REVIEW ARTICLE – TITLE PAGE

TITLE: ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury: A NICE Medical Technology Guidance

RUNNING TITLE: ReCell NICE MTG

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SCP and GCR evaluated both the clinical and economic evidence on which this manuscript is based. SCP conducted the survey of clinical opinion. GCR reviewed the full EAC report and this article, and can act as a guarantor for the overall content.

Acknowledgements

The authors thank Prof. Ceri Phillips, Kateryna Onishenko (Swansea Centre for Health Economics, Swansea University) and Kathleen Withers (Cedar) for their contributions to the External Assessment centre (EAC) assessment report and additional survey work. Also Dr Judith White for help with formating and editing the manuscript. This article has been reviewed by NICE and has not been externally peer reviewed by Applied Health Economics and Health Policy.

Disclosure of potential conflicts of interest

Cedar is funded by the National Institute for Health and Care Excellence (NICE) Medical Technologies Evaluation Programme to act as an EAC. SCP is employed by Cardiff University and GCR is an UK National Health Service (NHS) employee; the NHS has a financial interest in the guidance on which this project is based.

Statement on research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

ABSTRACT

The gold standard treatment for deeper burns is an autologous skin graft; in larger burns this may be meshed to increase the area covered. However, long-term aesthetic and functional outcomes of graft scars may be poor. ReCell is a medical device that processes skin samples in the operating theatre into a cell suspension to be sprayed or dripped onto a wound. It is claimed to improve healing and scar appearance.

This device was evaluated by the National Institute for Health and Care Excellence (NICE) Medical Technologies Evaluation Programme. Two groups were defined: ReCell compared to conventional dressings in shallower burns, and meshed grafts plus ReCell compared to meshed grafts alone in larger, deeper burns. The manufacturer's clinical evidence submission included 3 papers and 8 conference abstracts. The External Assessment Centre (EAC) excluded 2 of these and added 7 abstracts. In general the evidence did not fit the defined groups, but suggested that ReCell was clinically comparable to skin grafts for partial thickness burns; however ReCell is not used in this way in the UK.

The manufacturer submitted an economic model in which ReCell treatment of partial thickness burns reduced the requirement for later skin grafts. This indicated that ReCell alone was cost saving in comparison to conventional dressings. The EAC indicated that this model was clinically inappropriate, but data was not available to populate a new model. NICE Medical Technologies Guidance 21 recommended that additional research was needed to address the uncertainties regarding the potential benefits of ReCell.

Key points for decision makers

- Skin burn injuries vary in depth, size, location and cause, and are treated variably in different services; so categorising and comparing treatments is difficult.

- Published evidence from non-UK sources in general did not reflect UK practice and was of limited use as a basis for national guidance.

- The population and treatment modelled by the manufacturer was inconsistent with UK practice using ReCell.

- The EAC was unable to obtain any data with which to populate a more appropriate economic model and therefore potential cost savings could not be determined.

TEXT

1 Introduction

This is one of many articles in Applied Health Economics and Health Policy summarising guidance produced by the National Institute for Health and Care Excellence (NICE) Medical Technologies Evaluation Programme (MTEP). The MTEP process is explained in Campbell and Campbell (2012)[2]. This paper summarises the development of NICE Medical Technology Guidance for the ReCell Spray-On Skin system (Avita Medical Ltd) for treating burn injuries [1]. The External Assessment Centre (EAC) that produced the assessment report and additional survey work was Cedar (including Cardiff and Vale University Health Board, Cardiff University and Swansea University). The manufacturer of the product notified the technology to NICE.

2 Background

2.1 Burns

Thanks to effective prevention strategies and comprehensive emergency services, major burns are a relatively uncommon condition in most developed countries including the UK [3]. Healing and scar outcomes are related to the length of time that a burn wound takes to heal; burns that will heal within 14 days are at low risk of poor outcomes [4;5]. The aim of the acute phase of burn treatment is therefore to achieve wound healing within 10-14 days.

Skin burns and scalds are characterised by the extent and depth of the skin injury, commonly described as Total Burn Surface Area (TBSA) and expressed as a percentage of the total surface area of the patient. Burn depth indicates the deepest skin layer that has been damaged and can be expressed in a variety of ways: superficial, intermediate, deep, epidermal, dermal, partial thickness, full-thickness.

