Cedar

Healthcare Technology Research Centre

ReCell Spray-on Skin System

Additional Report following MTAC meeting of November 2013

Authors: Susan Peirce
Grace Carolan-Rees

Acknowledgements: Judith White
(Proofreading)

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GIG CYMRU NHS WALES | Bwrdd Iechyd Prifysgol Caerdydd a'r Fro
Cardiff and Vale University Health Board

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

Executive Summary

The primary purpose of this project was to obtain data from suitable expert advisers to answer MTAC questions prior to its recommendations on ReCell. The objectives were as follows:

- To confirm using expert advice or any relevant data whether the model parameters (length of in-patient stay, time to epithelialisation and requirement for a skin graft) have been accurately estimated in the sponsor's submission.
- To carry out an economic analysis of the cost impact of the ReCell Spray-On Skin System for treating burns which require grafting. This was to be considered as two subgroups:
  - ◊ Large area burns which are judged to need wide mesh grafting
  - ◊ Full thickness or deep partial thickness burns which are judged to need skin grafting
- To collect information from experts group and analyse responses about use of ReCell Spray-on skin to improve skin colour match in scars.

The EAC collected data from 10 UK expert advisers (9 consultant burn surgeons and 1 burns nurse consultant) from specialist Burn Units and Centres in England and Wales using semi-structured interviews. This report presents the collected expert adviser data. This provides useful information regarding the NHS treatment pathways for patients who are in need of treatment at this level of specialised burn service. The EAC has summarised the available evidence for the use of ReCell in these patient populations collected from the previous assessment report, additional literature review and the survey of expert advisers conducted here.

However, the participants were unable to provide quantitative data suitable for use in the economic models as they either thought that the use of ReCell conferred no clinical benefit or resource savings or they could not provide any numerical estimates to support its assessment. Therefore no new economic modelling was possible. The EAC:

- Found no difference in length of in-patient stay, time to epithelialisation and requirement for a skin graft between ReCell and comparators for partial thickness burns where mesh grafting is not required. This does not validate the sponsor model parameters.
- Was unable to carry out an economic analysis of the cost impact of the ReCell Spray-On Skin System for treating burns which require grafting
- Found no evidence to support the claim that the application of ReCell results in systematically improved long term scar outcomes, including pigmentation

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1 Introduction

1.1 Rationale for this project

The ReCell spray-on skin system is the subject of a NICE MTEP evaluation. Following the sponsor's submission and External Assessment Centre's (EAC) assessment report, MTAC considered that insufficient economic modelling had been conducted by the sponsor and that further modelling was required. The aim of this additional work was to obtain data from UK burns surgeons and other sources (such as audits or registries) for the following:

- To confirm using expert advice or any relevant data whether the model parameters (length of in-patient stay, time to epithelialisation and requirement for a skin graft) have been accurately estimated in the sponsor's submission.
- To carry out an economic analysis of the cost impact of the ReCell Spray-On Skin System for treating burns which require grafting. This was to be considered as two subgroups:
  - ◊ Large area burns which are judged to need wide mesh grafting
  - ◊ Full thickness or deep partial thickness burns which are judged to need skin grafting
- To collect information from experts group and analyse responses about use of ReCell Spray-on skin to improve skin colour match in scars.

The EAC was therefore asked to identify suitable experts, collect the data and conduct economic modelling for the use of ReCell in 3 populations of patients:

	Population	**Intervention**	**Comparators**
Group A	Partial thickness burns where mesh grafting is not required	ReCell alone ReCell plus biosynthetic dressing	Conventional dressings Biosynthetic dressings
Group B	Full thickness or deep partial thickness burns which are judged to need skin grafting	ReCell alone ReCell plus skin graft	Skin graft alone
Group C	Large area burns which are judged to need wide mesh grafting	Skin mesh graft in combination with ReCell and possible use of ReCell at donor site.	Skin mesh graft and current donor site treatment. Consider use of cultured cells with skin mesh graft.

Group A was modelled in the sponsor's submission. The EAC was asked to determine whether the parameters used in this model were accurately estimated and to revise and re-run the model as appropriate. Groups B and C required new economic models to be designed and executed by the EAC.

2 Methods

2.1 Initial study design

The original design of the project was to use three information sources for the data with which to define, populate and run the 3 economic models:

- data from the International/National Burn Injury Database (iBID, NBID, Section 2.2),
- additional data from a literature search for supplementation or validation (Section 2.3) , and
- a survey of burn surgeons working in Burn Centres and Units across England and Wales to provide quantitative data about actual practice (Section 2.4).

2.2 International Burn Injury Database (iBID)

iBID is co-ordinated from Wythenshawe Hospital in Manchester and collects data from specialist burn services around the UK. Data from this is combined with other data sources (Hospital Episode Statistics and National Burn Bed Bureau) to create the National Burn Injury Database. It contains data from 2003 onwards and information about the iBID database fields indicated that it contained data about dressing changes, treatment types and outcomes as well as epidemiology (Evolution Healthcare Systems).

Access to this resource was requested by the EAC as quickly as possible following the start of the project. However, the iBID team were unable to provide us with access to the data within our timeframe. We determined that the database and data entry software had undergone a redesign in 2012/2013 and were also advised that some of the apparently relevant fields may have been added recently and therefore would not contain a large amount of data. Although this resource was therefore unavailable for this MTEP project it may be of use in future research in burn care technologies.

2.3 Literature search

An initial scoping literature search was conducted to identify published information regarding current UK clinical practice and suitable parameters (resource use, costs and outcomes) for use in the economic models. The search strategy combined 'burns' (focused MeSH heading) with a series of keywords designed to limit the results to UK-based authors or institutions. It was conducted in Medline and Embase only and restricted to papers published since 2000. This search returned approximately 1500 results, which were searched by keywords to identify key papers that described aspect of standard care, economics, length of stay, healing times, use of cells or skin substitutes or other suitable candidate parameters. Information from these papers assisted with early development of both the model structures and the expert survey.

Medline, NHS EED and HEED were searched specifically for economic evidence on burns care. This search was intended to provide additional information regarding potential model parameters and to validate and supplement that obtained from the clinical experts. The strategy used to search Medline is provided in Table 1 (searched on 13-01-14). Of the 346 papers identified, 37 were

selected for further scrutiny based on title and abstract. NHS EED (searched on 08-01-14) and HEED databases (searched on 29-01-14) were searched using the terms 'burn' or 'scald'. NHS EED produced 40 results, of which 21 were selected for further scrutiny. HEED did not return any additional papers.

Table 1: Economic literature search strategy (Medline)

1	exp Burns/	18725
2	scald.mp.	908
3	exp "Costs and Cost Analysis"/	114621
4	econom*.mp.	125996
5	1 or 2	18886
6	3 or 4	213823
7	5 and 6	346

2.3.1 Main literature search

It was intended that following the issuing of the quantitative survey a targeted search strategy would be developed to identify published data in which outcomes and resource use data relevant to the economic model were reported. A few such papers had been identified during the work for the ReCell assessment report, but that search had primarily targeted literature that reported ReCell as an intervention. In this new search we would primarily look for data relevant to the comparators in the economic models; standard care, biosynthetic dressings and cultured cells. Any data identified in this way would be used to validate and supplement that obtained from the clinical experts.

As the data collection for the survey progressed it became apparent that there would be insufficient quantitative data on ReCell to populate the ReCell arm of the economic model (see below). As there was no new data for the ReCell intervention this systematic literature searching would only provide additional data for the comparators therefore this literature search did not proceed.

2.3.2 ReCell literature search

The EAC conducted an additional literature search for papers involving ReCell that included data from outside the scope of the original assessment report. This was done in order to identify any potential benefits of the technology that may be relevant to its use in burn care. In the assessment report literature search all relevant papers that reported ReCell had included its brand name. Also the use of alternative descriptors for the technology (e.g. 'spray', 'suspension', 'cells') produced more than 25,000 results. Therefore the search strategy adopted by the EAC for this work consisted solely of the keyword 'ReCell'. This was applied in Medline, Medline in progress, Embase, Web of Science, Scopus and the Cochrane Library databases.

2.4 Survey of Burn Surgeons

2.4.1 Expert advisers

Specialist Burns Centres and Units in England and Wales were identified from the NHS Specialised Services website (NHS Specialised Services). Burn Facilities were not included as these treat the more minor burn categories and would not treat the large area burns included in Group C; they were also excluded from the original scope. There are around 18 unique sites for Burn Centres and Units including adults and paediatric burn services. The exact number depends the defined entity (hospital

site or NHS Trust) and also some services are split across more than one hospital. Geographically close services may also be listed separately but actually share staff and common practices.

An individual consultant at each service was identified using a combination of Trust websites, regional Burn Care Networks and the membership of the national Burn Care Clinical Reference Group (NHS England). Each consultant was invited to participate by email or to nominate another consultant from their department. Initial invitations were followed up with further emails and telephone calls for around 2 weeks until 15 participants had been recruited. Additionally, a senior specialist burns nurse was invited to participate. Participants were not screened for their experience with ReCell as we wanted a representative selection of current standard care as well as direct experience with ReCell. We assumed that a sufficiently broad and large sample of participants would provide a range of experience levels and a general indication of the level of use of ReCell in the UK NHS. Participants were also self-selecting to a certain extent, as initial contacts who were unwilling to participate sometimes passed the invitation onto their colleagues. Previous experience with clinical experts indicated that a primary selection criteria should be willingness to participate rather than identification of ideal candidates who may decline.

2.4.2 Questionnaire design

The purpose of the survey was to elicit information with which to populate the economic models for the 3 patient populations. This entailed 2 distinct types of question:

1) Where are the potential differences in pathway, costs, resource use and outcomes when ReCell is used, compared to standard care?
2) What is the estimated size of those differences?

In the sponsor's submission their economic model included four parameters in which ReCell was thought to provide a resource saving:

- the proportion of patients treated as inpatients
- the difference between (full) conventional dressing changes and secondary dressing changes
- the proportion of patients requiring a skin graft at around 2 weeks post-treatment
- time to healing of the burn wound.

