsor states in Table B6a that multiple regression would correct for any differences, however gender and type of burn agent are not included in the model input variables. Also 48 patients out of the initial 770 were excluded, but the demographic and clinical characteristics of these is not reported so that the actual number of patients in each surgical group analysed is unknown. Burn depth is greater in patients treated with SSG than in patients treated with ReCell alone, although burn depth is controlled for in the multiple regression. This retrospective analysis is likely to include those patients in Wood et al. (2012) who received surgical treatment. However, as the methods, aims and outcomes of these studies are very different this overlap is not significant. One of the co-authors (F Wood) is the co-inventor of ReCell and a director of Avita Medical.

Results

Data was analysed for a total of 722 patients. The number of patients in each group is provided before the exclusion of 48 patients and is therefore given as a maximum; ReCell alone n=73, ReCell plus SSG n=264 and SSG alone n=387. Results are presented as odds ratios (OR) and 95% confidence interval with respect to treatment with SSG alone.

The presence of burn wound infection was defined by quantitative swab ($>10^5$ bacteria). Neither ReCell alone nor ReCell plus SSG were associated with burn wound infection: OR 0.78 (0.34-3.42) (p=0.98) and 1.23 (0.45-4.52) (p=0.97) respectively. Graft loss was defined as greater than around 0.25% TBSA failure or benefiting from "further acute surgical intervention by the Attending Burn Surgeon". Neither ReCell alone nor ReCell plus SSG were associated with graft loss: OR 0.89 (0.45-2.32) (p=0.09) and 1.56 (0.56-3.21) (p=0.67). Length of stay (LOS) was not defined, but is assumed to include only the first acute admission. ReCell alone was associated with a significant reduction in length of stay, but ReCell plus SSG was not: OR 0.70 (0.57-0.82) ($p<0.01$) and 0.98 (0.88-1.10) (p=0.85). The authors state that the reduction in hospital stay in ReCell patients should "be interpreted cautiously as the practice indications (wound depth) and timing of surgery...differs markedly from that of SSG". The authors postulate that the reduction in donor skin harvesting for the ReCell technique may have resulted in lower surgical morbidity and hence reduced LOS.

Dunne and Rawlins (2012a)

Method

The authors review the outcomes for paediatric patients treated according to a new algorithm of early surgical intervention in a UK burn service. Paediatric patients with scalds suitable for early surgical management admitted since January 2011 were included in the data. Wounds were treated 24-48 hours post injury; superficial dermal scalds were treated with Biobrane, mid and deep dermal scalds with ReCell plus Biobrane and full thickness scalds by SSG. The authors briefly report frequency of secondary SSG, hospital stay and scar assessments. Other outcomes are reported in comparison to delayed surgery.

Critical appraisal

The sponsor provides no criticism for case series. This is a non-comparative review of patients with different scald depths treated using different modalities and therefore can be regarded as three independent case series. No information regarding TBSA is provided.

Results

A total of 40 patients were included in the analysis; ReCell plus Biobrane n=13 (mid and deep dermal), Biobrane alone n=20 (superficial dermal) and SSG n=7 (full thickness). Five out of 13 (38%) patients in the ReCell plus Biobrane group, 6/20 (30%) in the Biobrane alone and 2/7 (29%) in the SSG alone groups required subsequent SSG. Mean hospital stay was 4.5 days. The authors report that hospital stay was shorter and scar assessments better in the ReCell plus Biobrane and Biobrane alone groups (values not reported), however these were the less severe burns.

Rawlins (2013), Dunn and Rawlins (2012b)

Methodology

This is a comparative retrospective observational study comparing ReCell and SSG for deep dermal scalds in paediatric patients in a UK burn service. Patients admitted between March 2011 and March 2012 were included if treatment was with ReCell or SSG (according to consultant preference) and patients were followed up for more than four months. TBSA, scar outcomes, operative time and length of physiotherapy follow-up was reported numerically. Five independent clinicians assessed scar quality by viewing images using a visual analogue scale (VAS); 0 (normal skin) to 10 (poor scar). Statistical tests are not reported.

Critical appraisal

The sponsor included this study in their submission but did not provide any critical analysis. TBSA is greater in the ReCell group indicating that the patient populations are different. It is unclear whether the five clinicians were blinded as to treatment allocation.

Dunne and Rawlins (2012b) report data for a subset of the patients in Rawlins (2013). The same number of ReCell patients are reported in both references and all outcomes in this group are identical, with the exception of scar quality. VSS is substantially greater in the earlier paper (4.6 in ReCell and 4.7 in SSG) suggesting an reporting error or a re-evaluation of the images. Information from one of the authors suggests different follow-up periods in the two references. (Further clarification could not be obtained by the EAC.) However, both references indicated that there is no difference in VAS between the two treatment groups, so the outcomes for Rawlins (2013) are presented here.

Results

Rawlins (2013) reports data for 26 paediatric patients; 11 treated with ReCell and 15 with SSG. Mean TBSA was significantly greater in the ReCell group, 6.5% versus 2.9% (p=0.04), and mean operative time longer, 87 minutes versus 58 minutes (p=0.05) . Mean VAS was similar in the two groups, 3.9 (95% CI, 2.8-4.9) versus 3.9 (3.3-4.5) (p=0.97). Mean length of physiotherapy follow-up was 21 days in the ReCell group and 40 days in the SSG group (p=0.29). Two patients in each group were treated for wound infections.

Rawlins (2011a), Rawlins et al. (2011a) and Rawlins et al. (2011b) (Rawlins 2011a, etc)

Methodology

This is a mixed method comparative pilot study in adult patients with deep dermal flame burns in Australia. Prospective recruitment was used for the intervention group who were treated with ReCell plus Biobrane at 48-72 hours post injury. Comparison was with data from matched controls who received *SSG.* (This is reported as SSG plus ReCell in Rawlins 2011a). Matching criteria are reported in Rawlins (2011a) as age, burn size and burn location. TBSA and wound healing are reported numerically. Analgesia requirements, and scar assessment at 6 months were reported graphically in Rawlins et al. (2011b). Statistical tests are not reported.

Critical appraisal

The sponsor included Rawlins et al. (2011a) in their clinical evidence submission but did not provide any critical analysis. Rawlins et al. (2011a) reports data for 5 prospectively recruited patients with deep dermal burns. Four of these patients with burns to the legs are reported in Rawlins et al. (2011b) and Rawlins (2011a). It is assumed that the control subjects are selected retrospectively, but this is not reported. There is a suggestion that the ReCell plus Biobrane group may have received earlier surgery than the SSG group. No blinding of assessment was reported and numerical values are only reported for time to healing. Other numerical data have been estimated by the EAC. The difference in time to healing between the two groups appears unusually large and the time to healing quite long in both groups. No information about frequency of wound assessment is reported and the authors have used mean values which may be substantially skewed in small and heterogeneous samples.

Results

Rawlins et al. (2011a) reported data for a total of 15 patients treated with ReCell plus Biobrane (n=5) and SSG (n=10). The mean TBSA in the ReCell plus Biobrane group was 15% (range 9-24%) and mean age was 29 years (range 17-59) – data for the SSG group was not reported (but is matched to the intervention group). Mean time to wound healing (not defined) was 18 days in the ReCell plus Biobrane group and 48 days in the SSG group. The authors state that analgesia at first dressing change and total analgesia requirements were less in the ReCell plus Biobrane group and scar quality using VSS was better (values not reported).

Graphical data from Rawlins et al. (2011b) for a subset of these patients (n=4 and n=10) are estimated as follows. Analgesia requirements for the 24 hour period around the first dressing change were approximately 280 mg Tramadol for ReCell versus 450 mg for SSG. VSS at 6 months was approximately 5.3 for ReCell versus 6.5 for SSG. Length of hospital stay (no data provided) was shorter for ReCell and the authors state that patients returned to work and daily activities faster. Nursing staff commented that ReCell patients were encouraged to mobilise from the day following surgery whereas SSG usually required two days of immobilisation.

Echlin et al. (2012a)

Methodology

This is a case series of patients with mid to deep dermal facial burns treated in a UK burn service. Patients were initially treated with debridement and allograft at 0-2 days. Four patients assessed at 9-11 days post injury and deemed unlikely to heal within 3 weeks from injury underwent debridement and treatment with ReCell and non-adherent dressings. Another patient with late presentation was assessed at 23 days post-injury and was treated with ReCell plus allograft as dressing. The first dressing change was at 3-4 days post surgery. Time to healing was reported numerically. No statistical tests are reported.

Critical appraisal

The sponsor does not provide any critical analysis of case series studies. The authors conclude that ReCell appeared to produce faster healing with reduced skin graft rate and scar formation in this patient population. However, they report no data for their previous standard care (allograft until assessment at 1 week). Very little numerical data is reported.

Results

Data for five patients are reported; 3 scalds and 2 flame burns. Four patients assessed at 9-11 days post injury had a mean time to complete healing of 5 days (maximum 7 days) post surgery. Another patient with late presentation required an additional small SSG to the forehead. The authors state that ReCell “appears to accelerate burn wound healing” and “has decreased the split skin graft rate and subsequent scar formation” in this patient population. The burns service changed their practice to treat such wounds with ReCell if unhealed at 1 week.

Sen et al. (2012), [redacted]

Methodology

Sen et al. (2012) [redacted] These are two case series of patients, with deep partial or full thickness burns >50% TBSA treated at a UK burn service. Split thickness dermal grafts (STDG) were used when conventional SSG sites were exhausted. The STDG graft and donor sites were treated with ReCell. [redacted] Epithelialisation was assessed by 2 independent observers and recorded by photographs in (Sen et al. 2012). Epithelialisation and graft take outcomes are narrative (Sen et al. 2012).
[redacted].

Critical appraisal

The sponsor does not provide any critical analysis of case series studies. [redacted]).

Results

Sen et al. (2012) reported outcomes for 5 patients. Dermal graft take was reported to be complete in all cases. Epithelialisation of graft and donor sites was considered to be comparable to conventional treatment.

[redacted].

Sood et al. (2009)

Methodology

This was an intra-patient comparative study in patients with partial thickness burns in the USA. Two wound areas of 320 cm^2 were defined; one was treated with ReCell and the other with meshed SSG. Graft take is reported.

Critical appraisal

The authors do not describe the selection of treatment sites or their location (e.g. contiguous or distant). Graft take is reported to one decimal place but the method of measurement is not reported. No other outcomes are reported.

Results

Outcomes for 10 patients are reported. Eight patients had 100% "take" (undefined) in sites treated with ReCell and with SSG. Two patients had reduced take on the ReCell site compared to the SSG site. In one patient (62.4% versus 100%) this was attributed to difficulty with the spray applicator and in the other (73.7% versus 81.5%) it was attributed to the deep partial to full thickness nature of the wound. The authors report a learning curve for use of the applicator and choice of wound.