Superficial/epidermal burns damage only the outer layer of the skin and these will heal well without significant specialist intervention. Full thickness burn injuries penetrate the entire thickness of the dermal layer and can involve subcutaneous tissues (fat, muscle, bone). These require skin grafts and may also involve the use of artificial dermal substrates/scaffolds. Burns that penetrate partly through the dermal layer may be treated with grafting or dressings, depending on the depth. Alternatively, the depth of burn may not be easily determined by clinical examination. NICE has recommended that the moorLDI2 Burn Imager be used in such indeterminate depth cases to predict healing time and aid clinical decision-making regarding treatment options [6].

Autologous split thickness skin grafts are the 'gold standard' treatment for deep burns and those that are expected to take more than 10-14 days to heal. Injuries to areas of cosmetic or functional importance (e.g. face, hands, groin) are usually treated with sheet grafts. Small burns in other areas that require grafting may also be treated with sheet grafts or be minimally meshed or fenestrated to prevent fluid build up and promote contouring. Where the patient has extensive wounds, and therefore less spared skin available to provide grafts, the mesh ratio may be increased in order to extend the area that the graft can cover. Meshing may also be used where skin sparing is important, e.g. in elderly patients who heal poorly. This has the disadvantage of poorer cosmetic outcomes (the mesh pattern may be visible in the healed scar) and contractures.

2.2 Organisation of burn care services in England and Wales

Burn care services are a specialised clinical service in England and Wales, [7] organised into 4 regions and designated by 3 levels (separately for adult and paediatric patients). The level defines the maximum severity of burn injury treated: Facility (least severe), Unit, Centre (most severe injuries). Data from the National Burn Injury Database indicates that around 900 patients per year have injuries severe enough to warrant referral to a Burns Unit or Centre in the UK [8].

2.3 The technology

ReCell Spray-On Skin System is a kit for use in the operating theatre that enables immediate processing of a skin sample into a cell suspension for spraying or dripping onto the burn wound, mesh graft or donor site. It is a Class III medical device and obtained a CE mark in March 2005. It consists of a sterile tray incorporating a battery-operated timer and warming chamber, preparation area and other necessary consumables. The biopsy is incubated in a trypsin solution for 15-30 minutes to disaggregate the cells. These are mechanically scraped and drawn up in a buffer solution ready for use. Each unit can process a biopsy up to 4 cm^2 which can treat an area of 320 cm^2. The suspension contains a mixture of keratinocytes, melanocytes, Langerhans cells and fibroblasts[1].

2.4 National Institute for Health and Care Excellence (NICE) scope

The NICE scope for the ReCell evaluation defined 2 sets of populations, interventions and comparators.

Population, intervention and comparator

[1] Avita Medical changed the specification of the ReCell device in 2015 and it can now process up to six 4 cm^2 samples to treat an area up to 1920 cm^2.

The populations, interventions and comparators of interest were divided into two subgroups and included adults or children treated in Burns Units or Centres (Table 1).

Outcomes

The outcomes specified for consideration in the scope included speed of healing, number of dressings (with or without anaesthesia), length of hospital stay, wound infection rates, degree of scarring (aesthetic and functional outcomes), degree of pigmentation, re-admission for scar management, number and size of donor sites, surgical procedure or theatre time and device-related adverse events.

Evidence was also submitted regarding postoperative pain and analgesia use, graft 'take/loss' and rate of subsequent skin grafting (following conservative treatment with ReCell). No evidence was submitted regarding re-admission, and pigmentation outcomes were included in overall measures of scar quality.

Manufacturer's claims

In their submission the manufacturer claims the following patient benefits from the use of ReCell:

- a reduction in skin graft donor site size and depth
- fewer complications, reduced morbidity and shorter healing time at the donor site
- shorter wound healing time at the recipient site, leading to:
    - improved burn wound aesthetic result with a lower likelihood of scarring and better match of skin colour
    - re-population of melanocytes to reduce hypopigmentation in healed wounds.
- reduced dressing change frequency (weekly rather than daily).
- less need for dressing changes under anaesthetic.

The claimed benefits to the healthcare system are reductions in:

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

3 Review of Clinical and Economic Evidence

The manufacturer submitted a review of clinical and cost evidence to NICE and presented a *de novo* cost-consequences model.