However, this model did not address most of the sponsor's claims as described in the scope, nor did it include other potential benefits and detriments identified in the published literature. The EAC used information from the scoping literature search and the work done during the ReCell assessment report to identify potential model parameters for question 1 above:

Table 2: Potential resource use and outcome parameters

Source	Parameter
Sponsor's model	Need for inpatient treatment
Sponsor's model, Wood et al. (2012)	Need for skin (re)graft
Sponsor claims	Graft donor size and depth
Sponsor's claims, sponsor's model	Donor site complications & healing time
Sponsor's claims	Burn wound healing time
Sponsor's claims	Aesthetic outcome, scarring, skin colour
Sponsor's claims	Hypopigmentation
Sponsor's claims	Dressing change frequency

Wood et al. (2012)	Number of dressing changes
Sponsor's claims	Need for GA during dressing changes
Sponsor's claims, Park et al. (2013)	Length of hospital stay
Sponsor's claims	Need for external laboratory support
Sponsor's claims	Need for later corrective surgery
Gravante et al. (2007), Wood et al. (2012), Rawlins et al. (2011)	Pain and analgesia
Gravante et al. (2007), Rawlins (2013)	Surgical procedure time
Rawlins (2013)	Duration of physiotherapy
Sponsor's model, Wasiak et al. (2013)	Dressing type/cost
Sponsor's model, Wasiak et al. (2013)	Nursing time

The MTEP lead team expert advisers were consulted about the patient pathway for standard care. These multiple sources provided the basis for the assumed patient pathway and the economic model and questionnaire design. The questions were developed collaboratively and iteratively, with EAC colleagues involved in brainstorming and discussion. We designed the survey in parallel with the initial development of the three economic models to ensure that the questions centred on collecting the data required. A generic patient pathway flowchart was designed to encapsulate the assumptions and options for treatment of patients admitted to a specialist burns service (see below) and this was sent to the participants as a visual aid alongside the questionnaire.

We considered a 2-part survey that would address questions 1 and 2 separately. This would have the advantage of only collecting detailed data about parameters that had been confirmed as significant. However due to the short timescale of this project and the difficulty of getting multiple rapid responses from participants we decided to collect all potentially relevant data in a single questionnaire. The main drawback of this approach was the increased length and complexity of the survey as it involved asking detailed information about all potentially important parameters. We included detailed questions about resource use alongside questions about clinical practice and outcomes. For example, we postulated that use of ReCell increases surgical procedure time (based on Gravante et al. 2007 and Rawlins 2013) and therefore included questions about staff and other resources included in typical burns surgery; this was needed to estimate any effect on costs. An example questionnaire is included in Appendix 1.

We further defined the patient populations as follows (TBSA – total burn surface area):

- Groups A and B – 10% TBSA
- Group C – 40% TBSA

The sponsor's submission defined the initial Group A as a burn area of 640 cm^2, which they stated as equivalent to approximately 5-10% TBSA. The EAC considered this equivalent to about 3.5% TBSA for an adult and 10-15% TBSA for a small child (Sacco et al, 2010; Sharkey et al. 2001). As the burns community traditionally uses TBSA as their measure of injury extent the EAC used this as the means to define the patient populations. The referral thresholds are between 2-10% TBSA for Burn Units and 20-40% TBSA for Burn Centres. Therefore a sensitivity range of 5-15% TBSA was considered to be appropriate for burns that would not require wide meshing of autografts, but would still require referral to this level of service. This was consistent with the sponsor's original model. A size of 40% TBSA was determined as suitable for Group C, as around 30-40% TBSA was suggested as the lower

limit at which wider meshing of autografts would be required due to paucity of donor sites. It was thought that there was effectively no upper limit to TBSA for this patient population.

The TBSA sizes were intended to serve as the base case scenarios for the economic modelling, allowing for a variation of ±5% TBSA in Groups A and B and ±10% TBSA in Group C in the sensitivity analysis.

This level of information covering three patient populations and multiple treatment options resulted in the questionnaire becoming a long document and the EAC considered that it would be complex for participants to complete by themselves. It was thought that significant differences between the care of adult and paediatric patients would require separate answers. Additionally there was the risk of misunderstanding of both questions and answers and that variations in local practice may not be consistent with the assumptions inherent in the questionnaire design. We therefore determined that conducting telephone interviews with participants using the questionnaire as a basis would be more effective and efficient and would enable misunderstandings to be clarified immediately. Participants were therefore offered the choice of completing the questionnaire themselves, being interviewed or a combination of the two methods.

SP conducted the interviews, which were digitally recorded and the recordings and handwritten notes used to complete the questionnaire. These were sent to the individual participants for review. The data from multiple participants was anonymised and summarised into tables for the 3 patient populations and these were sent to all participants to allow them to comment on the appropriateness of the data.

2.4.3 Patient pathway and questionnaire assumptions

The generic patient pathway was determined using the sponsor's submission, work conducted during the assessment report, the lead team expert advisers and the scoping literature search (Appendix 2). Explicit assumptions were provided in the questionnaire for each patient population and interviewees were asked to comment on their appropriateness. A description for each population group excluded injuries on complex anatomical or cosmetically important sites as these were likely to involve special consideration for treatment options. They also excluded patients with other injuries or co-factors so that clinical outcomes and resource use would be based on the skin burn wounds alone.

2.4.4 Economic modelling

Early development work for the economic modelling involved brainstorming and group discussion work in parallel with the questionnaire design. Clinical pathways and model designs were iteratively and collaboratively produced using information from the assessment report work, scoping literature review and lead team expert advisers. It was expected that the new model designs for patient Groups B and C would be substantially different to that produced in the sponsor's submission. This was due to the criticisms of the model identified in the assessment report and because the model failed to address many of the sponsor's claimed benefits and potential detriments listed in Table 2. It was also expected that it would be relatively simple to adapt the new models to account for Group A patients. It was therefore intended that the EAC would create a new model for this patient population as well as re-populating and running the sponsor's model.

The questionnaire was intended to identify *where* realisable differences in costs and outcomes existed between ReCell and comparator treatments as well as their estimated *magnitude*. Therefore the final designs for the economic models were to be completed using results from the survey. However, as interviews for the questionnaire proceeded it became clear that experts were not able to provide support for any generalisable benefits or resource savings resulting from the use of ReCell in the three identified patient populations (Section 3.2). As such, there was no data to inform the final model designs or to populate the intervention arms. No new economic models were created for patient Groups B and C.

3 Results

3.1 Literature search

3.1.1 Scoping search

Around 150 papers from the scoping literature search were identified as potentially useful in identifying standard UK clinical practice or suitable parameters for the economic models. However, no new parameters were identified from this literature in addition to those listed in Table 2.

Most of the economic evaluations identified by the search strategy consisted of comparisons of different dressings or other topical treatments or were related to burn prevention strategies. Only one UK economic evaluation paper on burns was identified that could potentially provide data on NHS resource use and costs for standard care treatment of burns (Phillips et al. 2011). There were no economic evaluations involving ReCell in burns. As the EAC did not proceed with the economic modelling the information identified was not used.

3.1.2 Additional ReCell papers

A total of 54 papers were retrieved from the literature search using the keyword 'ReCell'. This included studies examined during the assessment report work and some that were excluded at that point as out of scope. Three comparative studies were identified that examined the effect of ReCell in the repigmentation of stable vitiligo lesions. No comparative studies in donor sites were identified.

Daniel et al. (2011) is a conference abstract reporting interim results from an intra-patient randomised comparison of ReCell versus mini-grafting in 14 patients with stable vitiligo. Percentage repigmentation at 3 months was 27% for ReCell-treated areas versus 11% for mini-grafting, but at 12 months the proportions were 15% and 12% respectively (not statistically tested). Qualitative assessment of the donor site was better for ReCell but "most subjects preferred the speckled pigmentation at recipient sites of the mini-grafting".

Venugopal et al. (2009) is a conference abstract reporting results from an intra-patient randomised comparison of ReCell versus mini-grafting in 12 patients with stable vitiligo who completed a 6 month follow-up. Percentage pigmentation results were 'highly variable' with no difference between treatments, although ReCell produced a more uniform repigmentation when it worked. Patients reported more post-operative pain of the ReCell donor site than the mini-grafting site.

Mulekar et al. (2007) conducted an intra-patient comparison of ReCell versus melanocyte-keratinocyte transplantation (MKT) in five patients with stable vitiligo. At 4 months post-operatively results were comparable with 100% repigmentation in both sites in 2 patients, no repigmentation in either site in 1 patient, 65% versus 100% and 40% versus 30% repigmentation (ReCell versus MKT) in the remaining two patients.

Other papers retrieved were case studies and non-comparative studies or case series. Additionally one interviewee referred to a study using a method similar to ReCell. Back et al. (2009) is a randomised intra-patient comparison of autologous melanocyte-keratinocyte spray versus placebo spray (suspension medium) in 13 patients with vitiligo. There was no difference in the time to epithelialisation (median of 7 days) between treatment and placebo. Normal pigmentation was achieved in 5 out of 13 patients at 1 or more time points, but at 12 months follow-up 11 out of 13 patients had no pigmentation in the treated area. Additionally 2 patients developed normal pigmentation temporarily on areas treated with the placebo solution. Repigmentation was described as 'unpredictable' and 'infrequently persistent'.

The EAC has not conducted a systematic review or critically appraised these papers. This summary is provided as background to the question of whether ReCell affects pigmentation outcomes in acute burns and whether data from *repigmentation* studies could be extrapolated to outcomes in burns (Section 3.4). Overall, these studies indicate that the use of ReCell can produce repigmentation in stable vitiligo, but that outcomes are highly variable, comparable to other treatments and that early positive results may deteriorate.

3.2 Expert survey

3.2.1 Participants

Initially 14 surgeons and 1 specialist burns nurse agreed to participate. Due to the length of the questionnaire several of these were unable to complete the interviews in the timescale available. Interviews were conducted with 10 individual expert advisers (9 consultant surgeons and 1 specialist burns nurse) and an additional participant provided commentary on the summary data (Appendix 3). These individuals represent a mixture of Burn Centres and Units for both adults and paediatric patients as shown in Table 3. Note that NHS Trusts can provide burns services for either or both patient groups, at the same or different levels and that one Trust may provide both services at the same or separate hospital sites. Staff may also work across hospital sites.

Table 3: Sites participating in the survey

	Adult	Paediatric
Centre	3	5
Unit	4	4

3.2.2 ReCell experience of the participants

Three of the 10 interviewees had no personal experience of using ReCell. The others varied from semi-regular current users to those who had used it a few times several years previously. All participants indicated familiarity with the technology and with published evidence regarding it. None indicated that they had been involved in any formal or semi-formal studies or evaluations of ReCell.