Rennekampff *et al.* (2011)

Methodology

This is a case series of patients treated with ReCell for facial burns in Germany. It is unclear whether only partial thickness burns were treated (with ReCell) or whether full thickness burns were also treated (using skin grafting or grafting plus ReCell). No other details of patients or treatment were reported. Time to epithelialisation and scar quality were reported.

Critical appraisal

The authors state that "full thickness burns required skin grafting" but it is unclear whether this was part of the initial treatment or later revision. Very little information about methodology or numerical results are reported.

Results

Outcomes for 5 patients were reported. Time to epithelialisation was 7-9 days post surgery. No hypertrophic scars or severe contractions occurred. Skin pigmentation was slightly reduced in comparison to surrounding skin (location of the biopsy was not reported).

Dunne and Rawlins (2013)

Methodology

This is a non-comparative retrospective review of patients treated by the second author. Patients with mid-deep dermal burns suitable for surgical intervention admitted to a UK or Australian burn service between 2009 and 2013 were included. Burns were treated with ReCell and Biobrane at 48 hours post-injury. Narrative outcomes are presented for scar pigmentation and degree of hypertrophy.

Critical appraisal

This review includes 11 children with scalds who may have been included in Dunne and Rawlins (2012b) and Rawlins (2013). A further 8 adults with flame burns may have been included in Rawlins (2011a, etc). No numerical results are reported.

Results

Outcomes were reported for 11 children treated for scalds (mean TBSA 7%) and 10 adults, 8 of whom were treated for flame burns (mean TBSA 9%). The authors report "early wound coverage with good pigmentation and minimal evidence of hypertrophic scarring or donor site morbidity". One paediatric patient required a later SSG.

Hiller et al. (2013)

Methodology

This is a case series of adult patients with partial thickness facial burns conducted in Germany. Patients were treated with ReCell using a biopsy taken from the retroauricular area and full thickness burns required grafting. Scars were evaluated using the Vancouver scar scale and Cutometer (time not reported). Narrative outcomes are reported, apparently in comparison to the authors previous standard care.

Critical appraisal

This may be the same patient group as reported in Rennekampff et al. (2011), but insufficient information is reported to conclude this. The EAC attempted to contact the authors but received no response.

Results

Outcomes were reported for 5 patients (27-81 years). The authors state an "acceleration in epithelialisation and healing time as well as improvement in scar quality".

3.5 Results summary

The results from the studies included in section 3.4 are summarised here in Table 3 to Table 9, grouped by outcome and Decision Problem group.

Table 3: Wound healing

Study	Outcome	Measure	Popn. group
Wood et al. (2012) ReCell+Biobrane (n=5) Biobrane only (n=4) Standard care (n=4)	 16.0 (11.5 - 18.0) 16.0 (14.25 - 23.0) 36.5 (18.5 - 47.7)	Time to healing (days) Median (IQR)	A
Wood et al. (2012) ReCell+Biobrane (n=5) Biobrane only (n=4) Standard care (n=4)	 95.0% 83.2% 71.2%	Healing at 10 days	A

Wood et al. (2012) ReCell+Biobrane (n=5) Biobrane only (n=4) Standard care (n=4)	100.0% 97.7% 90.1%	Healing at 21 days	A
Rennekampff et al. (2011) ReCell (n=5)	7 - 9	Time to healing (days)	A
Hiller et al. (2013) ReCell (n=5)	'acceleration in epithelialisation and healing time'		A
Gravante (2007) ReCell (n=42) Un/meshed SSG (n=40) p	13 ± 2 12 ± 2 NS	Time to healing (days) Mean ± SD	B
Rawlins (2011a, etc) ReCell+Biobrane (n=5) SSG (n=10)	18 48	Time to healing (days) Mean	B
Echlin et al. (2012a) ReCell (n=4)	5 , 7	Time to healing (days) Mean, max	B
Philp et al. (2013) ReCell + STDG (n=8)	12	Time to healing (days) Mean	B
Dunne & Rawlins (2013) ReCell + Biobrane (n=21)	'early wound coverage'		B

NS = not significant

Table 4: Scar outcome

Study	Scar outcome	Measure	Popn. group
Wood et al. (2012) ReCell+Biobrane (n=4) Biobrane only (n=4) Standard care (n=4)	0, 3, 5, 6 2, 3, 3, 9 0, 5, 6, 6	VSS	A
Rennekampff et al. (2011) ReCell (n=5)	'no hypertrophic scars' 'pigmentation slightly reduced'		A
Hiller et al. (2013) ReCell (n=5)	'improvement in scar quality'		A

Gravante (2007) ReCell (n=42) SSG (n=40) P	Not reported Not reported NS	Simplified VSS	B
Gravante (2007) ReCell (n=42) SSG (n=40) p	12/42 15/40 NS	Contractures	B
Rawlins et al. (2011b) ReCell (n=4) SSG (n=10)	5.3 6.5	Approx. VSS	B
Echlin et al. (2012a) ReCell (n=5)	'decreased...scar formation'		B
[redacted]	[redacted]		[redacted]
Dunne & Rawlins (2013) ReCell + Biobrane (n=21)	'good pigmentation' 'minimal evidence of hypertrophic scarring'		B

Table 5: Subsequent graft and initial graft take/loss

Study	Outcome	Measure	Popn. group
Wood et al. (2012) ReCell+Biobrane (n=5) Biobrane only (n=4) Standard care (n=4)	0/5 (0%) 1/4 (25%) 3/4 (75%)	Surgery at 10 days	A
Dunne & Rawlins (2012a) ReCell+Biobrane (n=13) Biobrane alone (n=20) SSG alone (n=7)	5/13 (38%) 6/20 (30%) 2/7 (29%)	Subsequent SSG	B
Dunne & Rawlins (2013) ReCell + Biobrane (n=21)	1/21 (5%)	Subsequent SSG	B
Echlin et al. (2012a) ReCell (n=5)	'decreased the split skin graft rate'		B
Park et al. (2013) ReCell alone (n=73) p ReCell+SSG (n=264) p	0.89 (0.45-2.32) 0.09 1.56 (0.56-3.21) 0.67	Graft loss Odds ratio (CI) vs. SSG alone (n=387)	B
Sood et al. (2009) ReCell (n=10) SSG (n=10)	93.6% 98.2%	Graft take	B
Sood et al. (2009)			

ReCell (n=10) SSG (n=10)	8/10 (80%) 9/10 (90%)	100% graft take	B

Table 6: Pain and analgesia

Study	Outcome	Measure	Popn. group
Wood et al. (2012) ReCell+Biobrane (n=5) Biobrane only (n=4) Standard care (n=4)	4.0 to 3.0 (-1.0) 4.0 to 2.0 (-2.0) 4.5 to 5.0 (+1.0)	Pre/post intervention pain at dressing change Median VAS	A
Gravante (2007) ReCell (n=42) Un/meshed SSG (n=40) p	3.3 ± 1.6 6.8 ± 1.2 0.03	Pain, VAS Mean ± SD	B
Gravante (2007) ReCell (n=42) Un/meshed SSG (n=40) p	No difference in analgesia, but SSG group has 'additional painful site'	Analgesia	B
Rawlins et al. (2011b) ReCell+Biobrane(n=4) SSG alone (n=10)	280 450	Analgesia (mg Tramadol) around 1st dressing change	B

Table 7: Resource use

Study	Outcome	Measure	Popn. group
Wood et al. (2012) ReCell+Biobrane (n=5) Biobrane only (n=4) Standard care (n=4)	5.0 (4.0-6.0) 7.0 (5.5-9.5) 12.5 (8.0-15.0)	Number of dressing changes Median (IQR)	A
Gravante (2007) ReCell (n=42) Un/meshed SSG (n=40) p	59 ± 4 20 ± 6 <0.001	Procedure time (mins) Mean ± SD	B
Rawlins (2013, etc) ReCell (n=11) SSG (n=15) p	87 58 0.05	Operative time (mins) Mean	B
Park et al. (2013) ReCell alone (n=73) p ReCell+SSG (n=264) p	0.70 (0.57-0.82) <0.01 0.98 (0.88-1.10) 0.85	Length of stay Odds ratio (CI) vs. SSG alone (n=387)	B

Rawlins et al. (2011b) ReCell + Biobrane (n=4) SSG (n=10)	'was shorter in the ReCell and Biobrane group'	Length of stay	B
Rawlins (2013) ReCell (n=11) SSG (n=15) p	21 40 0.29	Length of physiotherapy follow-up (days) Mean	B

Table 8: Wound infection

Study	Outcome	Measure	Popn. group
Wood et al. (2012) ReCell+Biobrane (n=5) Biobrane only (n=4) Standard care (n=4)	 1 + 1 /5 1/4 0/4	Wound infection or sepsis	A
Gravante (2007) ReCell (n=42) Un/meshed SSG (n=40)	 0/42 0/42	Infection rate	B
Park et al. (2013) ReCell alone (n=73) p ReCell+SSG (n=264) p	 0.78 (0.34-3.42) 0.98 1.23 (0.45-4.52) 0.97	Wound infection Odds ratio (CI) vs. SSG alone (n=387)	B
Park et al. (2013) All patients (n=770)	 67/770 (8.7%)	Infection rate	B
Rawlins (2013) ReCell (n=11) SSG (n=15)	 2/11 (18%) 2/15 (13%)	Infection rate	B

Table 9: Donor site area

Study	Outcome	Measure	Popn. group
Gravante (2007) ReCell (n=42) Un/meshed SSG (n=40) p	 2.2 ± 1.0 110 ± 50 <0.001	Area harvested (cm^2)	B

Relevance of the clinical evidence to the scope

The two Decision Problem groups interpreted by the EAC (section 2.3) are:

	Population	Intervention	Comparator
Group A:	Partial thickness burns or scalds where skin grafting (meshed or unmeshed) is not required	ReCell alone, or in combination with biosynthetic or standard dressings	Biosynthetic dressings OR standard dressings
Group B:	Full thickness or deep partial thickness burns where skin grafting (including meshed grafting in larger burns) is required	Skin mesh graft in combination with ReCell	Skin mesh graft alone OR skin mesh graft plus biosynthetic dressing

The papers are shown according to their Decision Problem Group compatibility in Table 10. (See also Section 2.3.)