3.1 Manufacturer's submission of clinical effectiveness evidence

The manufacturer included 11 references in their clinical evidence submission, three peer-reviewed publications and 8 conference abstracts, including 1 unpublished abstract that overlapped with Sen et al (2012) [9]. The three papers included two randomised controlled trials [10;11] and an observational study [12]. The conference abstracts included one service review [13], two comparative studies [14-15] and five case series [9,16-18,unpublished]. The EAC considered that two of the conference abstracts did not fit the scope; one used ReCell to treat donor sites [17] and the other to treat hypertrophic scarring [18].

Additionally the manufacturer searched for pigmentation outcomes in any population, producing 5 studies in which ReCell had been used to treat established scars or stable vitiligo. The EAC considered that these studies were outside the scope. The studies identified by the manufacturer and included by the EAC are described in Table 2.

Due to the degree of heterogeneity in the populations, treatments and comparators in the published evidence the manufacturer conducted a qualitative analysis of each study in their submitted clinical evidence. The only biological dressing reported in the clinical evidence was Biobrane (Smith and Nephew). This is a commonly-used dressing in superficial and partial thickness wounds that adheres to the wound until healed.

The manufacturer's interpretation of the evidence stated that:

- ReCell was comparable to split thickness skin grafts (SSGs) for wound healing, scar outcome and infection risk in partial thickness burns,
- the addition of ReCell to SSGs increased the rate of epithelialisation,
- the use of ReCell with biological dressings was associated with faster healing, lower costs and shorter hospital stay than SSGs,
- the combination of ReCell plus biological dressing was not shown to be more effective than either component individually,
- the use of ReCell on donor sites allows more rapid healing and faster re-cropping,

- the use of ReCell on burn scars and vitiligo produced significant aesthetic improvement.

3.2 Critique of manufacturer's submission of clinical evidence

The EAC literature search was broader than that conducted by the manufacturer. An additional 9 conference papers were identified (Table 3). Two were unobtainable and 4 others contained data that potentially overlapped with references identified by the manufacturer. Overall the EAC included 11 or 12 studies reported in 15 papers[2].

Gravante et al (2007) [10] conducted a randomised controlled trial comparing ReCell alone (n=42) with SSG (n=40) in deep partial thickness burns of up to 320 cm^2. The method of patient randomisation was unclear but the groups were matched for age, gender, burn type and TBSA. There was no difference between the treatment groups for burn treatment size, mean time to epithelialisation or aesthetic outcome at 6 months (using a simplified Vancouver scar scale, VSS). Donor site size was smaller in the ReCell group and post-operative pain was reduced, however operation time was longer using ReCell. Healing assessment was by 1 blinded and 1 unblinded assessor at weekly intervals so the precision of the time to epithelialisation is likely to be poor. The study design also does not match the groups defined in the evaluation scope. Healing time and VSS were similar between the groups, indicating that ReCell alone has similar effect on the burn wound as SSG alone. However, ReCell alone is not used on deep partial thickness burns in the UK.

Park et al (2013) [12] conducted a retrospective multivariate logistic regression analysis including all patients in a burn centre who required skin replacement from 2004 to 2011. Primary outcome was the risk of infection compared to SSG alone. Of 770 eligible patients, 73 were treated with ReCell alone, 264 received ReCell plus SSG, and 387 received SSG alone (48 patients were excluded overall, but final numbers in each group are not reported). There was no effect of treatment type on burn wound infection or graft loss. Length of stay was significantly reduced in the ReCell alone group (OR 0.70, $p<0.01$), however the authors note that the patient groups were not strictly comparable as "practice indications (wound depth) and timing of surgery" were different. Interpretation of these results should be cautious. The co-inventor of ReCell and a non-executive director of Avita Medical is a co-author (F Wood).

[2] There was insufficient information to determine the overlap of 2 of the papers and the authors did not respond to enquiries.