Table 4: Summary of interviewees' ReCell experience

1	Used semi-routinely over last 3-4 years.
2	Involved in use ~6 times a couple of years ago. Personal use on animal models.
3	Used some time ago.
4	Used ~12 times.
5	Used up to ~10 times.
6	Used during training in Australia, ~10 cases in UK.
7	Used during training in Australia.
8	No personal experience. Seen it used on several patients by colleagues.
9	No personal experience. Seen evidence.
10	No personal experience. Seen it demonstrated.

Interviewees were asked which of the treatment options was used by them for each patient population. Data presented in this report represents the personal experience of the interviewees or their observations of colleagues. Interviewees were not asked to speculate about resource use or outcomes in treatments or patient groups in which they were not experienced. For example, paediatric Burn Units do not treat patients in the Group C population as these would be transferred to the appropriate Burn Centre.

3.2.3 Nature of the data collected

By interviewing participants, their responses were commonly quite discursive. They provided additional information in response to a single question and talked about other patient groups (e.g. 'In a 5% burn I would...'). Conducting the interviews was a balance between the breadth of information wanted, the detail that interviewees went into, the precision/vagueness of their responses and the duration of the interview. Also, as the interviews progressed it became apparent that some information was very consistent (e.g. healing time for donor sites) and that some questions were essentially unnecessary (e.g. the repetition of questions about long term outcomes and data sources at the end of each patient group). The data collection method is best described as semi-structured interviews. Full coverage of the questions was not achieved, although where information was missing or ambiguous following transcription, interviewees were asked to complete the data or clarify their responses by email. Interviewees were given the opportunity to review their transcribed questionnaires and to compare their responses with those provided by other (anonymised) interviewees.

One interviewee mentioned internal audit data – the EAC requested this but it was not provided during the timescale of the project. In addition, length of stay is used as a key performance indicator with a target of 1 day/% TBSA for non-elderly patients, so interviewees tended to use this as an estimation method where they did not recall a value. However, in most cases it was difficult for respondents to provide quantitative values and the data reported here often represents their best guess. In some cases they were unable or reluctant to provide estimates for some parameters. There was also occasional ambiguity with the definition of the parameters (e.g. theatre time or time to healing). Both of these factors will have contributed to the apparent variance in the data, but some is the result of real differences in practice and outcome.

Participants regularly referred to the variability of patient circumstances and number of other factors that influenced resource use and outcomes. For example, burns patients may often be either

elderly, paediatric or have issues with mental health, substance abuse or challenging social circumstances. As burns care is a specialist service patients may be referred from a considerable distance, especially to Burn Centres. Such non-clinical factors will have a particular influence on (for example) length of hospital stay and compliance with outpatient care. Comorbidities and non-uniform burn depth are common and mean that the patient populations defined for the modelling are significantly different from real patient populations. Data from more homogeneous populations, as used in well-controlled trials, are obviously more suited to providing data for economic models, which involve inherent simplification of the patient pathway.

3.2.4 Group A patients – 10% TBSA partial thickness burns, not requiring grafting

Our questionnaire was based on information gathered during the assessment report. However it became clear that the assumption that patients with a partial thickness burn of 10% TBSA would be treated in theatre was erroneous. Most adults have such an injury cleaned and treated with conventional dressings on the burns ward by nurses, using oral or inhaled analgesia and possibly sedation. Children are more commonly taken to theatre and treated with Biobrane. Some adults may also have Biobrane but in most services this is rare.

The interviewee responses are summarised in Table 5 for adult patients. Most participants felt that ReCell had no place in the treatment of this type of burn as these should normally heal without complication within 2 weeks. Alternative treatments were thought to have no impact on clinical outcomes. Differences in patient pathways between sites were occasionally conspicuous. For example, in one site adult patients with these injuries were likely to be treated using conventional dressings on the burns ward and sent home the same day, whereas in another site burns greater than 5% TBSA were considered for treatment in theatre, requiring a general anaesthetic (GA), surgical team and a minimum of a couple of days hospital stay.

Table 5: Data summary for 10% TBSA partial thickness burns in adults

	Conventional	**ReCell**[1]	**Biosynthetic**[2]	**ReCell + Biosynthetic**[3]
Treatment	Most often treated on the burns ward by nurses, with a review by burns surgeon. Three sites indicated a greater likelihood of patients being taken to theatre for treatment. Variety of dressing types used, mostly silver-containing.	Would generally require a GA and treatment in theatre with surgical team. Would require 20-30 mins longer than conventional treatment in theatre and may be associated with greater likelihood of Versajet use. Telfa Clear used as interface dressing, antimicrobials not used or reduced. Additional dressing for the donor site.	Would generally require a GA and treatment in theatre with surgical team. Would require 20-30 mins longer than conventional treatment in theatre and may be associated with greater likelihood of Versajet use. Biobrane may be covered with additional dressing or simple gauze.	Similar to ReCell

[1] Extremely limited use in this patient group. Based on two interviewees; one had been involved with a single patient the other used ReCell most often in children with darker skin types.
[2] Uncommon for adults in most sites.
[3] Based on one interviewee.

	Conventional	**ReCell[1]**	**Biosynthetic[2]**	**ReCell + Biosynthetic[3]**
Dressing changes	Dressings changed generally every 2-3 days, usually requiring 1-2 nurses. Generally requires oral and/or inhalational analgesia/sedation. Depending on the type of interface dressing and quantity of exudate, only secondary dressings may be changed.	*Same as conventional dressings*. Try to leave interface dressing undisturbed for 5-6 days. Donor site dressing may stay on until healed.	*Same or slightly reduced frequency.* Outer dressings changed – Biobrane lifts off as wound heals. Generally faster and less painful than conventional dressings.	*Same as Biobrane.* Donor site dressing may stay on until healed.
Length of stay	Typically 4-6 days, range of 0-7 days. Adults are often treated as outpatients in 1 site, but in most cases they stay until the 1st or 2nd dressing change.	*Same as conventional dressings.*	*Generally same as conventional dressings*, maybe slightly reduced.	*Same as Biobrane.*
Healing	'By definition' in 7-14 days	*Same as conventional dressings for burn wound.* Donor site takes 7-10 days to heal.	*Same as conventional dressings.*	*Same as conventional dressings.*
Need for patch grafting due to poor healing	This would only occur if the initial burn depth assessment was incorrect or the wound became infected. Estimates between 0-10% of patients.	*Same as conventional dressings.*	*Same as conventional dressings.*	*Same as conventional dressings.*
Hypertrophic scarring	In general considered due to incorrect depth assessment – most likely in deeper areas that take longer to heal and/or require a graft. Variable estimates from 0-30%.	*Same as conventional dressings.*	*Same as conventional dressings.*	*Same as conventional dressings.*

Paediatric patients were:

- more likely to have Biobrane as a treatment option
- more likely to have early dressing changes in theatre under general anaesthetic
- may not require as many theatre staff as adults and may take less time for procedures
- likely to have a play specialist present during procedures when they were awake
- may have a shorter length of hospital stay (range 1-5 days) as they are more likely to receive Biobrane and to have carers at home.

Biobrane was used primarily for its pain relieving properties and was not thought to contribute to faster healing, reduced need for later patch grafting procedures or improved scar outcomes by most interviewees. One interviewee indicated that Biobrane was associated with a more supple scar in the long term that was less prone to breakdown. Biobrane may contribute to shorter length of stay due to the ease and reduced pain of dressing changes, although it does require additional resource use initially due to the need for surgical treatment under a general anaesthetic.

Those participants who would use ReCell in this patient group indicated that ReCell required a surgical procedure under general anaesthetic, with additional procedure time compared to conventional dressings applied in theatre. These participants could not substantiate any clinical benefits in terms of reduced healing time, reduced need for later patch grafting or improved scar outcomes. There was no indication of resource saving in terms of reduced dressing changes or nursing time.

3.2.5 Group B Patients – 10% TBSA deep dermal or full thickness burns expected to require meshed grafting

We found that most interviewees were likely to use sheet autografts rather than meshed ones in this size burn. The decision whether to mesh or not depended on burn location (complex areas, contouring or the need for enhanced cosmesis) and the expected amount of bleeding or exudate. Grafts may also be meshed or fenestrated with little or no actual expansion in order to improve adhesion. ReCell would not be used in combination with a sheet graft. Almost all interviewees indicated that ReCell, alone or with Biobrane, was not an appropriate treatment in this patient group (i.e. as an alternative to autografting) as it did not provide any replacement dermis. ReCell use was therefore uncommon in this group of patients. The interviewee responses are summarised in Table 6 for adult patients.

Table 6: Data summary for 10% TBSA deep partial thickness or full thickness burns in adults

	Autograft	**Meshed graft + ReCell**
Treatment	Generally a sheet autograft; may be meshed 1:1.5 or 1:2 occasionally. Takes 1-2.5 hrs in theatre with 2 surgeons and a surgical team. Variety of dressing types used for burn and donor site wounds.	ReCell adds at least 15-30 mins to the operating procedure time. Low adhesion dressings generally used.
Dressing changes	First wound check is generally at 2-5 days. In some sites 5-20% of patients may have this done under GA with a surgical team. Otherwise IV, oral and/or inhalational analgesia/sedation is used. Later dressing changes are every 2-3 days. Depending on the dressing type and the amount of exudate only outer dressings may be changed. Ward or outpatient dressing changes are conducted by 1-2 nurses.	*Same as for autograft.*
Length of stay	Most patients can go home by the second dressing change. Typically 5-7 days, range of 4-14 days.	*Same as for autograft.*
Healing	Around 10-14 days for the burn wound, but small patches may still require dressings for up to 21 days. 10-14 days for the donor site.	*Same as for autograft.*
Need for grafting due to poor healing	5-15% of patients. This is generally related to infection.	*Same as for autograft.*
Hypertrophic scarring	Around 15-50% of patients. Some sites indicated that all grafted patients get scar management (pressure garments, silicone creams).	*Same as for autograft.*

Paediatric patients were:

- more likely to have sheet autografts
- likely to require slightly less time in theatre
- more likely to have early dressing changes in theatre under general anaesthetic
- likely to have a play specialist present during procedures when they were awake
- more prone to hypertrophic scarring.