Table 10: Clinical evidence studies arranged by patient population, intervention and comparator

Study	Country	Patient population		Intervention		Comparator	
Wood et al. (2012)	Australia	Part. thickness scald Part. thickness scald Part. thickness scald	A A A	ReCell+ Biobrane	A	Std. dressing Biobrane	A A
Rennekampff et al. (2011)	Germany	Burns	A	ReCell	A	*NA*	
Hiller et al. (2013)	Germany	Burns	A	ReCell	A	*NA*	
Park (2013)	Australia	Deep reticular dermal burns	B	ReCell + un/meshed SSG	B	Un/meshed SSG	B
Sen (2012)	UK, USA, Australia	Deep partial or full thickness burns	B	ReCell+STDG	B	*NA*	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Gravante (2007)	Italy	Deep partial thickness	B	ReCell	A	Un/meshed SSG	B
Park (2013)	Australia	Deeper mid-dermal burns	B	ReCell	A	Un/meshed SSG	B
Dunne & Rawlins (2012a)	UK	Mid-deep dermal scalds	B	ReCell + Biobrane	A		
Rawlins (2013), Dunne & Rawlins (2012b)	UK	Deep dermal scalds	B	ReCell	A	SSG	B
Dunne & Rawlins (2013)	UK	Mid-deep dermal burns	B	ReCell + Biobrane	A	*NA*	
Rawlins et al. (2011a); Rawlins et al. (2011b); Rawlins (2011a)	Australia	Deep dermal burns	B	ReCell + Biobrane	A	SSG	B
Echlin (2012a)	UK	Mid-deep dermal burns	B	ReCell	A	*NA*	

Sood et al. (2009)	UK	Partial thickness burns	B	ReCell	A	Meshed SSG	B

Subsidiary literature search for skin pigmentation outcomes

The sponsor conducted an additional literature search specifically to identify studies that evaluated the effect of ReCell on skin pigmentation. They widened the patient population to include all patients with hypopigmentation or vitiligo and combined this with the same search terms to represent ReCell as used in the main search. The sponsors acknowledge that these studies are out of scope, but indicate that they believe the outcomes are relevant for patients with burn injuries. Several of the included studies assess scar quality outcomes using numerical scales (Gravante et al. 2007; Rawlins 2011b; Rawlins 2013; Wood et al. 2012) but pigmentation is not reported separately.

Information from the expert advisers indicated that outcomes from repigmentation treatments for scars and vitiligo was not generalisable to the patients population defined in the Decision Problem.

3.6 Description of the adverse events reported by the sponsor

The sponsor states that no adverse events have been reported by them. The EAC conducted a search of the MAUDE database and did not identify any adverse events related to ReCell.

The sponsor collated adverse events reported in the studies included in their submission. These were limited to typical negative outcomes of burn injuries and are not related to the use of the ReCell device itself. Wound infections, graft loss, additional graft procedures and contractures are reported in several studies and have been included as outcomes in the Results section of this Assessment Report. There is no evidence of any differences in the rates of these events between patients treated with ReCell and other surgical modalities. However, Sood et al. (2011) conducted an intrapatient comparison between ReCell and SSG and ascribed a reduced graft take on the ReCell site in one patient (62.4% versus 100%) to difficulty with the spray application of cells. The authors noted a learning curve with respect to choosing appropriate wounds and with the use of the spray applicator.

The device is battery-operated and has a self-test function to be used before being operated. Information on training requirements were not provided. The sponsor indicates that sensitivity to trypsin or sodium lactate could result in an adverse response. However, this is listed in the contraindications on the device instructions and expert advisers indicated that such sensitivity is unlikely as the trypsin is rinsed off the cells before application and sodium lactate is in common use in other applications.

3.7 Description and critique of evidence synthesis and meta-analysis carried out by the sponsor

The sponsor did not carry out a meta-analysis or evidence synthesis due to the heterogeneity of patient populations, interventions and methodologies in the included studies. This is considered

appropriate. The sponsor provided a narrative summary of each study included in their submission although with little critical appraisal.

3.8 Additional work carried out by the External Assessment Centre in relation to clinical evidence

The EAC conducted an additional literature search for studies including ReCell (detailed in Appendix 1 , see also Section 3.1). Briefly, the terms 'spray' OR 'suspension' AND 'cell' were used as alternative search terms for 'ReCell'. The following databases were searched: Medline, Medline in process, Embase, Scopus, Web of Science and Cochrane Library. Google Scholar, the Health Management Information Consortium and the York CRD database were also searched using simpler strategies. The journal websites for 'Burns' and 'Burn Care and Research' were searched for articles including the term 'ReCell'. Proceedings for the four conferences identified by the sponsor plus the Birmingham Burns Congress were searched if they were available online. The EAC also checked the sponsor's database of known studies and recreated the sponsor's search strategy as closely as possible.

The EAC's search strategy identified an additional 9 conference abstracts not included in the sponsor's submission. Five of these were determined to be multiple reports of data that was the same or overlapped with references identified by the sponsor.

- Rawlins (2010) may report early results from Wood et al. (2012) – abstract unavailable.
- Rawlins et al. (2011b) and Rawlins (2011a) reported a subset of data from Rawlins et al. (2011a)
- Rawlins (2011b) may report early results from Dunne and Rawlins (2012a) – abstract unavailable.
- Dunne & Rawlins (2012b) was summarised in the ReCell Briefing Note and reports early data from Rawlins (2013).

There were 4 references that provided new or additional information not included in the sponsor's selection.

- Sood et al. (2009)
- Rennekampff et al. (2011)
- Dunne & Rawlins (2013) – may include some patient data from other Rawlins papers.
- Hiller et al. (2013) – possibly the same study as Rennekampff et al. (2011).

All these additional references should have been identified by the sponsor's search strategy. The reasons for excluding these papers is not known. The data from these references have been included in Sections 3.4-3.6.

For the economic evidence submission the sponsor obtained questionnaire data from 4 clinical experts regarding their use of ReCell. Two of these were also NICE MTEP expert advisers, another was a clinician who had experience of using ReCell in the UK and the forth was the co-inventor of ReCell. The EAC has summarised the relevant clinical information here to supplement the evidence from the clinical studies.

3.9 Conclusions on the clinical evidence

The evidence from all studies included by the EAC is summarised here according to the population groups defined in the scope and in section 2.3. No conclusions can be drawn on four outcomes in the Decision Problem for which no studies provided data: re-admission to hospital for management of scarring; transfusion rates during skin grafts; number of donor sites, growth rate in children.

Decision Problem Group A population and intervention

Only Wood et al. (2012) conducted a study that compares a Group A intervention (ReCell plus Biobrane) with a Group A comparator (standard or biosynthetic dressings). Although this was an RCT the number of patients in each group were too small to allow robust conclusions to be drawn. However the results suggest that ReCell may reduce healing time and may reduce the number of patients that require subsequent grafting in comparison to both other treatment options. Although this study has been included in the patient population for Group A the patients were described as "anticipated to benefit from surgery and therefore would not heal within 10 days". In other studies this patient population may have been treated with early surgical intervention using either ReCell or SSG. It may also be appropriate therefore to consider this study as using a Group A intervention in a Group B population. However, this is the only study identified that compared ReCell with standard dressings so the results are kept separate.

Decision Problem Group A intervention in Group B population

Most of the studies included by the EAC used either ReCell alone or in combination with Biobrane in a population of patients with mid-deep dermal burns that would otherwise have required additional epithelial cover (e.g. SSG). There are five studies (8 references) in which this treatment is compared with meshed or unmeshed SSG (Gravante et al. 2007; Park et al. 2013; Rawlins 2013; Rawlins 2011a, etc; Sood et al. 2009). Healing times for ReCell alone were not different to SSG in Gravante et al. (2007), but in Rawlins et al. (2011a, etc) they were reduced in the ReCell plus Biobrane group (48 versus 18 days, no statistical test). Scar assessments, infection rates and rates of graft loss/take were similar between the two treatment options. Pain and analgesia requirements tended to be reduced in the intervention group, potentially related to the smaller donor site. Length of stay may be reduced (Park et al. 2013; Rawlins 2011a, etc). Operative time is increased by around 30 mins when using ReCell in comparison to SSG only (Gravante et al. 2007; Rawlins 2013).

Three other studies do not provide comparative data. Echlin et al. (2012a) state that ReCell "appears to accelerate wound healing" (complete healing was achieved in 7 days or less) and has "decreased the split skin graft rate" compared to their previous practice of using SSG. Dunne and Rawlins (2013) state that ReCell "was effective at early wound coverage with good pigmentation and minimal

evidence of hypertrophic scarring" (note that the intervention was ReCell plus Biobrane). Dunne and Rawlins (2012a) state that scar assessments were "good to excellent" in patients treated with ReCell plus Biobrane.

Group B intervention in Group B population

Only 2 studies (3 references) used ReCell in combination with either SSG or STDG. Park et al. (2013) reported that infection rates, graft loss and length of stay were similar to SSG. Author statements in Sen et al. (2012) [redacted] indicate that healing time and scar outcomes are comparable to conventional grafting. [redacted] is similar to that reported in Gravante et al. (2007) for SSG alone.

Completeness of the sponsor's submission

The sponsor did not include 9 relevant references identified by the EAC (as described above). However these additional references are all conference abstracts and do not add significantly to the comparative data provided. The EAC does not believe that there was a selection bias by the sponsor. Studies in indications other than acute burn injuries have been excluded from the EAC's evaluation as these are outside the scope.

The sponsor has commented on the relevance of the evidence to the scope. However they have considered the patient populations, interventions and comparators separately and indicated that each is covered adequately by the submitted evidence. That is, both patient populations, both indicators and both comparators have been covered by some part of the clinical evidence submitted. The EAC has commented on the difference between the groups defined in the scope and those reported in the included studies in sections 2.3 and section 3.6 and summarised the included studies according to the groups (above). This demonstrates that the pre-defined combinations of patient population, interventions and comparators have not been covered by the available clinical evidence.

Sponsor's interpretation of the clinical evidence

The sponsor's broad interpretation of the clinical evidence is that ReCell produces outcomes comparable to SSG. However, the sponsor's statement that adding ReCell to grafts allows more rapid epithelialisation than with SSG alone (section 7.9.1) is not supported by the evidence. Only one study compared ReCell plus SSG with SSG alone and this did not report healing rates (Park et al. 2013). Sen et al. (2012) [redacted] reported the use of ReCell plus STDG, i.e. recropping of the same donor site in the same operation. The use of this technique would allow greater wound coverage at one time and may thus enable total patient healing time to be reduced.

The sponsor's statement that ReCell plus Biobrane is associated with more rapid healing, lower costs and shorter length of hospital stay than with SSG is based on a single study of 5+10 patients (Rawlins 2011a, etc).

The EAC concurs with the sponsor that use of ReCell is at least as effective as standard care (standard or biosynthetic dressings or SSG alone). Differences in outcomes that are a necessary

requirement of the use of ReCell are not in doubt; for example, donor site area and therefore the pain associated with these are expected to be reduced in comparison to SSG alone. Following the application of ReCell the wound should be undisturbed for at least 5 days (manufacturer's instructions) whereas standard dressings are normally changed every other day (Wood et al. 2012; expert adviser opinion). However, the use of ReCell is associated with an increase in operative time. There was no evidence that the addition of ReCell to Biobrane confers any clinical benefits and there was no data comparing the use of ReCell alone with the use of Biobrane alone.

4 Economic evidence

4.1 Published economic evidence

Critique of the sponsor's search strategy

The sponsor searched three databases; Medline (including in-process), Embase and one specialist health economic database, NHS EED. Other economic databases were not included in the search, for example Econlit.