Wood et al (2012) [11] conducted a pilot study to determine whether early intervention could reduce the need for skin grafts. The 3-arm randomised controlled trial, compared ReCell plus Biobrane (n=5), Biobrane alone (n=4) and standard care (n=4). The patient population was paediatric patients with a scald injury greater than 2% TBSA that was likely to benefit from surgery (not expected to heal within 10 days). Standard care patients received silver and hydrocolloid dressings on alternate days. Only 13 patients were enrolled in the study (45 were intended) so that only descriptive statistics or individual values were reported. In the standard care group 3 of 4 patients received a skin graft at 10 days post-treatment, compared to 0 of 5 in the ReCell plus Biobrane group and 1 of 4 in the Biobrane alone group. Healing appeared to be faster in the two intervention groups, although this may have been due to complications in 2 of 4 patients allocated to standard care. Other outcomes are difficult to interpret and do not support comparative conclusions. There was a disparity between the treatment groups such that patients in the ReCell plus Biobrane group were younger and had smaller burn areas. This may have significantly impacted the outcomes. The patient population also does not match that in Group A of the scope. The low patient numbers and consequent lack of statistical power mean that conclusions cannot be drawn from this study regarding the benefits of ReCell. Again, the main author (F Wood) has a conflict of interest in the product.

Multiple conference abstracts reported data from the same patients, and it was not always clear where overlap existed. Therefore the total number of 'studies' is uncertain. There were 3 comparative studies ([14] and [19]; [15], [25] and [24]; [27]), two service reviews [13;20], with potential for overlap with each other and with 2 of the comparative reviews. The rest were case series ([9],[16] and unpublished; [21] and [22]).

Rawlins (2013) [14] and Dunne and Rawlins (2012) [19] reported a retrospective comparison between ReCell (n=11) and SSG (n=15 in [14]; n=10 in [19]) in deep dermal scalds in paediatric patients. There was no difference in scar appearance (visual analogue scale) between the groups, operation time was longer and physiotherapy duration shorter in the ReCell treatment group. However, TBSA was greater in the ReCell group and no other information about the physiotherapy delivered or duration of follow-up was reported. No data other than TBSA was presented to allow baseline comparison of the groups. There was a suggestion of blinded assessment of scar appearance, but there were disparities in the scar results reported in the 2 abstracts not attributable to the difference in the size of the control groups. The intervention does not match the defined scope groups and ReCell alone is not considered appropriate as an alternative for SSG in the UK.

The second comparative study was reported in three conference abstracts [15;24;25]. Adults with deep dermal flame burns were recruited prospectively for treatment with ReCell plus Biobrane (n=5 in [15]; n=4 in [24] and [25]) and compared to matched controls who received SSG (n=10). Mean time to healing, analgesia requirements for the first dressing change and length of stay were lower, and scar assessment (VSS at 6 months) better, for the ReCell plus Biobrane group. However, there is no indication of the variance of any of the data or the statistical significance of the results and the use of means in such small samples may be misleading. No blinding of assessors was reported and the patient matching is poorly described. Again the intervention does not match the scope groups and ReCell alone is not considered appropriate as an alternative for SSG in the UK.

Sood et al (2009) [27] conducted an intrapatient comparison between ReCell alone and meshed SSG in partial thickness burns (n=10). Only graft take is reported; 8 of 10 patients had 100% take on both areas and 2 had reduced take in the ReCell treated area. These were attributed to difficulty with the ReCell applicator and increased wound depth. Little detail is provided.

The evidence available is mainly of poor quality and is not a good fit with the groups defined in the scope. However, taking the evidence as a whole the EAC concurs with the manufacturer that ReCell appears to be at least as effective as SSGs for wound healing, scar outcome and infection risk in partial thickness burns. However, in the UK cell therapies are not used as an *alternative* to SSGs, and evidence comparing SSGs with ReCell plus SSGs (as per the decision problem) was only available in Park et al (2013)[12]. In the scope the use of ReCell alone is only considered in Group A populations as an alternative to biological or standard dressings. The EAC found that there was no evidence to support the claim that the addition of ReCell to SSGs was associated with faster healing and better scar outcomes, and that there were minimal indications for any system benefits (reduced length of stay and frequency of dressing changes). The EAC also concluded that there was no evidence to indicate that the use of ReCell as an adjunct to Biobrane conferred any additional benefit over Biobrane alone.

3.3 Additional work carried out by the EAC

The available evidence was highly heterogeneous and did not correspond to the scope. The groups in the scope were somewhat ambiguous and were redefined by the EAC:

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

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

The EAC categorised the included studies according to these groups (Table 4). Wood et al (2012) [11] described their patient population as partial thickness scalds but these were expected to benefit from surgery and do not strictly fit with the Group A definition. However, the intervention and comparator match with those of the Group A population, so this study was categorised as Group A. Only Park et al (2013) [12] is completely consistent with the groups, however the authors note that the populations and treatments were not directly comparable in their retrospective analysis.