The addition of ReCell to meshed autografts in this patient group was not associated with any clinical benefits or resource saving.

3.2.6 Group C Patients – 40% TBSA deep dermal or full thickness burns expected to require wide mesh grafting

Excision and coverage of the entire burn area within 3 days is the prime intent of initial treatment in these patients. If insufficient suitable donor sites are available initially, temporary wound cover is used until the patient is taken back to theatre (e.g. different patient position or additional consent taken) or donor sites are healed sufficiently to allow re-cropping. If a skin biopsy is taken for laboratory culture then cultured cells are generally available from around 14 days onwards, but this does not delay treatment. Therefore in a site that routinely cultures cells for all such burns, the first areas treated will not receive cultured cells. Cultured cells are only available from one NHS laboratory and one commercial provider. The interviewee responses are summarised in Table 7 for adult patients.

Table 7: Data summary for 40% TBSA deep partial thickness or full thickness burns in adults

	Meshed autograft	**Meshed autograft + ReCell**	**Meshed graft + Cultured Cell**
Treatment	Around 1-3 operations in the first week. Generally requires 2 surgical teams including 3-4 surgeons. Autograft mesh ratios are generally 1:1.5 to 1:4. These are dressed with allograft or a variety of commercial dressings. Allograft, Biobrane, skin substitute or other dressings are used for temporary cover.	*Same operations as meshed autograft.* Telfa may be used as interface dressing. No silver dressings directly on cells.	Cultured cells used for minimum of 25-40% TBSA in most sites. *Same operations as meshed autograft.* Telfa may be used as interface dressing. No silver dressings directly on cells.
Dressing changes	Initial dressing changes are conducted alongside and in between treatment operations. Dressing changes are conducted in theatre under GA for between 1-4 weeks.	*Same as for meshed autograft.*	*Same as for meshed autograft.*
Length of stay	Around 3-6 weeks in total[4]. Patients are at least 95% healed before discharge. Around 1 day/% TBSA for younger fitter patients.	*Same as for meshed autograft.*	*Same as for meshed autograft.*
Healing	See length of stay. Depends on number of operations and delays between them. Patients may need up to another month of outpatient wound care.	See text	See text
Need for patch grafting due to poor healing	33-100% of patients.	*Same as for meshed autograft.* ReCell may be used instead of autograft for smaller areas.	*Same as for meshed autograft.* Cultured cells may be used instead of autograft for smaller areas.
Hypertrophic scarring	Generally all patients have some hypertrophic areas, maybe 15-33% need corrective surgery.	See text	See text

The clinical pathway for this patient group was more variable and difficult to describe. Data from iBID indicates 716 patients with 40% or greater TBSA injury from 2003 to 2013; an average of around 8 or 9 patients per year per Burn Centre. Therefore providing estimates in this group was especially difficult for interviewees. Burn injuries of this extent are commonly associated with inhalational and other injuries; length of hospital stay is particularly affected by such factors. The use of skin

[4] If solely dependent on skin burns.

substitutes is more common and the difference between adult and paediatric patients is less marked in this patient group.

The rationale for the use of both cultured cells and ReCell on top of meshed autografts is to increase the speed of healing and improve the appearance in the interstices. Interviewees voiced an *expectation* of faster healing, but were unable to substantiate this with estimates of healing time. There was the suggestion that early healing (at round 2 days) and/or early scar appearance may be slightly improved, however interviewees generally indicated that they did not notice any long term difference in appearance between meshed autografts with and without cells. Three interviewees noted that *if* healing time were reduced then there was potential for improved scar outcomes.

In general ReCell was considered for use where larger mesh ratios were required and cultured cells were not available. Several interviewees indicated that cultured cells were preferable to ReCell, citing the increased volume, concentration and viability of cultured cells. Three interviewees described ReCell as ideally only for use on pieces of donor skin that were not needed for autografting and would otherwise be discarded. The use of ReCell on donor sites was contentious; some interviewees cited published and local evidence that ReCell can reduce donor site healing time by about 24 hrs. However it was debateable whether this difference would be clinically significant.

3.3 Summary of effect of ReCell on specific parameters

We summarise here the evidence from the assessment report, additional literature search and the expert survey for the claimed or potential benefits and detriments of the use of ReCell in acute burns and scalds.

3.3.1 Theatre time and resources

Gravante et al. (2007) and Rawlins (2013) both indicated an increase of around 30 minutes in the operating procedure time using ReCell alone as an alternative to autografts. The interviewees here also consistently supported the need for extra time in theatre when ReCell was used as an adjunct to meshed autografts. Two interviewees indicated that either an additional staff member was required or the organisation of the staff and space in theatre would need to be altered to allow for the processing of the biopsies. A 10% TBSA burn in an adult would equate to approximately 1800 cm^2 (Sacco et al. 2010), requiring 6 ReCell kits for full coverage. We conclude that the use of ReCell incurs additional resource use in terms of theatre time, staff time and consumables

3.3.2 Graft donor size and depth

No information about graft thickness was collected. Gravante et al. (2007) demonstrated that, when used as an alternative to autografting, ReCell results in a smaller and less painful donor site. This follows logically from the method of use and is uncontentious. However, if ReCell were used in Group A patients this would require an additional (if small) donor site, as the other treatments do not require donor skin. When used as an adjunct to meshed autograft there is no reduction in the size of the donor site. Interviewees indicated that samples for use in ReCell kits would not increase the size of the donor site taken but would use otherwise unused pieces of donor site skin. Interviewees stated that the availability of ReCell did not influence the mesh ratio chosen for the autograft, i.e. surgeons would not use a higher mesh ratio plus ReCell *in order to* create a smaller

donor site. We conclude that the use of ReCell would only reduce donor site size if it were used as an alternative to autografts, and this indication is not supported by interviewees.

3.3.3 Pain and analgesia

Wood et al. (2012) reported improved pain scores (not statistically tested) with Biobrane alone or Biobrane plus ReCell versus conventional dressings in children with partial thickness scalds not anticipated to heal within 10 days. Patients with deep partial thickness burns treated with ReCell or ReCell plus Biobrane have reduced pain or analgesia requirement in comparison to autografts (Gravante et al. 2007; Rawlins et al. 2011). However the former does not demonstrate any additional benefit for ReCell over Biobrane and the latter is attributable to the reduced donor site size with respect to autografts. Interviewees here reported no effect of the use of ReCell on pain or analgesia requirements or the requirement for patients to have a general anaesthetic during dressing changes. We conclude that when ReCell is used as an adjunct to meshed autografts in deeper burns or as an alternative to conventional dressings in partial thickness burns there is no clinical or resource benefit related to pain. When ReCell is used in conjunction with Biobrane there is no pain-related benefit beyond that from using Biobrane alone.

3.3.4 Dressing changes

In the scope the sponsor claimed that the use of ReCell reduced the frequency of dressing changes from daily to weekly. Wood et al. (2012) reported a reduction in the number of dressing changes (not statistically tested) for both Biobrane and ReCell plus Biobrane with respect to conventional dressings in children with partial thickness scalds not anticipated to heal within 10 days. The sponsor's economic model separated dressing changes into £166 for a conventional dressing change and £25 for dressing changes for the other treatments (ReCell alone, Biobrane alone and Biobrane plus ReCell); the basis for these costs was unclear (see assessment report, p55).

Interviewees were specifically asked about the frequency, duration, staff resources and nature of the dressing changes to determine any effect of ReCell on these parameters. Interviewees here did not report a reduction in the frequency of dressing changes or a reduction in healing time (and therefore number of dressing required) with the use of ReCell in any patient group, nor any difference in resource use. Most sites would inspect the burn wound at around 2 days post-intervention, which would require at least secondary dressing changes. Some interface dressings are clear and allow wound inspection without removal. Some interviewees indicated that they would avoid disturbing autografts or cells for up to 5 days but that outer dressings would be changed in the meantime. In Group C patients early dressing changes tended to be interspersed between, or conducted during, operations to provide burn wound treatment. Differences between sites, between different interface dressings and between patients (with different injury sites, levels of exudation and pain tolerance) introduce substantial variability in the resource implications for dressing changes. We conclude that there is no demonstrable benefit of the use of ReCell on the frequency, type, number or other resource use for dressing changes.

3.3.5 Healing of the donor site

We found no evidence to suggest that the ReCell donor site would heal faster than an autograft donor site, although we accept that as an alternative to autografts ReCell requires a substantially smaller donor site that may heal faster. Interviewees here referred to a potential reduction in time

to healing of autograft donor sites that were treated with ReCell or cultured cells. One interviewee referred to a controlled trial reporting a 24 hr reduction in healing time with the use of ReCell. The EAC was unable to locate a paper that fitted this description. The Avita website refers to a study in which surface electrical capacitance measurements are used to quantify the healing rate of donor sites treated with cultured cells versus cell medium (Magnusson et al. 2007). However, this study does not report time to healing or use ReCell. Another interviewee stated that although a local audit of cell use had not shown any clinical benefit of their application, anecdotal evidence showed that donor sites in children could be re-cropped at one week when cells were used. Other interviewees also indicated an expectation of faster healing of donor sites with the application of ReCell or cultured cells, but could not substantiate this with evidence from their own practice. We conclude that there is potential for faster healing of donor site wounds that are sprayed with ReCell, although evidence is poor and the clinical significance of this is debatable.

3.3.6 Healing of the recipient burn wound

Wood et al. (2012) reported reduced time to healing and increased rates of healing at 10 and 21 days (not statistically tested) with Biobrane alone or Biobrane plus ReCell versus conventional dressings in children with partial thickness scalds not anticipated to heal within 10 days. Rawlins et al. (2011) reported a reduced time to healing (not statistically tested) in 4 patients with deep dermal burns treated with Biobrane plus ReCell compared to 10 patients treated with meshed autograft. However, given the criticisms of this evidence detailed in the assessment report, there is no evidence that ReCell improves speed of healing over and above any benefit that may be conferred by the use of Biobrane. Gravante et al. (2007) reported no difference in time to healing between deep partial thickness burns treated with ReCell alone and with autografts. The sponsor's economic model used the data from Wood et al. (2012) to estimate a percentage reduction in healing time for ReCell alone, Biobrane plus ReCell and Biobrane alone versus conventional dressings.