The strategy used to search for clinical evidence in Medline and Embase, was sufficient to have identified any economic or cost studies on ReCell within these databases. The search strategy for economic evidence in these two databases was extended by the sponsor to include any intervention. The studies identified were comparative cost analyses of dressings or general assessments of the cost of burns care and therefore do not address the questions in the scope. The NHS EED database includes economic studies identified by an extensive weekly literature search. None of the studies identified by the sponsor's search of NHS EED concerned the use of ReCell.

The sponsor included [redacted]

Critique of the sponsors study selection

The sponsor's selection criteria were broader than those of the Decision Problem in the scope, such that the intervention was not limited to ReCell or biosynthetic dressings. The rationale for the broader search strategy seems to have been to identify resources for the de novo model. None of the selected studies include ReCell, but either comparative studies of dressings or general assessments of the cost of burns care.

Included and excluded studies

The sponsor included 8 published studies and one unpublished audit, listed in Table C2 of the sponsor's submission.

Wood et al. (2012) contains data on the cost of treatment with ReCell in an Australia burn service. It was included in the sponsor's clinical evidence but not the economic evidence, although it is referenced several times in the economic submission. Since there were no other published comparative studies including cost analysis identified, the EAC considers it should be included. It is not clear why the study was excluded by the sponsor.

The EAC excluded all of the sponsor's selected studies as being outside the scope, since they do not include ReCell. The EAC recognises that some of these studies include relevant sources providing resource data for standard care for the de novo cost model.

Overview of methodologies of all included economic studies

Sponsor included economic studies

- Carayanni et al. (2011) is a comparative cost-effectiveness analysis of oil-based versus povidine iodine-based dressings in Greece.
- Caruso et al. (2006) is a cost effectiveness analysis alongside an RCT of two types of dressing, aquacel and silver sulfadazine based in the USA.
- Fong et al. (2005) is an audit from Australia reporting costs of care for patients receiving two different dressings; acticoat and silvazine.
- Silverstein et al. (2011) is a US RCT comparing two dressings, silver-containing soft foam dressing and silver sulfadiazine cream that includes cost data.
- Pellatt et al. (2010) is a UK (Bristol) assessment of cost of standard care for major paediatric burns.
- Hemington-Gorse et al. (2009) is a UK (Swansea) assessment of cost of standard care for major burns and comparison with HRG costs.
- Griffiths (2006) is a UK (Bristol) assessment of the cost of standard care for 3 paediatric scalds.
- Ahn and Maitz (2012) is an Australian assessment of costs of standard care for 20 adult burns patients.
- [redacted]

EAC included economic study

Wood et al. (2012) includes a resource analysis alongside a three-arm RCT conducted in Australia. Paediatric patients with scald injuries were randomised to receive either Biobrane (n=4), or Biobrane plus ReCell (n=5) or standard care (n=4).

Overview and critique of the sponsor's critical appraisal for each study

The sponsor has applied the quality checklist provided in Table C3 of the sponsor submission template to each of their selected studies, except [redacted]

The EAC has completed the quality checklist for Wood et al. (2012) (Appendix 2). The limitations of the Wood study are that it was conducted in Australia and may not reflect UK practice, the very small number of patients included (n=13), the heterogeneous patient population and the limited details of the resources, unit costs and total costs. The range of total costs was very large in each arm and the number of patients very small so it would be unwise to generalise the results.

Does the sponsor's review of economic evidence draw conclusions from the data available?

From the review of economic evidence the sponsor concludes that there are no published economic studies that answer the questions in the scope, therefore a de novo analysis is required and this is appropriate.

Wood et al. (2012) report the mean costs per treatment arm of the study. These were lowest for the standard treatment arm (Table 11, medians calculated by the EAC).

Table 11: Cost results from Wood et al. (2012) – Aust$

	ReCell plus Biobrane	Biobrane	Standard dressings
Mean	11337	22733	9431
Median	11745	26174	6751

The authors conclude that the number of bed hours occupied by the patient was the primary driver in determining the overall costs. As this resource use was significantly affected by non-clinical considerations (e.g. distance from home) overall costs do not reflect the treatment modality. The EAC considers the economic evidence from Wood et al. (2012) to be of limited value. Other papers selected by the sponsor include some relevant resource data but do not address the questions in the scope. The main economic evidence to consider is from the de novo model.

4.2 De novo cost analysis

Include a description and critique of the key assumptions related to the model structure.

An executable model was provided in TreeAge format. It is written from the perspective of the NHS. The model was supplied with the inputs set at the base case values. In order to check the results from sensitivity analysis the EAC changed each of the inputs in turn to correspond with those given in the 'Range' column of Table C5 in the sponsor submission, re-ran the model and saved the results.

Patients

The patients included in the de novo model are limited to Group A in the Decision Problem. In section 9.1.2 of the sponsor's submission the patient population is defined as "patients of any age presenting for acute care of partial thickness burns or scalds, where there is no immediate need for mesh grafting". In section 9.1.5 the indication is described as "partial thickness with no definite areas of deep involvement" – this is consistent with the first description. However the sponsor has used questionnaire data from four clinical advisers to provide data for their model. In their instructions to

these advisers the sponsor describes a "5-10% partial thickness burn of indeterminate depth". This indicates a burn injury that may require skin grafting and is inconsistent with the other descriptions of the patient population given in the sponsor's economic submission. Also, in section 9.2.1 the sponsor describes the probability of requiring skin grafting as being dependent on evidence of areas of full thickness burn at 10-12 days. This again indicates a difference between the burn injury actually being modelled and that described in the patient population as consistent with Group A.

The sponsor also uses data from four clinical trials of conventional topical treatments to provide data for the time to healing and proportion of wounds progressing to delayed skin grafting when treated with standard dressings (Caruso et al. 2006; Cuttle et al. 2007; Ostlie et al. 2012; Silverstein et al. 2011). However, these studies have a heterogeneous patient population including partial thickness burns, burns of mixed depth and full thickness burns whereas burn injuries that are consistent with the Group A patient population are (by definition) unlikely to require delayed grafting.

No modelling was conducted for the Group B patient population as the sponsor states that there is insufficient evidence to provide input parameters.

Technology

There are two treatment interventions in the model that include ReCell in accordance with Group A in the Decision Problem; ReCell with biosynthetic dressing (Biobrane) and ReCell with conventional dressings.

Comparator(s)

There are two comparators in the model in accordance with Group A in the Decision Problem; biosynthetic dressings (Biobrane) and standard dressings.

Model structure

The model structure chosen is a decision tree with four primary branches corresponding to the two interventions and two comparators under consideration. Figure 6 in the sponsor submission shows only part of the model structure. The full structure is shown in Appendix 3 of this report. It is reasonable to use a simple decision tree approach in this model because of the limited data available to populate the model. The EAC considers the basic structure to be appropriate.

Assumptions - overt

The sponsor lists five assumptions.

1. The first assumption is that the burn is considered to be partial thickness at the start of treatment, in keeping with the scope (but see Population section above).

2. The second assumption is that the burn requiring treatment is 640cm^2. The EAC has calculated this as around 3.5% TBSA for a UK adult (Sacco et al. 2010) or up to 10-15% TBSA

for a small child or baby (Sharkey et al. 2001). The sponsor states this corresponded to approximately 5-10% TBSA, depending on the size of the patient. This size of wound is justified by the sponsor as large enough to warrant treatment in a specialist burns service. Also they state that costs for burns care decrease rapidly below 5% TBSA. However, the EAC considers that the two references cited by the sponsor (Wood et al. 2012; [redacted] do not provide evidence to support this conclusion. The EAC considers this an appropriate burn size for Group A in the Decision Problem.

3. The pathway of care is as described in the submission of clinical evidence in section 3.3 of the sponsor submission. All burns are assumed by the sponsor to require initial debridement in theatre. Patients receiving conventional or Biobrane dressings require 20 minutes of theatre time and those being treated with ReCell require 30 minutes. This was based on feedback from the sponsor's clinical advisers but appears to rely on a single response. Two clinical studies demonstrate that the application of ReCell alone requires a mean of 29 minutes additional procedure time compared to SSG alone (Gravante et al. 2007; Rawlins 2013). Although these studies use a different comparator the EAC suggests that the extra procedure time may have been underestimated by the sponsor, particularly for surgeons unfamiliar with the technology. Sood et al. (2009) indicate a learning curve associated with successful use of the ReCell device.

4. Patients are assumed to be treated as in-patients until day 2 when a proportion are discharged and receive dressing changes as outpatients. This assumption is appropriate based upon the sponsor's survey of expert opinion and the EAC communications with clinical advisers.

5. The final assumption is that patients are managed either on a general burns ward or as outpatients.

The sponsor excludes treatment in ITU on the grounds that its high cost obscures other treatment cost differences. If treatment in ITU strongly drives cost as suggested, it should be included in the model unless the sponsor is confident that treatment in ITU is the same in all of the interventions. For this Group A population with 640cm^2 partial thickness burns it may be appropriate to exclude this because few such patients are likely to require care in ITU [redacted]. However the reason given in the sponsor submission for excluding ITU costs is invalid.

Assumptions - hidden

The EAC has identified the following additional underlying assumptions used by the sponsor:

- In-patients are assumed to remain in the burns ward until complete re-epithelialisation. One expert adviser indicated that patients will be discharged unless the size or site of the burn or the level of pain contraindicates this. As patients may be referred from a large geographical area distance from home may also contribute to the decision to remain an in-patient (Griffiths et al. 2006; Wood et al. 2012).

- The sponsor assumes that a greater proportion of patients with conventional dressings are treated as in-patients compared with patients receiving ReCell alone, ReCell plus Biobrane and Biobrane. The EAC has not found supporting evidence for this. Two of the sponsor's clinical advisers suggest that patients in all four treatment arms of the model may be discharged after the first COD on day 2-3 post intervention. A third states that for a 10% burn patients with Biobrane or Biobrane plus ReCell may be discharged at 2-4 days post treatment, patients with ReCell alone at 5-10 days and patients with conventional dressings at 7-14 days.

- It is assumed that the decision to progress to an SSG is made after ten days for all treatments. This is consistent with published clinical evidence although the actual time point for this decision may vary from 7-14 days.

- It is assumed that patients initially treated with Biobrane alone or ReCell plus Biobrane who progress to SSG will then continue with Biobrane dressings after grafting. Three of the clinical experts consulted by the sponsor noted that it is not usual practice to use Biobrane over an SSG.

- It is assumed that complication rates are the same for all interventions, since this is not included in the model. The EAC considers this to be a reasonable assumption based on the clinical evidence for more severe burns.