3.4 Manufacturer's economic submission

The manufacturer included 8 published studies and one unpublished audit in their economic submission. None of the evidence related to ReCell but was used to identify cost data for the standard care comparator. The manufacturer did not include Wood et al (2012) [11] which contained some cost data relating to their 3-arm randomised controlled pilot study. The economic evidence was supplied as a *de novo* cost model, implemented in TreeAge Pro (TreeAge Software Inc).

The manufacturer only modelled Group A from the scope, stating that there was insufficient evidence available to model Group B. The model was a simple decision tree, comparing four treatment options: ReCell plus conventional dressings, ReCell plus Biobrane, Biobrane alone and conventional dressings alone. They used published evidence and information from a questionnaire sent to four burns surgeons who had experience of using ReCell. Three of these were (or had been) based in the UK, of which two were also acting as expert advisers to the NICE evaluation. The fourth was a co-inventor of ReCell and non-executive director of Avita, based in Australia.

The model base case was a 640 cm^2 partial thickness burn, surgically debrided and treated according to one of the four options above under general anaesthetic. Patients were then treated as either inpatients or outpatients. Change of dressings was defined as major (conventional dressings) or minor (Biobrane and/or ReCell) and occurred at intervals dependent on the treatment type. At 10 days post-treatment a decision to progress to a skin graft is taken. Following a skin graft the wound is assumed to heal within a further 10 days. Otherwise the patient is assumed to be healed at 15 days for conventional dressing (base case) and a proportionate reduction of this time is used for the other three treatment types. The time frame of the model was the acute treatment of the

burn wound. The structure is identical for all four treatment sub-trees so only part of the model is shown in Fig 1. Probabilities and resource inputs are shown in Table 5 and Table 6.

The base case results for the economic model are shown in Table 7. The manufacturer calculated that ReCell and ReCell plus Biobrane were both cost saving in comparison to conventional dressings, but that Biobrane was the lowest cost treatment overall. Cost savings for ReCell treatments are driven by the lower proportion of patients requiring an SSG and the shorter healing time. Incremental Biobrane savings were driven by the lower technology costs compared to ReCell for similar outcomes.

Due to the significant uncertainty in the model parameters the manufacturer conducted one-way sensitivity analyses using broad ranges of values for each parameter. Although the total payoffs varied, the relative cost ranking of the treatments did not. The manufacturer also conducted scenario analyses, varying the burn size by ±50%, all hospital costs by ±25% and reducing all benefits by 50%. ReCell and ReCell plus Biobrane remained cost saving with respect to conventional dressings for all scenarios except the reduced burn size (TBSA of 320 cm^2), however Biobrane remained the cheapest treatment in all scenarios.

3.4.1 Critique and interpretation of cost evidence

The manufacturer did not attempt to model the Group B population, intervention and comparator and did not include long term outcomes. There was a poor fit between the available evidence and the defined groups and the longest follow-up in any of the included studies was 6 months. No data was identified for effect on scar treatments or duration of rehabilitation. The model was robust to the sensitivity and scenario analysis regarding the relative cost ranking outcomes. Most of the parameters used for the model were based on weak or poorly described evidence and this rendered these outcomes doubtful. The manufacturer used an unpublished audit of burns patients in a UK burns service for all the resource costs used in the model with the exception of list prices for Biobrane and ReCell. This data was available to the EAC as a spreadsheet but lacked descriptions of how the data was collected and specifically how cost information was obtained.

The manufacturer also used data from the questionnaire in which the manufacturer described the patient population as ‘5-10% partial thickness burns of indeterminate depth’. This is not fully consistent with the Group A patient population nor with the description of the population given in the model (‘partial thickness burns or scalds, where there is no immediate need for mesh grafting’ and ‘partial thickness with no definite areas of deep

involvement'). The experts answered the questions in a variety of ways, making interpretation and aggregation of the data very difficult.