The interviewees here indicated no difference in burn wound healing time in any of the patient groups. Advocates of both cultured cells and ReCell indicated that the rationale for the use of cells as an adjunct to meshed autografts was to achieve faster healing and improved aesthetic appearance. However, when pressed for estimates these interviewees were not able to substantiate this approach with numbers from their personal experience. Phrases such as 'anecdotally', 'we expect that', 'we hope that' and 'the science is reasonable that' were used. One ReCell user noted that quicker healing might be apparent at around 2 days but that the range of healing times was not different. Another interviewee provided the sole quantifiable estimate of benefit of the use of cells in the Group C population:

"That's hard to say isn't it? Say it would speed it up by one and a half times. It makes a significant difference to have them than not have them. I use the cultured cells more, but I think having the ReCell in these situations is very good as well."

However, this interviewee indicated that the range of other factors that influenced hospital stay meant that faster healing would not necessarily translate into shorter hospital stay.

There was contention about the mechanism of effect of cell application – whether it was the cells that proliferated and covered the wound or whether it was (e.g.) growth factors that the cells produced. One interviewee was aware of a recently completed randomised controlled trial of

cultured cells in burns. The EAC contacted the investigator in this study and requested additional information on the basis that the rationale for any potential benefit of ReCell on speed of healing and long term scar outcomes (with the exception of pigmentation) is similar to that for cultured cells. Publically available information indicates that this is an intra-patient 4-way randomised comparison of 1:4 meshed autograft alone versus meshed autograft plus sprayed cells, cell sheets and sprayed solution (Maitz et al. 2014).

[redacted]

The EAC did not conduct a literature review of the use of cultured cells in burns treatment.

Despite a general expectation of benefit in terms of speed of healing amongst users of cultured cells and ReCell in larger burns we conclude that there is no evidence from expert opinion that this has been realised in actual practice.

3.3.7 Length of hospital stay

In the sponsor's economic model 50% of patients treated with conventional dressings remained as inpatients until healed versus 25% of patients who received the alternative treatments (ReCell alone, Biobrane alone or ReCell Plus Biobrane). This was based on the assumption that these treatments require only secondary dressing changes and was challenged by both the EAC and the lead team expert advisers. Park et al. (2013) reported a reduced length of stay for patients treated with ReCell alone versus patients treated with autograft, although the authors state that different indications and timings for these treatments mean that this outcome should "be interpreted cautiously".

Interviewees here indicated that the type of treatment would have no effect on the length of hospital stay or the need for intensive/high dependency care. They were keen to point out that the patients described in the questionnaire were not typical and that there were many reasons for keeping patients as inpatients other than the condition of their skin burns; e.g. difficult social circumstances, mental health issues, co-morbidities, substance abuse, inhalational and other injuries, long journey times, complex wound management (not delegated to community nursing), need for physiotherapy. These factors are most likely to confound length of stay in the largest burn population. We conclude that there is no evidence of benefit of the use of ReCell on length of stay or need to remain as an inpatient.

3.3.8 Need for patch skin grafting

Wood et al. (2012) reported lower rates of autografting at 10 days (not statistically tested) for both Biobrane and Biobrane plus ReCell versus conventional dressings in children with partial thickness scalds not anticipated to heal within 10 days. This patient group is difficult to compare to the patients populations considered in this work. Group A patients are those expected to heal within 2 weeks and not expected to need grafting. Group B and C patients are expected to need grafting and would be treated within 1-2 days. It may be that the patients in Wood et al. (2012) are closest to intermediate, indeterminate or mid-dermal burns in which the need for grafting is not initially clear. This patient population is not considered in this project.

The sponsor's economic model used published data for the conventional dressings and estimates from their own expert advisers for the other treatment types to populate the proportion of patients progressing to skin grafts in their economic model. The base case estimates were 30% for conventional dressings and Biobrane alone and 10% for ReCell alone and ReCell plus Biobrane. The interviewees here provided estimates that were much lower, but quite variable and they also noted its dependence on factors such as infection and the accuracy of the initial burn depth assessment. However, none of the interviewees indicated an effect of the treatment type on the requirement for later patch grafting. We conclude that this parameter is particularly difficult to estimate and highly dependent on the nature of the injury. There appears to be no evidence to suggest that the use of ReCell affects the effectiveness of burn wound healing or graft take and therefore the need for additional surgical treatment at around 10-14 days.

3.3.9 Long term scar outcomes, including pigmentation

In the assessment report all published data that reported long term scar outcomes indicated comparable results between different treatment options. Gravante et al. (2007) reported no difference in simplified Vancouver Scar Scale (VSS) and number of contractures between ReCell alone and autografts at 6 months. Wood et al. (2012) reported individual VSS values for 4 patients in each of three treatment arms at 6 months (ReCell alone, ReCell plus Biobrane and conventional dressings) that do not appear to differ. Rawlins et al. (2011) reported VSS values at 6 months of 5.3 for ReCell alone and 6.5 for autografts (not statistically tested). VSS values range from 0 (normal skin) to 13 (worst scar possible) and as the variance of their data is unknown the EAC does not consider this difference to be significant. Sood et al. (2011) reported modified VSS at 12 months in 10 patients in an intra-patient comparison of ReCell alone versus autograft. Pigmentation, colour match and modified VSS were comparable for the two treatments, with 1 out of 10 patients indicating a preference for the appearance of the ReCell-treated site.

Interviewees here indicated no effect of treatment type on the incidence of hypertrophic scarring. Incidence increases with time to healing; in a retrospective audit Cubison et al. (2006) reported an incidence of 0% in children with scalds that took less than 10 days to heal (n=55), whereas it was 8% for 10-14 days (n=79) and 20% for 15-21 days (n=75). Interviewees indicated that in Group A injuries incidence should be very low and would be related to wound infection and inaccurate assessment of the wound depth. In deeper burns that are grafted, incidence is higher and in large and full thickness burns interviewees indicated that some areas of hypertrophic scarring are to be expected.

Some interviewees were of the opinion that the use of any cells did not affect long term appearance, quality or function of burn scars. There was also the view that *if* time to healing was reduced by the addition of cells then improved scar outcomes could be expected. One interviewee described more flexible and softer scars when cultured cells were used with skin substitute and an expectation of a similar effect with ReCell, but could not attribute this outcome directly to the use of cells. Pigmentation outcomes were also equivocal for ReCell use in acute burns. Many interviewees did not think that ReCell made any difference to long term pigmentation. One indicated that they had not considered this outcome specifically in relation to ReCell use. Two noted that pigmentation may recover slowly over 2-3 years. Three indicated that they might be more inclined to use ReCell in patients with darker skins. The most positive expert opinion was:

"We've had some encouraging results, but we've also had occasional results where it's not been obvious that it helps. So I can't say definitively that it always improves repigmentation. But that partly, I feel, again depends a bit on the depth of the burn and how much normal reservoirs of melanocytes are left...Yes, anecdotally we do feel that it can improve pigmentation post burn."

We conclude that there is no evidence to support the claim that the application of ReCell results in systematically improved long term scar outcomes, including pigmentation. There is the suggestion that shorter term scar outcomes may be slightly improved.

3.4 Applicability of outcomes from repigmentation indications

The sponsor's submission included published evidence for the use of ReCell in hypopigmented lesions (vitiligo and chronic scars) that the EAC determined to be outside the scope of the evaluation. However, the specification for this project requested additional expert opinion as to whether this evidence should be considered relevant. Pigmentation outcomes were felt to be of particular importance to patients with darker skin and this was noted in the special considerations in the scope. The EAC has reviewed three comparative studies of the use of ReCell in vitiligo (Section 3.1.2) and concluded that the repigmentation outcomes are equivocal.

In general interviewees here indicated that there was a substantial physiological difference between an acute burn and a surgically created wound in (e.g.) vitiligo or hypopigmented scars. A burn wound was a less ideal environment, with potential contamination and variable depth. However, opinion was divided about whether outcomes were transferable between indications. Several interviewees stated that they did not think that ReCell had any positive effect in vitiligo, whereas others stated that they had seen some positive effect in their own vitiligo patients. *If* ReCell could be shown to have a benefit in hypopigmented conditions then even some sceptical interviewees stated that they might consider it for this reason in acute burns.

3.5 Role of ReCell in burns care in the UK

Interviewees were additionally asked about what role they felt ReCell had in the treatment of acute burns and where any potential benefit might lie. All interviewees were open to the possibility that ReCell may have some benefit. The options for this were:

- Large burns that require grafting – 7 interviewees either had used it in this way or would consider it. ReCell is readily accessible in the early stages of wound cover when cultured cells are not yet ready or in burn services that did not have easy access to such laboratory services. Also, ReCell can be used for 'left over' pieces of donor skin that are not suitable for grafting and would otherwise be discarded. However this use has the disadvantage of occurring towards the end of a surgical procedure and therefore extending theatre time.
- Mid-dermal, mixed depth, intermediate or indeterminate burns – 2 interviewees had used it in these injuries in the hope of speeding up healing in comparison to conservative treatment and reducing the need for later autografting.
- Deep facial burns – 1 site had used it in this indication. A very conservative, non-grafting approach was generally used in these cases and ReCell was described as a 'last ditch' treatment where the burn had not healed well after about 2 weeks. Echlin et al. (2012)

reported a case series of 4 patients with facial burns who were treated with ReCell at 9-11 days post injury and indicated positive outcomes (see assessment report, p32).

Several interviewees had used, or were considering using, ReCell for treating hypopigmented scars or vitiligo.

3.6 Economic modelling

The primary purpose of this project was to obtain data with which to populate an economic model for the use of ReCell in acute burns. The EAC was unable to do this as virtually no quantitative data for clinical benefit or resource saving was obtained from the survey of clinical experts. Essentially interviewees were either of the opinion that ReCell did not provide any additional clinical benefit or resource saving over the comparator treatments, or were unable (or unwilling) to provide numerical estimates.

The use of ReCell would incur a cost of £950 per kit (each treating up to 320cm^2) and require additional time in theatre, whether it was used as an adjunct to meshed grafting in deeper burns or as an alternative to conventional dressing in shallower burns. The EAC has been unable to identify any evidence to support clinical benefit or resource savings resulting from ReCell use (with respect to the comparator treatments) that would balance or outweigh these additional costs in the three patient populations defined here. We have further determined that the economic model in the sponsor's submission was inappropriate as it included a patient population in which almost all expert advisers indicated they would not use ReCell.