- The sponsor calculates the *percentage* reduction in healing times for ReCell plus Biobrane and Biobrane compared with standard dressings from Wood et al. (2012) as 23%-62%. They also use intra-patient comparisons from Echlin et al. (2012b) in which 2 patients had graft donor sites treated with ReCell compared to conventional dressings. In this case they calculate a 35% and 80% reduction in healing time. The sponsor also quotes one of their clinical advisers as stating that they achieved a 25-50% reduction in healing time with ReCell. However, the EAC has concluded that the adviser actually described a 25-50% reduction in the need for delayed SSG following treatment with ReCell. None of the four clinical advisers provide information regarding healing time. The sponsor applies a percentage reduction to the healing time for conventional care to calculate values for ReCell alone, ReCell plus Biobrane and Biobrane. The EAC considers that it is reasonable to cautiously apply this reduction to ReCell plus Biobrane and Biobrane alone, but there is no evidence for this in ReCell, since Wood et al. (2012) does not include a ReCell alone treatment group.

The EAC completed a quality check on the sponsor model and submission and found the economic submission to be of acceptable quality and well reported.

Clinical parameters and variables

The time horizon used in the model is intended to be the period of the acute episode of care and is chosen to be 21 days. This is appropriately long for the patient population in the model. Because of the short time horizon, no discounting was applied and this is appropriate. The model is constructed from the NHS perspective.

Healing time

The sponsor has identified three studies of conventional topical burn treatments and used the healing times as a surrogate for the conventional dressing treatment arm of their model (Caruso et al. 2006; Cuttle et al. 2007; Silverstein et al. 2011). The values range from 13 days to 18 days and the sponsor takes the median value of 15 days as their base case. As described above the patient populations in these studies are heterogeneous, however Cuttle et al. (2007) reports time to healing only for patients who did not require grafting (in a paediatric population). This is consistent with the patient population for Group A in the Decision Problem and indicates that the sponsor's estimate is appropriate. In the clinical evidence submission only Wood et al. (2012) reports healing time for burn wounds treated with conventional dressings. Their median time for 4 paediatric patients with scalds is 36.5 (18.5 - 47.7) days for approximately 4-5% TBSA.

The sponsor has used a percentage reduction in the healing time for conventional dressings to determine healing times for Biobrane alone, Biobrane plus ReCell and ReCell alone. The sponsor has chosen conservative estimates of a 30% reduction for Biobrane or ReCell alone and 40% reduction for ReCell plus Biobrane. Although the EAC has noted concerns with the basis for this choice (above) the sponsor has varied the values from 0-50% for all three. The EAC considers this approach appropriate given the paucity of data on which to base the model.

Requirement to be treated as an in-patient

The sponsor correctly identifies the range of factors that influence the decision for a patient to remain as an in-patient during treatment. However, they reason that treatment with ReCell alone means that the wound surface is covered and that only secondary dressings require a COD. The manufacturer's instructions indicate that primary and secondary dressings should remain in place for 5 days. Clinical advisers indicate that the first COD and wound inspection occurs at 2-5 days post surgery. Biobrane adheres to the wound and is not removed until it lifts away from the surface as healing occurs. The EAC concludes that there is little evidence to support the assumption that the use of ReCell alone contributes to an earlier discharge.

The sponsor has adopted "arbitrary values" of 50% in-patient care for conventional dressing and 25% for the other 3 treatment arms. The EAC considers these to be high given the clinical opinions provided to the sponsor. However, as none of the respondents provided an answer to the question about proportions of patients we have no basis to choose other values.

Probability of skin grafting

The sponsor states that review of the burn injury at 10-12 days will determine the requirement for delayed skin grafting. They have used data from published studies on topical burn treatments to determine that 30% of burns treated with conventional dressings will require later SSG (Caruso et al. 2006; Cuttle et al. 2007; Ostlie et al. 2012; Silverstein et al. 2011). Estimates from two of the sponsor's clinical advisers indicates a graft rate of 5-10% for conventional dressings. The EAC agrees with the sponsor that the small number of patients in Wood et al. (2012) and the expectation that these injuries would require grafting means that the data from this study cannot be used reliably

here. The sponsor has referred to information from their clinical advisers. The pattern is mixed and is presented in Table 12.

Resource identification, measurement and valuation

The sponsor states (section 9.3.1 of sponsor submission) that burns are excluded from the Payment by Results (PbR) tariff and that there are no burns-specific codes in HRGv4. However NHS Reference Costs includes Health Resource Group (HRG) codes and data on burns (Department of Health 2012). NHS reference data is potentially valuable for validating the results of the model.

In the model a small number of published cost analyses on general burns care and the [redacted] are the main source of resource use and valuation data, supplemented by the opinions of a panel of four experts. Of the four experts chosen, one is the inventor of ReCell with a potential conflict of interest and is based in Australia. Whilst it is reasonable to approach such an expert with extensive knowledge of the product, the conflict of interest remains and should be noted and taken into consideration when interpreting the results. The other three experts surveyed by the sponsor are likely to be familiar with standard UK practice (one has worked in the UK, but also in Australia). The EAC considers the expert opinion from the Australian expert to be less pertinent to UK practice.

Technology and comparator costs

Summary of variables applied in the cost model

Table C5 in the sponsor submission lists the model inputs.

The proportion of patients treated as in-patients is the first set of inputs and the source of the data is the expert opinion questionnaire. None of the experts directly answered the question, indicating the difficulty in quantifying this. Two of the experts responded that for all of the treatment options, the patient may go home after the first dressing change if all is going well. The third expert gave estimates of length of stay for each of the treatment groups. Clarifying comments from the third expert indicate that with conventional dressings the patient is more likely to require morphine analgesia which requires admission to a ward for monitoring. The values in the sponsor's Table C5 appear to have been based on this comment. Given the uncertainty in the values it is essential to include robust sensitivity analysis for this parameter.

The proportion of patients progressing to SSG is based upon expert opinion for all of the treatments except conventional dressings. For conventional dressings the source is four studies (3 from the USA and one from Australia) from the sponsor's searches for clinical and economic data. The patient population in these studies does not match the scenario presented to the expert panel in the questionnaire and varies between studies. For example one study includes partial thickness burns of 5-40% TBSA (Caruso et al. 2006), and another 2.5-20% TBSA (Silverstein et al. 2011). The third study patients had burns up to 25% TBSA (Ostlie et al. 2012) and the fourth paper only reported the mean TBSA of the two groups as 4.4% and 5.2% (Cuttle et al. 2007). Therefore using the studies may over-estimate the proportion of patients requiring SSG compared with the expert view for alternative

treatments because the patient populations in the studies include more severe cases. The sponsor asked the expert panel for their opinion on this question and the responses are summarised in Table 12.

Table 12: Expert opinion - proportion of patients requiring SSGs

	Expert 1	**Expert 2**	**Expert 3**	**Expert 4 (Non-UK)***
Conventional dressings	5%	10%	(*no response)*	Many may need surgery depending on initial assessment
Biobrane alone	<5%	10%	same	50% (trial)
ReCell	<5%	5-10%	no experience	I would expect very few
ReCell + Biobrane	<5%	5-10%	reduced by 25-50%	none in trial (small numbers)

* Refers to data from Wood et al. 2012.

The sponsor's base case values (conventional dressings or Biobrane alone - 30%, ReCell or ReCell plus Biobrane - 10%) seem higher than those of the sponsor's UK experts, but there did appear to be agreement from the experts that ReCell alone and in combination with Biobrane reduced the number of patients going on to SSG. The absolute values can be further explored in sensitivity analysis.

The mean time to 100% epithelialisation is the next variable in the sponsor's Table C5. This is a clinical end point, rather than a resource variable, but is linked to resources through the length of stay (LOS) for in-patients and the number of dressing changes required up to the point of healing because of assumptions in the model. The sources for the LOS used in the conventional dressings arm of the model are the same four studies used to determine the proportion of patients progressing to SSG, and the same limitations apply. None of the studies are from the UK, and the populations are heterogeneous.

The LOS for the other interventions is calculated from a fixed percentage reduction in healing times. This is based on Wood et al. (2012), which included a total of 13 patients in the three arms of the trial. This showed a reduction in median time to heal from 36.5 days with conventional dressings (n=4) to 16 days for Biobrane only (n=4) and 16 days for Biobrane plus ReCell (n=5). The time to heal using conventional dressings is considerably longer than in the sponsor's model (15 days). It does not necessarily follow that the same percentage reduction in healing time would be achieved for the population in the model.

The other study cited to justify the reduction in LOS is Echlin et al. (2012a). The description of the study identified as Echlin (2012a) in section 9.2.1 appears to correspond to another paper, Echlin et al. (2012b). Echlin et al. (2012b) is a conference abstract of a case series that additionally reports an

intra-patient comparison in 2 patients between ReCell and conventional treatment of graft donor sites. The sponsor acknowledges that the data from these two studies is not sufficiently robust to generate estimates of healing times. The sponsor therefore set baseline healing rate reduction for Biobrane or ReCell alone at 30% and in combination at 40% whilst undertaking wide sensitivity analysis from 0-50% for all three.

Wood et al. (2012) does not include a treatment arm for ReCell alone, therefore it does not provide evidence for a healing time reduction of 30%. In this small study there was a substantial reduction in healing time between both Biobrane alone and Biobrane plus ReCell compared with standard dressings (no statistical testing). There is minimal evidence for reduced healing time for ReCell alone from Hiller (Hiller et al. 2013), but this is an abstract of a case series (n=5) from conference proceedings and contains little detail. The abstract claims 'acceleration in epithelialisation and healing time'. Rennekampff et al. (2011) gives a healing time of 7-9 days for ReCell in a case series of 5 patients, but as there is no comparator it is not possible to say if this is reduced (this may be the same study as (Hiller et al. 2013). Other clinical evidence is for Group B in the Decision Problem.

Cost of resources

The sponsor's cost of re-dressing using conventional dressings [redacted] based on the [redacted] Although a stay in ITU is not excluded in the scope, the sponsor has excluded this from the model. [redacted] Uncertainties can be explored in sensitivity analysis.

For secondary dressing changes in the other treatment arms, the sponsor estimated the cost to be £25 based on assumption of 30 minutes of nurse time plus consumables. Again the derivation of this figure is unknown. The sponsor's expert advisers were asked about the proportion of patients requiring a general anaesthetic (GA) for conventional and secondary dressing changes. Two of the UK advisers responded 'rare' and 'zero' for both types of dressing change. The third UK adviser indicated that greater than 50% of patients would require a general anaesthetic for re-dressing using conventional dressings, but less than 5% for Biobrane or Biobrane plus ReCell. (They did not respond

to this question on the proportion of patients requiring GA for ReCell alone.) Again, it is not clear if these responses represent a genuine diversity of practice. It is feasible that differences in the cost of re-dressing arise because changing conventional dressings is more painful and hence more likely to be undertaken under general anaesthetic, by more highly paid staff e.g. medical consultants, or takes longer because of the pain. It is not clear that the two costs have been calculated on the same basis or that they are comparable. Therefore this will require scrutiny in the sensitivity analysis.

The cost of ReCell is given as £950 per 320 cm^2 and the cost of Biobrane is £60.80 per 320 cm^2 treated. These values have been verified by the EAC.