Healing times (time to complete epithelialisation) for conventional dressings were drawn from published studies comparing different dressing types in heterogeneous burn injuries. The EAC considered the value for the base case (15 days) to be appropriate when compared to other available data. The percentage reduction in healing times for the three other treatments (see Table 5) are partly based on calculations using outcomes from Wood et al (2012)[11] and Echlin et al (2012) [17]. Wood et al (2012) [11] had only 4-5 patients for each arm and did not include ReCell alone. Echlin et al (2012) [17] was an intra-patient comparison of graft donor sites in 2 patients using ReCell alone versus conventional dressings. The manufacturer recognised the paucity of evidence and described the 30% and 40% reductions in healing time as a 'conservative estimate'. The one-way sensitivity analysis varied this percentage reduction from 0-50% of the base case value (7.5-15 days). The EAC considered that a percentage reduction in healing time was inappropriate, however the range of values tested in the one-way sensitivity analysis was broad and included parity with the other treatment arms.

The manufacturer provided an extra 10 minutes of theatre time for the use of ReCell. Published data reported that ReCell requires an additional 28-39 minutes of theatre time in comparison to SSGs [10,14]. The EAC considered that 10 minutes may be an underestimate in comparison to treatment with conventional dressings, where only debridement and dressings are conducted in theatre in the model. As theatre time is estimated at £5,214 per hour this may have a significant effect on the relative cost rankings.

Estimates of the proportion of patients needing SSGs after 10 days were much lower from two experts (up to 10% of patients) than that used by the manufacturer. The manufacturer's estimate of 30% for conventional dressings comes from several papers comparing different topical treatments but includes heterogeneous patient populations. The information from the clinical experts suggested a reduction in the proportion of patients requiring SSGs for the other three treatment types, but there was no overall consensus. The manufacturer used a broad range of values for the one-way sensitivity analysis (5-20%); this was increased by the EAC for the ReCell treatments to include parity with conventional dressings.

The proportion of patients who require inpatient treatment following surgery is dependent primarily on the patient's pain level and the site and extent of the burn. However there are non-clinical reasons for patients to remain on a burn ward rather than be discharged to outpatient care. Despite confusing information from the

questionnaire it seemed that most patients with injuries consistent with the modelled population would be discharged following the first dressing change on day 2-3 post-procedure. The manufacturer used an 'arbitrary' estimate of 50% for conventional dressings and 25% for all other treatment types. There was no evidence that ReCell alone reduces the need to remain as an inpatient. The manufacturer's reasoning appeared to be based on a clinical adviser comment that conventional dressing changes ("major change of dressing") are more likely to require morphine anaesthesia and therefore inpatient treatment than the other treatment types ("minor/secondary dressings only"). The manufacturer used a range of 25%-75% for all treatment arms in their sensitivity analysis. Biobrane adheres to the wound and remains until it lifts off as the wound heals. The EAC therefore expects that the use of Biobrane can reduce the complexity, pain, time and cost of dressing changes. This may reduce the need to remain as an inpatient for treatment arms that include this product.

In the manufacturer's model any patient being treated as an inpatient following the first dressing change remained as an inpatient until the burn was healed or required an SSG. This is inappropriate, as patients who are healing well are likely to be discharged as soon as reasonably possible. As daily bed and staff costs are £621, this could contribute to the differences in cost outcomes for each treatment.

MTAC accepted that assumptions and parameters used in the manufacturer's model were of uncertain validity and noted the lack of modelling of the Group B patient population. The committee requested that the EAC conduct additional work to obtain data from clinical experts to validate the manufacturer's model and to provide an economic model for large area full or deep partial thickness burns.

3.4.2 Additional economic analysis conducted by the EAC

The EAC extended the ranges of the inputs for the sensitivity analysis for the proportion of patients progressing to an SSG and the cost of a change of dressing (both major and minor). The model remained robust to one-way analyses and the cost rankings of the treatment arms did not alter.

The EAC conducted a literature search to identify current UK clinical practice and suitable parameters for use in the additional modelling. This information and the assistance of two clinical expert advisers was used to develop a questionnaire survey for UK burns specialists. The aim was to obtain detailed information regarding treatment of different categories of burn injuries. The questionnaire included current standard treatment and participants' experience with both ReCell and cultured autologous cells. Participants were interviewed by telephone by the main author (SCP) and the data tabulated and aggregated.

Information was obtained from 9 consultant burn surgeons and one specialist burns nurse from a mixture of UK adult and paediatric Burn Units and Centres during February 2014. Of these, 7 had direct experience of using ReCell. Specialists were unable to provide quantitative estimates with which an economic model could be populated. As a result no additional economic modelling could be conducted.