4 Discussion

4.1 Summary of findings regarding use of ReCell in acute burns

No new data about the use of ReCell in acute burns was obtained from published literature or existing UK databases. Expert opinion was collated from 10 UK NHS burns specialist clinicians by using a questionnaire and semi-structured interviews. In general these experts did not express any quantifiable benefits from the use of ReCell in comparison to current standard practices. ReCell was not in common use amongst participants, but even those with the most experience and positive opinion of the technology could not substantiate their expectation of improved clinical outcomes with estimates from their own practice.

4.2 Comparison with findings from assessment report/November MTAC meeting

In the assessment report the EAC concluded that in partial thickness burns ReCell alone or in combination with Biobrane was not shown to be clinically superior to Biobrane alone. The cost savings of ReCell alone or ReCell plus Biobrane versus conventional dressings that were identified in the sponsor's economic model in partial thickness burns were based on estimates and assumptions that are seen to be erroneous in the light of information from a wider base of expert advisers.

In the assessment report the EAC also concluded from the published evidence that ReCell was at least as clinically effective as the use of split thickness autografts in mid to deep dermal burns, and

was a suitable alternative treatment. In this context the use of ReCell was associated with a smaller donor site wound and related pain. The UK expert advisers consulted here were consistent in their opinion that it was not appropriate to use ReCell directly on deep partial burns and that it should only be used in these injuries on top of meshed autograft. The disparity between the published evidence (mostly non-UK) and this opinion has not been explained. It may be due to differences or ambiguities in the description of the burn injury or in national approaches to burn care. The EAC has attempted to contact the authors of the studies to clarify this but has not received any responses. The outcomes from the use of ReCell as an adjunct to meshed autografts in deeper burns were not addressed in either the published literature or the sponsor's economic model.

The responses of the expert advisers here also contrast with those obtained both by the sponsor and the EAC in the assessment report. The sponsor obtained written estimates of model parameters from 4 clinical experts, one of which was the inventor of the technology. The questions were answered variably, but in general suggested a slight reduction in the proportion of patients with partial thickness burns requiring later autografts. The apparent difference between the information provided to the sponsor and that obtained by the EAC could be explained by:

- Different participants – the sponsor identified clinical users of ReCell (in the UK and Australia) whereas the EAC attempted to obtain information from each relevant burn service in the UK. There were also 4 expert advisers identified by NICE for the assessment report. Of these 2 were also in the sponsor's group, but only one of these contributed to the EAC's survey. The other adviser provided written evidence for the assessment report in which they considered that ReCell was clinically beneficial and also agreed to participate in the expert survey here, but did not respond in the available time.
- Different methods – the sponsor collected data from their expert advisers by providing a written set of questions. Some advisers responded briefly and others provided longer explanations and qualifications to their answers. Occasionally they responded to the same question in different terms (see assessment report, Table 12). The EAC conducted semi-structured interviews which allowed the interviewer and participant to explore the underlying information and to adapt when the assumptions or questions were found to be inappropriate. Respondents may have found it more uncomfortable to provide unsubstantiated numerical estimates in discussion (and 'on the record') than when filling in a table. There is also more scope for misunderstanding by the respondent and the investigator when only written communication is used. This was apparent when one of the survey interviewees completed the first part of the questionnaire by hand and was then interviewed for the rest of the questionnaire.

4.3 Strengths and weaknesses of the study design

The initial study design for this work was appropriate to answer the specification given the short timescale available. The method was altered as the work progressed in response to the non-availability of the burn injury database and the nature of the data being collected.

The survey of clinical expert advisers could have been improved methodologically by piloting the questionnaire or by conducting it as a two-part survey. The short timescale for the project and the difficulty of obtaining rapid responses from busy clinicians precluded both of these approaches. As a

result the questionnaire was not ideally suited for completion by hand and was also found to be based on assumptions that were not always appropriate to local care pathways. The EAC considers that if a more robust survey had been conducted it is unlikely that it would have identified additional useful data as it was primarily respondents' opinion of the technology and their ability to estimate values that precluded the attainment of suitable data.

We did not achieve 100% coverage of UK Burn Centres and Units. Five additional clinicians initially agreed to participate but did not respond to the questionnaire or the invitations for telephone interview. The short timescale and lengthy nature of the questionnaire are the most likely reasons for non-participation. We also did not include burns services in Scotland or Northern Ireland. An alternative strategy for identification of expert advisers would have been to ask the manufacturer or distributor for a list of UK users of ReCell and compared these to other services. We chose to attempt to enlist all specialist Burn Centres and Units in England and Wales and allow the consultant surgeons at each to determine who would participate. In doing so we assumed that each respondent would have a reasonable knowledge of the practice and outcomes of colleagues at their site.

Despite applying as early as possible we did not obtain access to NBID/iBID due to the short timescale. Initially, publically-available information suggested that appropriate resource-use data was included in this database (Evolution Healthcare Systems), but later discussion with the database owners indicated that these fields may not be well-populated yet. Also it is unlikely that information regarding treatment with ReCell would be recorded there. We did obtain some general reports from the owners, but this aggregated information is of little use for economic modelling. It is probable that existing local and national datasets may be obtained if more resources were available. However, one interviewee did refer to a local audit that indicated no clinical benefits for the use of cells.

We did not conduct the intended targeted literature search. As we became aware that the expert survey was not providing the required quantitative data we decided not to continue with this part of the project. As no new ReCell data since the assessment report had been identified this search would only have provided additional data for the comparator treatments.

The patient populations defined in the specification did not appear to be entirely appropriate for the evaluation of ReCell. In the UK it appears that most burn surgeons who use ReCell reserve it for larger burns. The EAC definition of the Group C population as 40% TBSA may have been rather low, although practice varied between services in terms of the threshold for cultured cells use or the mesh ratios used. However, with increasing burn area the number of patients becomes smaller and the variability in the injuries increases. Fewer burn services are involved in the care of these patients (Centres only) and data collection becomes more difficult. Also interviewees here provided no indication that they could substantiate any potential benefit of the use of cultured cells or ReCell in these or in larger burns. The EAC defined the Group B population as 10% TBSA based on prior information that autografts for this size burn are likely to be meshed. However, most interviewees indicated a preference for sheet grafting at this burn size.

Several interviewees were vocal in their antipathy for the use of ReCell in the treatment of acute burns, although many also stated that they would like to see well-conducted trial evidence. In the absence of such data, it is unlikely that burns services would be convinced to change their current practice. Proponents of ReCell were open about the lack of data to back up their hopes and

expectations of clinical benefit. There is some wide variation in clinical practice and the complexity of factors that influence outcomes and resource use in patients requiring specialist burn services means that any potential benefits or detriments may not be realisable in actual use.

The EAC concludes that the information provided by the expert survey indicates no perceived benefit for ReCell for an increase in resource use.

4.4 Research ideas

Many of the interviewees noted the difficulty of conducting research in patients with burn injuries. Wood et al. (2012) attempted to conduct a three armed randomised controlled trial including ReCell but failed to recruit sufficient patients for an effective study. Problems with research in this patient population include variability in burn type, size, location and depth, possible contamination with accelerants, complex social circumstances and issues with mental health conditions. Other difficulties are shared with general wound healing research such as the high number of available treatment options (e.g. dressings and topical treatments) and ambiguous outcome measures (e.g. healing).

The question of which patient population would be most appropriate is also non-trivial. Smaller partial thickness burns are more common and therefore would be easier to recruit in suitable patient numbers. Alternatively variability of the wound could be accounted for by conducting a study in donor site wounds. However clinicians are unlikely to want to use an expensive technology to treat an injury that should heal without complication. Also even if such a study were to demonstrate clinical benefits for ReCell it may be dismissed by clinicians as not relevant to actual clinical practice. In larger burns low and unpredictable patient numbers suggest the need for multi-centre studies or long study durations, and large travelling distances to these specialised services could frustrate the long term follow up that would be required to determine the effect of ReCell on pigmentation and other scar outcomes. The mid-dermal or intermediate/indeterminate depth burns may be most suited for the determination of potential clinical benefit from the use of ReCell, but this type of injury and its treatment are likely to be particularly variable. Large numbers of patients may be required to overcome this.

There is potential for the use of iBID/NBID or local data resources in future research. The availability and suitability of such sources is not known, but they may not contain sufficiently specific information to inform further evaluations of ReCell.

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5 Appendix 1 - expert adviser questionnaire

To understand what the variability in practice is we have asked for an average and a range – the range should reflect typical patients, not the extreme values (e.g. typical length of stay might be 5 days with a range of 2-10 days for most patients). We are especially interested in differences between the options (e.g. if theatre time for biosynthetic dressing is 1 hour but it takes another ten minutes if ReCell is also being used).

1. Pigmentation outcomes:
   a. Does ReCell affect long term pigmentation of the healed burn wound compared to standard treatment? If so, how?
   b. Does the skin colour of the patient affect your decision to use ReCell? If so, how?
   c. ReCell has also been used to try to treat hypopigmentation in established scars and in stable vitiligo (repigmentation). Do you believe that outcomes from the use of ReCell in such repigmentation treatments can be used as surrogates for outcomes in burns? I.e. if the use of ReCell improved pigmentation in non-burn indications would you realistically expect to see the same improved outcomes if it were used in acute burns?

Group A patients: 10% TBSA partial thickness burns that are not expected to require grafting

The burn does not involve complex areas (e.g. face, hands, genitals) and has no obvious infection. Patients' length of stay and care is dependent only on their skin burn wounds, i.e. there are no other injuries (e.g. inhalational, fractures), difficult social circumstances or large distance to home that preclude discharge.

Assumptions:

- Patients go to theatre within 2 days (48 hours) post injury.
- All surgical treatments require the same wound preparation.
- Patients stay as inpatients until the first dressing change post-procedure.
- Inpatients remain on the burns ward until discharge.
- Any patient that requires their first dressing change to be carried out in theatre under a general anaesthetic (GA) will remain as an inpatient and that those who only require simple analgesia will be discharged to outpatient care.
- Any patient requiring later surgical intervention for unhealed burns will only require one instance of treatment to achieve healing.

Treatment options:

The burn can be treated in one of four ways:

- conventional dressings,
- ReCell plus conventional dressings (e.g. Telfa),
- biosynthetic dressing (e.g. Biobrane) alone,
- ReCell plus biosynthetic dressing.