- The general hospital costs in the model are taken from the [redacted] daily bed cost in the burns unit [redacted]
- daily staff cost in the burns unit (£[redacted])
- hourly cost of theatre time (£[redacted]

[redacted] The EAC has compared these figures with the staff costs published in Curtis (2012) and [redacted] £35 per hour for a nurse on a 24 hour ward in Curtis (2012), and the Consultant Surgeon is [redacted] £147 per hour [redacted] In the NHS Reference Costs, the national average cost of an excess bed day for the burns codes JB12B, JB13B and JB21B are £583, £554 and £516 respectively (Department of Health 2012). [redacted]

Hemington-Gorse (2009) conducted a top-down cost analysis of the Welsh Burns Unit at Morriston Hospital, Swansea. Unit costs were calculated as shown in Table 13. The EAC has converted the currency to GBP and adjusted for inflation. The values used in the model compare reasonably well with these.

Table 13: Unit costs from Hemington-Gorse et al. (2009)

Resource	Euros 2008	GBP 2008	GBP 2013
Low dependency ward	€477 per day	£379.69	£429.01

Theatre time	€6660 per hour	£5301.36	£5990.00
COD	€200	£159.20	£179.88
ITU bed	€2961	£2356.96	£2663.12

In Table C5 of the sponsor submission, the overall cost of an SSG is derived from time to healing outcomes from Ostlie (2012) a study comparing two different topical treatments, based in the USA. A third of patients went on to have skin grafts. The average LOS for all patients was 11 days, but the sponsor has used this as evidence of graft healing at 11 days following operation. This is inappropriate. Mean time to healing for a burn treated with SSG is reported in Gravante et al. (2007) as 12 days (for 320 cm^2 TBSA) and in Rawlins (2011a, etc) as 48 days (approximately 10-25% TBSA).

The sponsor states that the overall SSG cost is calculated based upon 30 minutes in the operating theatre, discharge at 4 days followed by secondary dressing changes every other day. The clinical evidence is in reasonable agreement with these values; operating times of 20 minutes time (Gravante et al. 2007) and 58 minutes (Rawlins 2013).

Cost per treatment/patient associated with the technology in the cost model

The list price for ReCell is given in Table C6 of the sponsor submission as £950 per pack, each of which can treat up to 320 cm^2. The base case in the model is based on the use of 2 packs to treat 640 cm^2. There are no consumables, maintenance or training costs in the model. This is appropriate since the manufacturer provides training and because the ReCell device is single use. The only additional cost identified by the sponsor is for an additional 10 minutes in the operating theatre at the initial procedure for debridement and dressing.

Cost per treatment/patient associated with the comparator technology (standard care)

The sponsor has based the cost per treatment/patient on a 10 day in-patient stay with re-dressings every 2 days at a cost of £166 each (Table C7a of sponsor submission). The reference given to justify the cost is [redacted]

Of the UK experts two indicated that patients having conventional dressings go home after 2-3 days, depending on pain and if the wound is healing well. This is consistent with the NHS reference data under codes JB13B 'Other burn with other procedure, without major critical care' (mean LOS 2.88 days) and JB21B 'Other burn without other procedure, without major critical care' (mean LOS 2.28 days)(Department of Health 2012). The third UK expert indicated LOS to be 7-14 days for conventional dressings. These differences may relate to real variation in practice or to a different understanding of the patient population under consideration. In free text comments the third expert indicated that their responses related to burns ≥ 10% TBSA, whereas the sponsor asked the experts about burns 5-10% TBSA and this is indicated as an assumption of the model. Therefore it is likely that this is the source of difference in the responses. [redacted]

[redacted]. Also, the mean LOS for moderate/severe burns (the lowest category to be associated with a Burns Unit) provided in the International Burn Injury Database is 15.3 days (NBCG 2008).

Cost per treatment/patient associated with the comparator technology (Biobrane)

The only additional input not yet considered in the Biobrane arm of the model is the cost of Biobrane. The EAC has checked the sponsor's value of £60.80 per 320 cm^2 and found it to be correct.

Cost per treatment/patient associated with the comparator technology (Biobrane plus ReCell)

There are no additional inputs for Biobrane plus ReCell.

Sensitivity analysis

The range of values tested in sensitivity analysis was considered by the EAC to be too narrow for some inputs where there is considerable uncertainty. There is considerable uncertainty regarding the sponsor's value of 10% of patients progressing to SSG for ReCell. The sponsor's sensitivity analysis considered the range 5%-20%. The EAC considered this should be extended to 30%, to examine the case where there is no difference between ReCell and standard care. The EAC considered that there was uncertainty around the cost of dressing changes, for conventional dressings and secondary dressings, and therefore extended the range in sensitivity analysis for these inputs.

4.3 Results of de novo cost analysis

Base-case analysis results

The EAC checked the model outputs and found no errors in the base case calculation. Overall Biobrane is the lowest cost, followed by Biobrane plus ReCell as reported in Tables C11a and C11b in the sponsor's submission. The lower costs of Biobrane arise because of the considerably lower technology costs compared with the alternatives, the reduced number of dressing changes and reduced healing time. ReCell is cost saving compared with conventional dressings in the sponsor's base case analysis. Cost savings for ReCell are driven by the reduction in the proportion of patients requiring SSG following ReCell, and the shorter healing time. Cost savings also depend on the differential dressing costs between changing conventional dressings and changing secondary dressings with ReCell.

Sensitivity analysis results

The sponsor's sensitivity analysis was checked by the EAC and discrepancies were found with the reported results in Tables C13a-C13d in the sponsor submission. The EAC calculated values are given in Table 14 to Table 17 below where there are differences with the reported values.

Table 14: ReCell differences from table C13a of sponsor submission

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	**High** EAC (sponsor)
Proportion of patients treated as an in-patient	25% - 75%	£7891 (£7,106.82)	£ 10,515 (£9,205.79)

Table 15: ReCell plus Biobrane differences from table C13b in the sponsor's submission

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	**High** EAC (sponsor)
Proportion of patients treated as an in-patient	25% - 75%	£7787 (£7,125.69)	£9991 (£8,889.33)

Table 16: Conventional – differences from table C13c in sponsor submission

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	**High** EAC (sponsor)
Proportion of patients progressing to SSG	5% - 20%	£8529 (£8,872.72)	£9137 (£9,989.47)
Mean time to 100% re-epithelialisation	7.5 – 15 days	£7476 (£8,991.87)	£9542 (£10,369.12)

Table 17: Biobrane differences from Table C13d in the sponsor submission

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	**High** EAC (sponsor)
Proportion of patients treated as an in-patient	25% - 75%	£6398 (£5,621.02)	£8991 (£7,695.16)
Proportion of patients progressing to SSG	5% - 20%	£4914 (£5,507.54)	£5805 (£6,993.01)

As the EAC considers that there is no supporting evidence that ReCell reduces the percentage of patients progressing to SSG we extended the range of the sensitivity analysis for this in the ReCell arm from 5-20% to 5-30%. If 30% of patients in the ReCell group progress to SSG, the total cost for ReCell increases to £9,079 but ReCell remains cost saving compared with conventional dressings (£9,543).

The EAC extended the range of values tested for the costs of COD; from £83-£249 to £25 -£249 for conventional COD and from £12.50-£37.50 to £12.50- £166 for secondary COD. ReCell remained cost saving compared with standard dressings. The results are shown in Table 18-Table 21 below.

Table 18: EAC's one-way sensitivity analysis – ReCell alone (cf. Table C13a)

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	**High** EAC (sponsor)
Proportion of patients treated as an in-patient	25%-75%	£7891 (£7106.82)	£10,515 (£9205.79)
Proportion of patients progressing to SSG	5% - 30%*	£7,596.84	£9079
Costs of resources.			
Conventional dressing change(cDressing)	£25* - 249	£7821	£7,933.43
Secondary dressing change (cDressminor)	£12.50 -£166*	£7,826.62	£8628

* Modified by EAC

Table 19: EAC's one-way sensitivity analysis – ReCell plus Biobrane (cf. Table C13b)

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	**High** EAC (sponsor)
Proportion of patients treated as an in-patient	25% - 75%	£7787 (£7,125.69)	£9991 (£8,889.33)
Costs of resources.			
Conventional dressing change(cDressing)	£25* - 249	£7716	£7,828.55
Secondary dressing change (cDressminor)	£12.50 -£166*	£7,730.20	£8428

* Modified by EAC

Table 20: EAC's one-way sensitivity analysis – conventional dressings (cf. Table C13c)

Variable	Range tested	Total cost per patient	
		Low EAC (sponsor)	**High** EAC (sponsor)
Costs of resources.			
Conventional dressing change(cDressing)	£25* - 249	£8379	£10,227.52
Secondary dressing change (cDressminor)	£12.50 -£166*	£9,542.77	£9542

* Modified by EAC

Table 21: EAC's one-way sensitivity analysis – Biobrane (cf. Table C13d)

Variable	Range tested	Total cost per patient	
		Low	**High**
Proportion of patients treated as an in-patient	25% - 75%	£6398 (£5,621.02)	£8991 (£7,695.16)
Costs of resources.			
Conventional dressing change(cDressing)	£25* - 249	£6187	£6,523.32
Secondary dressing change (cDressminor)	£12.50 -£166*	£6,334.14	£7128

* Modified by EAC

The sensitivity analysis showed the model to be very robust when each parameter is considered in isolation. The cost ranking for each treatment arm in the model remained consistent; Biobrane

alone, ReCell plus Biobrane, ReCell alone and conventional dressings. No probabilistic sensitivity analysis was undertaken due to lack of data on which to base the distributions.

Scenario analysis

The sponsor included scenarios based upon changing several inputs simultaneously to model a number of clinical scenarios. The scenarios were somewhat limited by the structure of the model:

- TBSA was reduced from 640 cm^2 to 320 cm^2
- TBSA was increased from 320 cm^2 to 1280 cm^2
- Hospital costs decreased by 25%
- Hospital costs increased by 25%
- All benefits reduced by 50% (proportion of patients remaining as in-patients, proportion of patients who have delayed grafting and time to heal)

Table C14 of the sponsor submission gives the results of the scenario analysis. There is an error in Table C10.2 of the sponsor submission. The bed cost in the base case is given as £166, whereas this is the base case cost of a dressing change and the bed cost is £152. The scenarios with "hospital costs reduced by 25%" were run by the sponsor with incorrect values. The EAC re-ran the scenarios with the correct inputs. In the scenario with "all benefits reduced by 50%" the sponsor did not change the percentage of patients requiring SSG in the Biobrane group (from the base case value, 30%). The EAC re-ran the scenario with the treatment effect for Biobrane reduced by 50%. The results of these changes are in Table 22-Table 23.