There was significant variation in treatment protocols between sites/clinicians; however a consensus was reached on several important points:

- Shallower partial thickness burns, such as those described in the Group A patient population, will heal within 2 weeks without special treatment. For adults these injuries are usually treated on the ward using conventional dressings. Most clinicians would not use ReCell on these patients and in general Biobrane would only be used in paediatric patients. Length of stay is typically 4-6 days. Neither ReCell nor Biobrane were thought to contribute to faster healing.

- A 10% TBSA full thickness or deep partial thickness burn is likely to be treated using a sheet graft and ReCell would not be used in conjunction with this. Where a meshed graft is used no effect of ReCell on any parameters (other than theatre time) was identified.

- Large burns (around 40% TBSA) requiring meshed grafts are rare events, are highly individual and complex, and data is difficult to aggregate. This is the group of patients most likely to receive either ReCell or cultured cell treatments in the *hope* of reducing healing time and improving aesthetic appearance. Length of stay for these patients is complicated by multiple factors. ReCell is advantageous when cultured cells are unavailable and to take advantage of unused donor graft skin.

- No evidence was found to support the claim that ReCell improves long term scar outcomes. Specifically regarding pigmentation outcomes, both expert opinion and additional published comparative studies (in which ReCell was used as a treatment for *re-pigmentation* of vitiligo) were equivocal.

The EAC found no evidence that claims of clinical or system benefit from the use of ReCell Spray-On Skin system had been realised in current UK practice. The survey indicates that the manufacturer's model was inappropriate, but no additional data was obtained with which to populate a more realistic model.

4 NICE Guidance

4.1 Preliminary Guidance

The NICE MTAC met in March 2014 and considered evidence from a range of sources, including the manufacturer's submission, the EAC assessment report, expert survey and testimony from clinical experts. The Committee provisionally decided that ReCell Spray-On Skin system shows potential to improve healing in acute burns and that research is recommended to address uncertainties about the claimed patient and system benefits of the ReCell Spray-On Skin system.

4.2 Consultation Response

Preliminary guidance was available for public consultation between 16th April and 19th May 2014. The manufacturer made several comments and provided additional evidence that had become available since the original submission. The EAC examined the additional evidence and concluded that it did not change the previous conclusions on the evidence.

NICE published Medical Technology Guidance on ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury on 12th November 2014 as MTG 21 [1].

5 Key Challenges and Learning Points

- Burn injuries are difficult to categorise and patients are likely to have a range of burn depths and therefore represent a continuum of injury severity.
- Study data is often presented at multiple conferences with overlapping or wholly reproduced patient samples without reference to previous publications.
- Studies from outside the UK may not represent UK practice and therefore be of limited applicability.
- Despite best efforts the scope may not reflect the most appropriate technology application.
- Data for long term outcomes is often not available, limiting the usefulness of economic modelling.

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TABLES

Table 1: Population, intervention and comparator defined in the NICE evaluation scope

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

Table 2 Summary of study methodology of manufacturer's included studies

Study	**Patient population**	**Country**	**Age**	**Study design**	**Notes**	**Sample size**
*Gravante et al (2007) [10]	Deep partial thickness burns <320 cm^2	Italy	Adult (30-65 years)	Randomised controlled trial		82
*Park et al (2013)[12]	Burns treated with skin grafting or replacement	Australia	All	Retrospective multivariate analysis		722
*Wood et al (2012) [11]	Scalds >2% TBSA, expected to require surgery	Australia	Paediatric (8 months – 9 years)	Three-arm randomised controlled pilot study	Assessment of early intervention protocol	13
Dunne & Rawlins (2012) [13]	Scalds of differing depth	UK	Paediatric (9 months-15 years)	Non-comparative retrospective review		40
Echlin et al (2012) [16]	Mid to deep dermal facial burns	UK	All (10 months-50 years)	Case series	1 patient treated at day 23	5
Rawlins et al (2011)[15]	Deep dermal burns	Australia (probably)	Adult (17-59 years in the intervention group)	Comparative pilot study using matched controls		15

Rawlins (2013) [14]	Deep dermal scalds	UK	Paediatric	Retrospective comparative observational study		26
Sen et al (2012) [9]	Deep partial or full thickness burns and donor sites, >50% TBSA	UK, USA, Australia	Adult	Case series	Overlap with unpublished	5
unpublished	Burns	UK, USA, Australia	Unreported	Case series	Overlap with [9]	10

* Peer-reviewed journal publication. All other references are conference abstracts.