2. Are any of the assumptions nonsensical?
3. Are any of these treatment options nonsensical?

Group A: 10% TBSA partial thickness		**Conventional Dressing**		**Difference from conventional dressing**					
				ReCell + conv. dressing		**Biosynthetic dressing**		**ReCell + biosynth. dressing**	
Initial surgical treatment	4. How long would you expect the surgery to take (procedure time)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	5. How many & what staff would you expect to need in theatre? (E.g. consultant surgeon, trainee surgeon, anaesthetic staff, ODA/ODP, scrub nurse, other.)								
	6. How is the burn wound dressed? a. Primary (contact) dressing b. Secondary (protective) dressing								
	7. How is the ReCell donor site dressed?	NA				NA			
	8. What are the differences in consumables used between treatment options (excluding the ReCell kits)? E.g. maybe contact dressings are stapled, but not Biobrane.								
Dressing changes	9. How many days are there between surgery and the first dressing change/wound assessment?	Avg	Range	Avg	Range	Avg	Range	Avg	Range

Group A: 10% TBSA partial thickness		Conventional Dressing		Difference from conventional dressing					
				ReCell + conv. dressing		Biosynthetic dressing		ReCell + biosynth. dressing	
	10. How frequent are dressing changes for the burn wound?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	11. What proportion of patients have their first few dressing changes in theatre under GA? a. For how long are these patients likely to require a GA for dressing changes (days)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	b. What staff are required in theatre?								
	c. How long does this take in theatre?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	12. For patients who only require simple analgesia for dressing change on the burns ward: a. What analgesia is used?								
	b. What staff are required?								
	c. How long will this take?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	13. What dressings are changed for the burn wound?								
	14. How frequent are dressing changes for the donor site?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	15. What dressings are changed for the donor site?	NA				NA			
Discharge/ Length of	16. What proportion of patients are discharged to outpatient treatment following the first dressing change?	Avg	Range	Avg	Range	Avg	Range	Avg	Range

Group A: 10% TBSA partial thickness		Conventional Dressing		Difference from conventional dressing					
				ReCell + conv. dressing		Biosynthetic dressing		ReCell + biosynth. dressing	
stay	17. What is the total length of stay in hospital for this patient population (days)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	18. Are there any substantial differences between dressing changes on the ward and those in outpatients (e.g. time required, number/type of staff, analgesia, frequency or dressing type)? Please comment.								
Healing and retreatment	19. For patients with uncomplicated wound healing how long do you expect the burn wound to take to heal (from initial surgical treatment to >95% healing, no further dressings required)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	20. For patients with uncomplicated wound healing how long do you expect the donor site to take to heal?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	21. What proportion of patients would require secondary surgical intervention (e.g. regrafting) due to poor healing? a. At what point is the decision taken to provide surgical intervention (days post-surgery)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	b. What are the options for secondary surgical intervention?								
	c. Is the choice of secondary intervention affected by the initial treatment?								

Group A: 10% TBSA partial thickness		Conventional Dressing		Difference from conventional dressing					
				ReCell + conv. dressing		Biosynthetic dressing		ReCell + biosynth. dressing	
	d. How does the second procedure differ from the first (e.g. procedure time, size of graft, materials used, staff)?								
	e. How long would you expect the wound to take to heal following secondary surgical treatment?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	22. What proportion of patients do you expect to develop hypertrophic scars?	Avg	Range	Avg	Range	Avg	Range	Avg	Range

Use of ReCell	23. Are there specific circumstances under which you would or would not use ReCell, other than standard contraindications (e.g. not on burns smaller than 3% TBSA, not on face burns)?	
	24. Does the use of ReCell affect analgesia requirements for background pain?	
Long term outcomes	25. Does the use of ReCell improve the appearance and/or function of the eventual scar? If so, how: a. pigmentation outcomes? b. incidence of poor scarring? c. use of conservative scar treatments (creams, compression, steroid injections)? d. requirement for surgical scar revisions?	

	26. Does the use of ReCell affect any other long term outcomes? (E.g. psychological, need for occupational therapy, need for social services support.) If so, how?	
Source	27. Are your answers in general based on personal recall of experience, access to collected data (e.g. local audit or national databases) or other?	

Additional comments (e.g. on the treatment of this type of patient, on the questions asked or on the use of ReCell)

Group B patients: 10% TBSA deep dermal/partial thickness or full thickness burns that are expected to require (meshed) split thickness skin grafts (SSG)

The burn does not involve complex areas (e.g. face, hands, genitals) and has no obvious infection. Patients' length of stay and care is dependent only on their skin burn wounds, i.e. there are no other injuries (e.g. inhalational, fractures), difficult social circumstances or large distance to home that preclude discharge.

Assumptions:

- Patients go to theatre within 2 days (48 hours) post injury.
- All surgical treatments require the same wound preparation.
- Patients stay as inpatients until the first dressing change post-surgery.
- Inpatients remain on the burns ward until discharge.
- Any patient that requires their first dressing change in theatre under a general anaesthetic (GA) will remain as an inpatient and that those who only require simple analgesia will be discharged to outpatient care.
- Any patient requiring later surgical intervention for unhealed burns will only require one instance of treatment to achieve healing.

Treatment options:

The burn can be treated in one of four ways:

- meshed split skin autograft (SSG),
- meshed split skin autograft (SSG) plus ReCell,
- ReCell with conventional dressing (e.g. Telfa)
- ReCell with biosynthetic dressing (e.g. Biobrane).

28. Are any of these treatment options nonsensical?
29. Are any of the assumptions nonsensical?

Group B: 10% TBSA deep partial thickness or full thickness		**Meshed SSG**		**Difference from meshed SSG**					
				Meshed SSG + ReCell		**ReCell alone**		**ReCell + biosynth. dressing**	
Initial surgical treatment	30. How long would you expect the surgery to take (procedure time)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	31. How many & what staff would you expect to need in theatre? (E.g. consultant surgeon, trainee surgeon, anaesthetic staff, ODA/ODP, scrub nurse, other.)								
	32. How is the burn wound dressed? a. Primary (contact) dressing b. Secondary (protective) dressing								
	33. What mesh ratio is used?								
	34. How large is the donor site (cm^2)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	35. How is the donor site dressed?								

Group B: 10% TBSA deep partial thickness or full thickness		**Meshed SSG**		**Difference from meshed SSG**					
				Meshed SSG + ReCell		**ReCell alone**		**ReCell + biosynth. dressing**	
	36. What are the differences in consumables used between treatment options? E.g. autografts are stapled and require a meshing device, but ReCell does not require either.								
Dressing changes	37. How many days are there between surgery and the first dressing change/wound assessment?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	38. How frequent are dressing changes for the burn wound?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	39. What proportion of patients have their first few dressing changes in theatre under GA? a. For how long are these patients likely to require a GA for dressing changes?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	b. What staff are required in theatre?								
	c. How long does this take in theatre?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	40. For patients who only require simple analgesia for dressing change on the burns ward: a. What analgesia is used?								
	b. What staff are required?								

Group B: 10% TBSA deep partial thickness or full thickness		**Meshed SSG**		**Difference from meshed SSG**					
				Meshed SSG + ReCell		**ReCell alone**		**ReCell + biosynth. dressing**	
	c. How long will this take?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	41. What dressings are changed for the burn wound?								
	42. How frequent are dressing changes for the donor site?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	43. What dressings are changed for the donor site?								
Discharge/ Length of stay	44. What proportion of patients are discharged to outpatient treatment following the first dressing change?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	45. What is the total length of stay in hospital for this patient population (days)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	46. Are there any substantial differences between dressing changes on the ward and those in outpatients (e.g. time required, number/type of staff, analgesia, frequency or dressing type)? Please comment.								
Healing and retreatment	47. For patients with uncomplicated wound healing how long do you expect the burn wound to take to heal (from initial surgical treatment to >95% healing, no further dressings required)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range

Group B: 10% TBSA deep partial thickness or full thickness		**Meshed SSG**		**Difference from meshed SSG**					
				Meshed SSG + ReCell		**ReCell alone**		**ReCell + biosynth. dressing**	
	48. For patients with uncomplicated wound healing how long do you expect the donor site to take to heal?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	49. What proportion of patients would require additional surgical intervention (e.g. regrafting) due to poor healing?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	50. At what point is the decision taken to provide surgical intervention (days post-surgery)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	51. What are the options for secondary surgical intervention? (Is this affected by the initial treatment?)								
	52. How does the second procedure differ from the first (e.g. duration, size of graft, materials used, staff)?								
	53. How long would you expect the wound to take to heal following secondary surgical treatment (days)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	54. What proportion of patients do you expect to develop hypertrophic scars?	Avg	Range	Avg	Range	Avg	Range	Avg	Range

Use of ReCell	55. Are there specific circumstances under which you would or would not use ReCell, other than standard contraindications (e.g. not on burns smaller than 3% TBSA, not on face burns)?	
	56. Does the availability of ReCell affect the need for donor sites or their size, e.g. would you use a higher mesh ratio if you have the use of ReCell? If so, can you quantify this?	

	57. Does the use of ReCell affect analgesia requirements for background pain?	
Long term scar outcomes	58. Does the use of ReCell improve the appearance and/or function of the eventual scar? If so, how: a. pigmentation outcomes? b. incidence of poor scarring? c. use of conservative scar treatments (creams, compression, steroid injections)? d. requirement for surgical scar revisions?	
	59. Does the use of ReCell affect any other long term outcomes? (E.g. psychological, need for occupational therapy, need for social services support.) If so, how?	
Source	60. Are your answers in general based on personal recall of experience, access to collected data (e.g. local audit or national databases) or other?	

Any additional comments, e.g. on the treatment of this type of patient, on the questions asked or on the use of ReCell.

Group C patients: large, 40% TBSA, deep dermal/partial thickness or full thickness burns that are expected to require wide meshed split thickness skin grafts (SSG)

The burn does not involve complex areas (e.g. face, hands, genitals) and has no obvious infection. Patients' length of stay and care is dependent only on their skin burn wounds, i.e. there are no other injuries (e.g. inhalational, fractures), difficult social circumstances or large distance to home that preclude discharge.

Assumptions:

- Patients go to theatre within 2 days (48 hours) post injury.
- All surgical treatments require the same wound preparation.

- Patients have dressing changes under GA and remain on HDU for the same length of time and are then transferred onto the burns ward when dressing changes require simple analgesia.
- Any patient requiring later surgical intervention for unhealed burns will only require one instance of treatment to achieve healing.