Table 22: EAC's correction for scenario Table C14 – cost per patient

	Total cost per patient EAC (sponsor)			
Scenario	**ReCell**	**ReCell + Biobrane**	**Conventional**	**Biobrane**
TBSA = 320 cm^2	£5537	£5534	£5514	£4391 (£4491)
TBSA=1280 cm^2	£14,402	£13,870	£15,550	£10,684
Benefits reduced by 50%	£9311	£9277	£9542	£8235 (£7433)
Hospital costs reduced by 25%	£6447 (£7595)	£6395 (£6530)	£7499 (£7492)	£4924 (£5060)
Hospital costs increased by 25%	£9336 (£9185)	£9179 (£9041)	£11,586	£7873 (7734)

Table 23: EAC's correction for scenario Table C14 – incremental cost (grey shading indicates cost saving for ReCell or ReCell plus Biobrane)

	Incremental cost EAC (sponsor)			
Scenario	**ReCell vs conventional**	**ReCell+Biobrane vs conventional**	**ReCell vs Biobrane**	**ReCell+Biobrane vs Biobrane**
TBSA = 320 cm^2	£23	£20	£1146 (£1046.21)	£1143 (£1042.86)
TBSA=1280 cm^2	-£1148 (-£1696.12)	-£1680 (-£2228.12)	£3718	£3186
Benefits reduced by 50%	-£231	-£265	£1076 (£1878.53)	£1042 (£1843.70)
Hospital costs reduced by 25%	-£1052 (£103.12)	-£1104 (-£961.99)	£1523 (£2535.68)	£1471
Hospital costs increased by 25%	-£2250 (-£2402.56)	-£2407 (-£2546.99)	£1463 (£1450.93)	£1306

In all of the scenarios presented, ReCell was cost saving compared with conventional dressings, except for the smaller wound size of 320 cm^2 TBSA when ReCell and ReCell plus Biobrane were more costly than conventional dressings. In all of the other scenarios Biobrane was the lowest cost option followed by ReCell plus Biobrane, ReCell alone and conventional dressings. The cost savings for ReCell and ReCell plus Biobrane compared with standard dressings in the scenarios "Hospital costs increased by 25%" and "TBSA=1280cm^2" were lower after the corrections were applied.

The scenarios allowed the sponsor to change several model inputs simultaneously. The results of the scenario analyses showed the model to be robust.

Model validation

Sponsor's validation

The sponsor validated the model using a [redacted] The base case values in the model (£7891.93 ReCell, £6397.82 Biobrane, £7787.05 ReCell + Biobrane, £9,542.77 conventional dressings) [redacted]

[redacted] It would be better to find an alternative source for validation. The EAC considers the NHS Reference Costs to be an appropriate set since the sponsor did not use this source in the model and since it includes data from many UK centres (Department of Health 2012).

Validation with NHS Reference Costs

In the 2011-12 data the relevant codes are for 'major burns' (>20% TBSA) or 'other burns'. For comparison with the model the EAC has considered the data for 'other burns' given in Table 24. The base case results for conventional dressings in the sponsor's model are at the higher end of the inter-quartile range (IQR) for patients coded JB12B. The code is for patients having one graft procedure whereas in the model base case only 30% of patients having conventional dressings proceed to SSG. Therefore one would expect the base case costs to be lower. Average LOS in the model base case is 15 days, but in the patients coded JB12B it was 7.68 days. This may be explained by the sponsor's assumption that in-patients remain in hospital until complete epithelialisation. In practice there may be earlier discharge points for some patients. The NHS Reference Costs for JB13B and JB21B give very much lower overall costs and LOS. The patient populations in these two codes are likely to include patients with smaller TBSA than those in the model. Taking into account the assumptions in the model and the differences in the populations, the base case results are reasonably consistent with the NHS Reference Costs.

Table 24: National reference costs for 'other burns (Department of Health 2012)

Code	Description	National average unit cost (IQR)	Average LOS
JB12B	Other burn with one significant graft procedure without major CC	£8,046 (£6,400, £10,430)	7.68
JB13B	Other burn with other procedure , without major CC	£2,870 (£1,507, £3,771)	2.88
JB21B	Other burn without other procedure, without major CC	£1,749 (£939, £2,165)	2.28

Validation with Wood et al. (2012)

The results of the model differ from those in the cost analysis by Wood et al. (2012), which found that standard dressings were the lowest cost intervention, followed by ReCell plus Biobrane, and Biobrane alone was the most costly intervention. The key driver of the analysis was the number of bed hours occupied by the patients. The differences in these findings may be explained by:

- differences in clinical practice between UK and Australia
- differences in patient population
- geographical factors – some patients in Wood et al. (2012) were from remote areas, so could not be treated as out-patients

- small numbers of patients in Wood et al. (2012) – 13 in total for a 3 arm trial

4.4 Interpretation of economic evidence

Generalisability

The sponsor selected a population for the model, with the key parameter being the extent of the burn 640 cm^2 (5-10% TBSA). The burns were considered to be partial thickness at initial assessment. The sponsor considered that the model was not appropriate for burns greater than 20% TBSA, where there are more complex pathways. In more extensive burns, there is greater likelihood that patients require:

- skin grafting for full thickness injury
- ITU admission
- multiple trips to theatre

Together with the impracticalities of managing this burn size as an out-patient, the sponsor considers this takes larger burns out of the scope of the model. The EAC agrees with this distinction and this also fits with the decision problem in the scope.

The sponsor considered that the model was inappropriate for patients with burns <2% TBSA as they are unlikely to be treated in hospital. The EAC considers that this should refer to treatment in a specialist burns service rather than "in hospital".

Strengths

Despite the paucity of data the sponsor has produced a model of a particular patient population that is fit for purpose and has been validated by the EAC. The lack of data is inherent in the topic and does not reflect any reluctance to undertake studies by the research community.

Sensitivity analysis was undertaken and supplemented by scenarios. The results are robust in the one-way sensitivity analysis and in the scenarios, except for the scenario with "TBSA=320 cm^2".

Weaknesses

There were some errors in the results of sensitivity analysis recorded in the submission.

The model relies quite significantly on an unpublished study [redacted] for cost data, which has not undergone peer review and for which little information about data acquisition and cost derivation is known.

The factors in the model that drive the cost saving for ReCell compared with standard dressings are the reduction in the proportion of patients requiring SSG and the shorter healing time. Evidence for these improved clinical outcomes is very limited (Wood et al. 2012) and restricted to ReCell in combination with Biobrane. Clinical evidence from Rennekampff et al. (2011) indicated the healing

time to be 7-9 days for ReCell, but there was no comparator in this case series of facial burns. Hiller (2013) indicated 'acceleration in epithelialisation and healing time' but there were few details in this abstract (also possibly the same study as Rennekampff et al. 2011).

It has been challenging for the sponsor to ensure that all of the model inputs are based on the chosen patient population. The evidence was taken from a small number of published and unpublished studies and expert opinion, often with different populations.

4.5 Additional work undertaken by the External Assessment Centre in relation to economic evidence

The EAC searched Econlit, but found no additional economic studies of ReCell.

The EAC completed a quality check on the Wood et al. (2012) study (Appendix 2).

The EAC completed a quality check on the sponsor's de novo model and submission (Appendix 4).

The EAC used NHS Reference Costs to validate the model results (Department of Health 2012). The results of the model were also compared with the results of a published cost analysis Wood et al. (2012).

The EAC ran some extended sensitivity analyses to investigate the impact of key inputs.

4.6 Conclusions on the economic evidence

- The sponsor's model is robust and shows cost savings for ReCell compared with standard dressings in partial thickness burns of size 640 cm2 and 1280 cm2.
- The evidence underpinning the model is very limited and some of it is of questionable suitability given the heterogeneity of the patient populations, the variable nomenclature used and the multiple ways of grouping burn injuries.
- The sponsor did not model Group B in the Decision Problem - 'Large area burns; full thickness or deep partial thickness burns including where mesh grafting is required' .

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

Corrections made by the EAC to some input errors in the model for the scenario in which "hospital costs reduced by 25%", changed the outcome for ReCell alone compared with standard dressings, from cost incurring (£103.12 sponsor result) to cost saving (-£1052 EAC result). For the scenario in which TBSA was increased to 1280 cm^2, the corrections reduced the cost saving for ReCell compared with standard dressings (-£1696.21 sponsor, -£1148 EAC). The full scenario results are in Table 22 to Table 23.

5 Conclusions

The case for this evaluation of ReCell is equivocal. The evidence is difficult to interpret as it is not strictly consistent with the patient population, intervention and comparator groups as defined in the Decision Problem. The available clinical evidence is sparse and mostly of a low level. Only two studies were large enough and were reported in sufficient detail to provide robust evidence (Gravante et al. 2007; Park et al. 2013). However these did not demonstrate clinical benefit for the burn wound (although a reduction in donor site size and pain was reported) or indicate a basis for resource saving (reduced LOS partially attributed to differences in wound severity). The evidence does appear to demonstrate that ReCell is at least as effective as other current treatments in the care of acute burns suitable for treatment at a specialist burn service in the UK. The evidence has not demonstrated superiority over current treatments but suggests that there is potential for increased clinical benefit in burn injuries of different severities.

The claimed benefits for the patient are:

- **A reduction in skin graft donor site size and depth**: ReCell necessarily requires a smaller donor site with respect to a split thickness skin graft taken to cover the same burn wound size. This is self-evident given the mode of use and is also supported by Gravante et al. (2007). However, in patients for whom a skin graft was not initially indicated (i.e. Group A) the use of ReCell necessarily creates an additional wound, albeit a small one. None of the clinical studies defined the depth of their SSGs beyond 'split thickness' – indicating the removal of the epidermis and top layer of the dermis. Therefore the EAC cannot comment on the relative depth of the biopsy.

- **Fewer complications, reduced morbidity and shorter healing time at the donor site**: This is outside the scope of this evaluation.

- **Shorter wound healing times at the recipient site**: Faster healing has not been demonstrated in Group B burn wounds (ReCell plus SSG versus SSG alone). Faster healing as reported in two small and statistically non-significant studies in comparison to SSG is not convincing and superiority against treatment with Biobrane alone is unclear.

    - **leading to improved burn wound aesthetic result with a lower likelihood of scarring and better match of skin colour and repopulation of melanocytes to reduce hypopigmentation in healed wounds**: This has not been demonstrated in the clinical evidence. One expert adviser indicated that they thought cosmetic outcomes were better than would otherwise be expected.

- **Reduced dressing change frequency (weekly rather than daily)**: Fewer, or simpler (more superficial), dressing changes may result from use of ReCell, especially in the first few days following treatment. However, expert opinion indicates that standard care involves COD every 2-3 days and that this regime is maintained following the first COD. This outcome appears to be accepted for the use of Biobrane, and any superiority of ReCell (either in combination or alone) has not been demonstrated.

- **Less need for dressing changes under anaesthetic:** This outcome was not addressed by the clinical evidence and the responses from the sponsor's clinical experts were mixed; varying from no patients with any treatment requiring GA to more than 50% of conventional patients requiring GA (this latter for 10% or greater TBSA).