Table 3: Summary of methodology of additional studies included by the external assessment centre

Study	**Patient population**	**Country**	**Age**	**Study design**	**Notes**	**Sample size**
Dunne & Rawlins [19]	Burns	UK	Paediatric	Retrospective comparative observational study	Overlap with Rawlins (2013) [14]	21
Dunne & Rawlins [20]	Deep dermal burns	UK	All	Non-comparative observational study	Retrospective review of cases, overlap with [14];[13;19]	21
Hiller et al (2013) [21]	Partial thickness facial burns	Germany	Adult (27-81 years)	Case series	Potential overlap [22]	5
Rawlins (2010) [23]	*Scald*	*UK*	*Paediatric*	*RCT*	*Abstract unobtainable*	
Rawlins et al (2011) [24], Rawlins (2011) [25]	Deep dermal burns to the legs	Australia	Adults (17-59 years)	Comparative pilot study with matched controls	Overlap with [15]	14
Rawlins (2012) [26]	*Scalds*	*UK*	*Paediatric*		*Abstract unobtainable*	

Rennekampff et al (2011) [22]	Facial burns (assumed to be deep partial thickness)	Germany	Unreported	Case series	Potential overlap with [21]	5
Sood et al (2009) [27]	Partial thickness burns	USA	Unreported	Intrapatient comparative study		10

Table 4: Included studies categorised for the decision problem groups

Study	**Patient population**		**Intervention**		**Comparator**	
Wood [11]	Partial thickness scald	A A A	ReCell+ Biobrane	A	Std. dressing Biobrane	A A
Rennekampff [22]/Hiller [21]	Burns	A	ReCell	A	*NA*	
Park [12]	Deep reticular dermal burns	B	ReCell + un/meshed SSG	B	Un/meshed SSG	B
Sen [9]/unpubl	Deep partial or full thickness burns	B	ReCell+STDG (± Biobrane)	B	*NA*	
Gravante [10]	Deep partial thickness	B	ReCell	A	Un/meshed SSG	B
Park [12]	Deeper mid-dermal burns	B	ReCell	A	Un/meshed SSG	B
Rawlins et al; Rawlins [15;24;25]	Deep dermal burns	B	ReCell + Biobrane	A	SSG	B
Rawlins [14], Dunne & Rawlins [19]	Deep dermal scalds	B	ReCell	A	SSG	B
Sood [27]	Partial thickness burns	B	ReCell	A	Meshed SSG	B
Dunne & Rawlins [13]	Mid-deep dermal scalds	B	ReCell + Biobrane	A	*NA*	
Dunne & Rawlins [20]	Mid-deep dermal burns	B	ReCell + Biobrane	A	*NA*	
Echlin [16]	Mid-deep dermal burns	B	ReCell	A	*NA*	

STDG – split thickness dermal graft

Table 5: Clinical inputs to the manufacturer's base case economic model

Base case	**Conventional**	**ReCell only**	**ReCell + Biobrane**	**Biobrane only**	**Source**
Surgery time	20 mins	30 mins	30 mins	20 mins	Expert opinion
Proportion of patients treated as inpatients	50%	25%	25%	25%	Expert opinion
Proportion of patients needing SSG	30%γ	10%‡	30%‡	10%‡	γ Literature ‡ Expert opinion
Mean time to healing	15 days	0.7 x 15 days (10.5 days)	0.6 x 15 days (8 days)	0.7 x 15 days (10.5 days)	Literature

Table 6: Resource inputs to the manufacturer's base case economic model

Resource inputs	**Value**	**Source**
Cost of bed day	£152	Unpublished data
Cost of minor dressing change	£25 (30 mins nurse time + consumables)	Unknown
Cost of major dressing change	£166	Unpublished data
Theatre cost (per hour)	£5,411	Unpublished data
Cost of hospital staff (per day)	£469	Unpublished data
Cost of Biobrane (per 320cm^2)	£60.80	Manufacturer
Cost of ReCell (per unit, treats 320cm^2)	£950	Manufacturer
Total cost of SSG procedure	£5,214.50	Unpublished data

Table 7: Manufacturer's base case for costs in each treatment arm

Treatment arm	**Treatment cost**
Biobrane only	£6,398
ReCell plus Biobrane	£7,787
ReCell only	£7,892
Conventional dressing	£9,543

Fig 1: Tree diagram for the manufacturer's economic model (part)