Treatment options:

The burn wound can be treated in one of several ways:

- wide meshed split thickness autograft (SSG),
- wide meshed split thickness autograft (SSG) plus ReCell,
- wide meshed autograft plus cultured cells,
- ReCell plus conventional dressing (e.g. Telfa),
- ReCell plus biosynthetic dressing (e.g. Biobrane).

61. Are any of these treatment options nonsensical (e.g. you would not use ReCell alone in this patient population)?
62. Are any of the assumptions nonsensical?

Group C: 40% TBSA deep partial thickness or full thickness		**Wide meshed SSG**		**Difference from wide meshed SSG**							
				Wide meshed SSG + ReCell		**Wide meshed SSG + cultured cells**		**ReCell alone**		**ReCell + biosynth. dressing**	
Initial surgical treatment	63. How many operations do you expect to need for the initial surgical treatment?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	64. What would you expect the overall surgery time to be (sum of all procedure times)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	65. How many & what staff would you expect to need in theatre? (E.g. consultant surgeon, trainee surgeon, anaesthetic staff, ODA/ODP, scrub nurse, other.)										

Group C: 40% TBSA deep partial thickness or full thickness		**Wide meshed SSG**		**Difference from wide meshed SSG**							
				Wide meshed SSG + ReCell		**Wide meshed SSG + cultured cells**		**ReCell alone**		**ReCell + biosynth. dressing**	
	66. How is the burn wound dressed? a. Primary (contact) dressing b. Secondary (protective) dressing c. Untreated burn area (e.g. temporary dressing)										
	67. What mesh ratio is used?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	68. How large is the donor site (cm^2)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	69. How is the donor site dressed?										
	70. What is the typical delay between surgical treatments?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	71. What determines the time period between operations (not including theatre/staff availability)?										
	72. What are the differences in consumables used between treatment options (excluding the ReCell kits)? E.g. autografts are stapled and require a meshing device, but ReCell does not require either.										
Dressing	73. How frequent are dressing changes for the burn wound?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range

Group C: 40% TBSA deep partial thickness or full thickness		**Wide meshed SSG**		**Difference from wide meshed SSG**							
				Wide meshed SSG + ReCell		**Wide meshed SSG + cultured cells**		**ReCell alone**		**ReCell + biosynth. dressing**	
changes	74. For how long are patients likely to require an HDU stay/GA for dressing changes?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	a. What staff are required in theatre?										
	b. How long do dressing changes take in theatre?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	c. What dressings are changed for the burn wound?										
	75. How frequent are dressing changes for the donor site?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	76. What dressings are changed for the donor site?										
	77. When patients move onto simple analgesia for dressing changes on the burns ward: a. What analgesia is used?										
	b. What staff are required?										
	c. How long will the procedure take?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	d. What dressings are changed for the burn wound?										
	e. What dressings are changed for the donor site?										
Length of stay	78. What is the total length of stay in hospital (days)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range

Group C: 40% TBSA deep partial thickness or full thickness		Wide meshed SSG		Difference from wide meshed SSG							
				Wide meshed SSG + ReCell		Wide meshed SSG + cultured cells		ReCell alone		ReCell + biosynth. dressing	
Healing and retreatment	79. For patients with uncomplicated wound healing how long do you expect the burn wound to take to heal (from initial surgical treatment to >95% healing, no further dressings required)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	80. For patients with uncomplicated wound healing how long do you expect the donor site to take to heal?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	81. What proportion of patients would require secondary surgical intervention (e.g. regrafting) due to poor healing?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	82. At what point is the decision taken to provide secondary surgical intervention (days since initial surgery)?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range
	83. What are the options for secondary surgical intervention? (Is this affected by the initial treatment?)										
	84. How does the second intervention differ from the first (e.g. duration, size of graft, materials used, staff)?										
	85. How long would you expect the wound to take to heal following secondary surgical treatment?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range

Group C: 40% TBSA deep partial thickness or full thickness		Wide meshed SSG		Difference from wide meshed SSG							
				Wide meshed SSG + ReCell		Wide meshed SSG + cultured cells		ReCell alone		ReCell + biosynth. dressing	
	86. What proportion of patients do you expect to develop hypertrophic scars?	Avg	Range	Avg	Range	Avg	Range	Avg	Range	Avg	Range

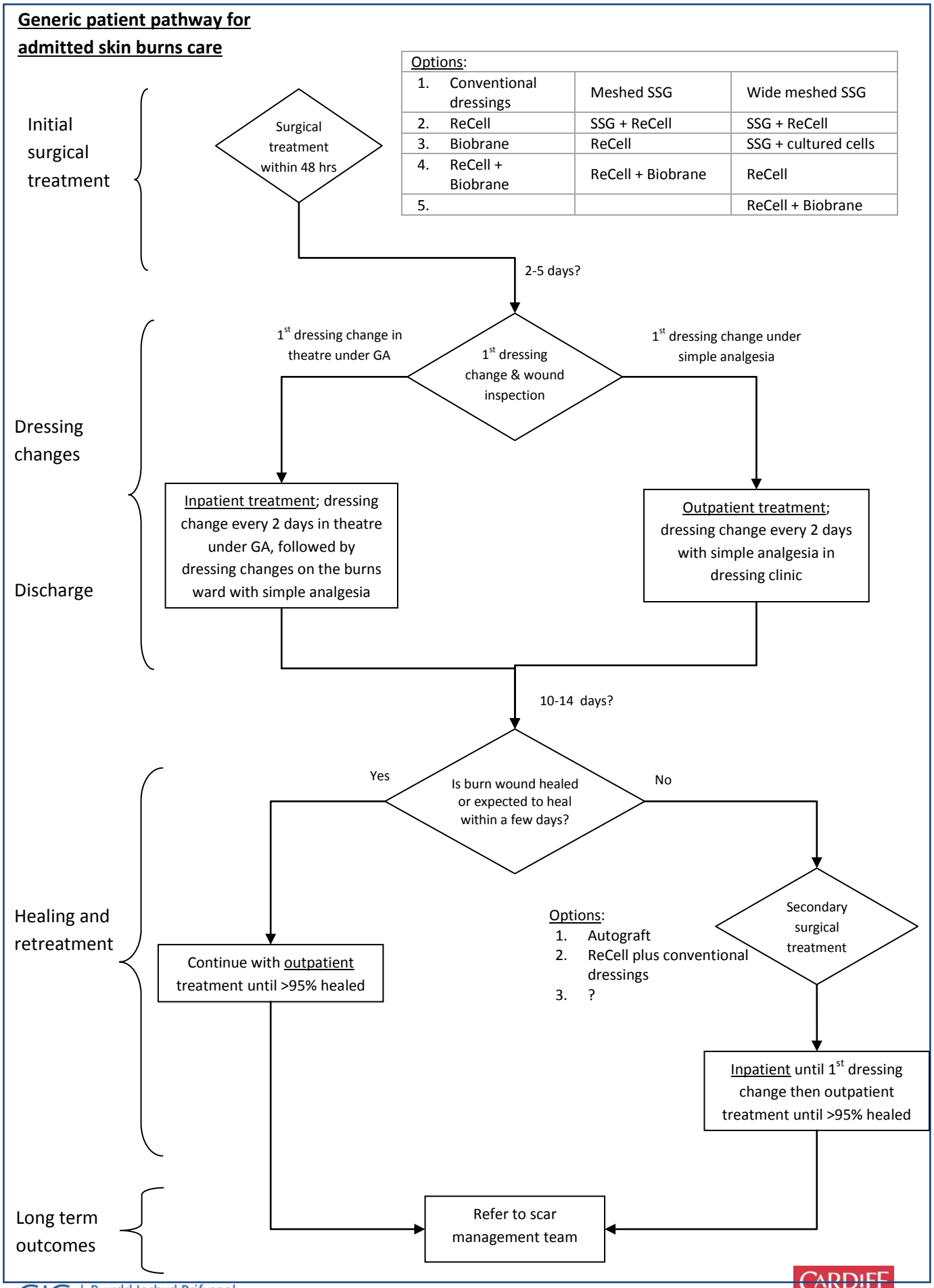
Use of cells	87. What is the upper TBSA limit above which you would not use ReCell on the burn wound?	
	88. What is the lower TBSA limit below which you would not use cultured cells?	
	89. Does the availability of ReCell affect the need for donor sites or their size, e.g. would you use a higher mesh ratio if you have the use of ReCell? If so, can you quantify this?	
	90. How do you use ReCell in these patients? (E.g. primarily over the meshed grafts, primarily on the graft donor sites, only on the donor sites if there is sufficient fluid left, only for certain mesh ratios?)	
	91. Does the use of ReCell affect analgesia requirements for background pain?	
	92. Do you consider that the use of ReCell may have an effect on survival in this patient population?	
Long term scar outcomes	93. Does the use of ReCell improve the appearance and/or function of the eventual scar? If so, how: a. pigmentation outcomes? b. incidence of poor scarring? c. use of conservative scar treatments (creams, compression, steroid injections)? d. requirement for surgical scar revisions?	
	94. Does the use of ReCell affect any other long term outcomes? (E.g. psychological, need for occupational therapy, need for social services support.) If so, how?	

Source	95. Are your answers in general based on personal recall of experience, access to collected data (e.g. local audit or national databases) or other?	

Any additional comments, e.g. on the treatment of this type of patient, on the questions asked or on the use of ReCell.

6 Appendix 2 – generic patient pathway

Generic patient pathway for admitted skin burns care



7 Appendix 3 – expert advisers

Name	Hospital
Jackie Edwards	Wythenshawe Hospital, Manchester
Sian Falder	Alder Hey Hospital, Liverpool
Ian James	Whiston Hospital, Liverpool
Ian Mackie	Frenchay Hospital / Bristol Childrens Hospital
Naiem Moiemen	Queen Elizabeth Hospital, Birmingham
Ciaran O'Boyle	Queens Medical Centre / City Hospital, Nottingham
David Ralston	Sheffield Children's Hospital/Northern General Hospital
Mamta Shah	Royal Manchester Children's Hospital
Paul Stephens	Stoke Mandeville Hospital, Aylesbury
Michael Tyler	Stoke Mandeville Hospital, Aylesbury
Yvonne Wilson	Birmingham Children's Hospital