The claimed benefits to the healthcare system are:

- **Reduction in length of stay (LOS) in hospital:** The evidence provided for the economic model (Group A) is from a study of 13 patients that does not include ReCell alone, but only includes ReCell plus Biobrane (Wood et al. 2012). The sponsor's expert panel gave varying responses about time to discharge when asked about the proportion of patients suitable for discharge after initial treatment, but tended to indicate that most patients would be suitable for discharge following the first COD. This model input has been included in sensitivity analysis.

- **Weekly rather than daily dressing changes:** As above. However there is potential for a system benefit because of the potential for reduced cost due to changing secondary dressings (for patients treated with ReCell), compared with full conventional dressing changes. There is remaining uncertainty about the costs of these dressing changes, but this has been explored in the sensitivity analysis.

- **Earlier discharge and outpatient management:** As above for LOS.

- **Reduced need for re-dressings under anaesthetic:** As above. The basis for cost of conventional dressing changes is unclear from the sponsor's submission, so it is unclear whether COD under anaesthetic was included for a proportion of the dressing changes for conventional dressings.

- **Reduced requirement for external technical laboratory support:** Not included in the model.

- **Reduced likelihood of later readmission for corrective surgery as a result of improved aesthetic results:** This was not explored in the model timeframe.

For patients where there is no immediate need for mesh grafting no claims were made in the scope regarding a possible reduction in the need for SSG at 10-12 days. However this featured in the model and evidence was taken from Wood et al. (2012) supplemented by the survey of expert opinion. There were differences in the numbers from the experts on the proportion of patients that would progress to SSG, but agreement that fewer patients in the ReCell arm would require SSG compared with conventional dressings.

6 Implications for research

The available clinical evidence does not support the claims made in the scope partly due to the design of the studies that have been conducted. Due to the inherent heterogeneity in the patient population robust evidence is unlikely to be produced using tightly controlled criteria such as that used in Wood et al. (2012) unless the screened population is very large. Much larger, multi-centre studies may provide the numbers of patients necessary to overcome any baseline differences. This has the additional difficulty of attempting to standardise treatment protocols between centres and consultants. Although the number of specialist burn services in the UK (and therefore the number of consultant burn surgeons) is relatively small there may be significant variation in practice and preference between them.

Patient pathways are relatively well-established for the more superficial and the obviously deep partial or full-thickness burns. The more superficial burn injuries that would be treated in a specialist burns service (i.e. Group A in the Decision Problem) are the most common; around 4500 patients per year are suitable for treatment in a Burns Facility (NBCG 2008). But these are also the most likely to heal well without intervention using an expensive technology. This may explain the lack of published evidence in this patient group.

The clinical evidence is also scarce in the larger and deeper burns (Group B in the Decision Problem). Very little evidence was identified regarding the use of ReCell in combination with split thickness skin grafts. The reason for this is unknown as information from the sponsor's clinical advisers indicates that this practice is not uncommon. The relative rarity of patients in this population in the UK may contribute to the difficulty; only around 900 patients per year have burn injuries severe enough to warrant referral to a Burn Unit or Centre (NBCG 2008). Also the risk of significant morbidity and death increases with burn TBSA; one clinical adviser to the sponsor indicated an upper limit of around 60% TBSA as appropriate for ReCell.

Research in this patient population may be difficult to organise due to the need to co-ordinate multiple centres and involve a long recruitment time. Also due to the small numbers and heterogeneity it is likely that one or two patients with especially long recovery times and high resource use could heavily skew the data, particularly for resource use and cost information. Long term scar outcomes are particularly difficult to measure in more serious burns as patients may travel a significant distance to reach a specialised service.

Expert adviser opinion demonstrates the lack of agreement regarding the best treatment protocol for patients with mid-deep partial thickness wounds or burns in which the depth is indeterminate. Assessment of burn depth and healing potential is based primarily on clinical skill but can be assisted by the use of the moorLDI2 Burns Imager (NICE 2011). Research in this group in particular would be necessary to determine the effect of the use of ReCell on the need for delayed skin grafting.

A further difficulty in this area of research is the multiple interventions and comparators. There are four potential treatment arms defined in this evaluation, to treat burn wounds that can be characterised by both burn depth (or estimated time to heal, or anticipation to require grafting) and

burn area. These are further complicated by potential effects from variations in burn source (e.g. scald or flame burn) and patient age. This is a lot of variables to try and control and suggests the need to define a few areas in which incremental benefit may be demonstrated or refuted. The available evidence for the use of ReCell in acute burn wounds appears to demonstrate some clinical benefit from using Biobrane and/or ReCell in comparison to conventional dressings. However, whether ReCell confers any additional benefit when used in combination with or instead of Biobrane remains unknown.

7 References

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Appendix 1 – EAC search strategy

Medline, Medline in progress and Embase

Search number	Search terms	Number of results
1	exp burns/	76189
2	(burn$ or scald$).tw.	119219
3	1 or 2	142849
4	recell.tw.	41
5	spray.mp.	31958
6	suspension.mp. or exp Suspensions/	144588
7	4 or 5 or 6	175315
8	3 and 7	1437
9	cell$.mp.	8393187
10	8 and 9	338
11	Limit 10 to yr="1995-Current"	313

Web of Science, Scopus

Search terms		WoS results	Scopus results
Burn* AND	(spray OR suspension) AND cell	209	149
	OR		
	ReCell		

Cochrane

Search number	Search terms	Number of results
1	exp burns/	1100
2	recell.ti,ab,kw from 1995 to 2013	5
3	exp Suspensions/	312
4	spray*.ti,ab,kw	3054
5	suspension*.ti,ab,kw	2209
6	3 or 4 or 5	5228
7	cell*.ti,ab,kw	46833
8	6 and 7	352
9	2 or 8	355
10	1 and 9	4

Total number of unique records retained: 389

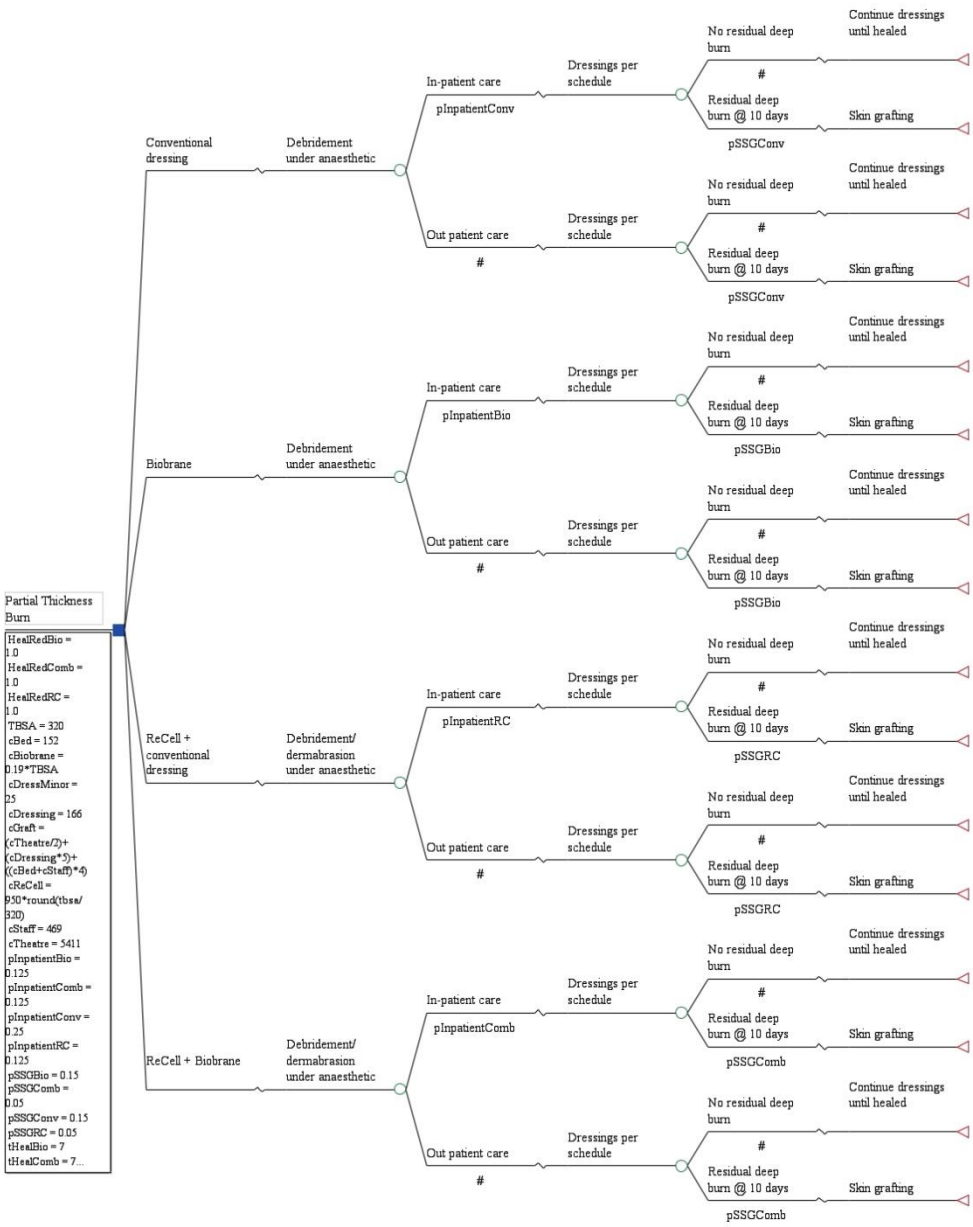
Appendix 2 – Quality checklist for Wood et al. (2012)

Study name Wood et al. (2012)		
Study design	**Resource analysis alongside a randomised pilot study of Biobrane with or without autologous cell suspension compared with standard care for scald injuries in paediatric patients**	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	Resource analysis was a secondary objective
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	No	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Cost consequences analysis. Clinical outcomes from within the study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	Pilot study with very small numbers of patients.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were	Yes	

obtained given?		
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Aus $
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	Yes	Acute episode only.
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as	Yes	

aggregated form?		
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Appendix 3 – Sponsor's de novo economic model



Appendix 4 – Quality check on the sponsor's de novo cost model

Study name ReCell sponsor model and submission		
Study design	**Decision tree cost model**	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	The first decision problem in the scope.
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Cost consequences analysis.
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question	n/a	

discussed?		
16. Were quantities of resources reported separately from their unit cost?	Yes	There was some aggregation. For example the cost of conventional dressing change was not disaggregated.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	For most inputs.
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	n/a	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	Acute episode only – 21 days.
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	n/a	Decision tree
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Results were given by technology cost, hospital cost and total cost.
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	

35. Were conclusions accompanied by the appropriate caveats?	Yes	The model is based on small studies and expert opinion.
36. Were generalisability issues addressed?	yes	Consideration of the extent to which the model applies to smaller and larger burns.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		