NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence:

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

Sponsor: Avita Medical Ltd

Date sections A and B submitted:

Date section C submitted:

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Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with 'see appendix X'.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]').Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked 'Response' or in the tables as appropriate. 'Response' text may be deleted.

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List of abbreviations

Abbreviation	Full format
SSG	Split (thickness) skin graft
TBSA	Total body surface area
MKT	Melanocyte-keratinocyte transplantation
RCT	Randomised controlled trial
VAS	Visual analogue scale

All abbreviations are also expressed in full the first time they appear in the text.

Section A – Decision problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1 Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	Adults or children treated in Burns Units or Centres for: a) partial thickness burns including scalds caused by hot water where mesh grafting is not required b) large area burns; full thickness or deep partial thickness burns including where mesh grafting is required	None	
Intervention	a) ReCell Spray-On Skin alone, or in combination with biosynthetic or standard dressings b) Skin mesh graft in combination with ReCell Spray-On Skin	None	
Comparator(s)	a) Partial thickness i. Biosynthetic dressings ii. Standard dressings b) Large area burns i. Skin mesh graft alone ii. Skin mesh graft plus biosynthetic dressing	None	
Outcomes	Both indications i. Speed of healing ii. Number of dressings iii. Length of stay per % total body surface area (TBSA) iv. Wound infection rates v. Scarring: aesthetic and functional outcomes vi. Pigmentation: aesthetic and functional outcomes vii. Re-admission rates for scar management viii. Transfusion rates during skin grafting ix. Number and size of donor sites x. Growth rate in children xi. Surgical procedure and theatre time xii. Device-related adverse events		
Cost analysis	Comparators: a) Partial thickness: ReCell alone vs: i. Biosynthetic dressings		

	ii. Standard dressings b) Large area burns: Skin mesh graft + ReCell vs: i. Skin mesh graft alone ii. Skin mesh graft + biosynthetic dressings Costing from the perspective of the NHS + personal social services Time horizon …… Sensitivity analyses …..		
Subgroups to be considered	None		
Special considerations, including issues related to equality	Effect of ReCell vs skin grafting on colour match in people with darker skin Use of porcine-derived trypsin in ReCell process		

2 Description of technology under assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

ReCell® Spray-On Skin® C3RL01:EU

2.2 What is the principal mechanism of action of the technology?

ReCell is a stand-alone autologous cell harvesting device that enables a thin split-thickness skin biopsy to be processed to produce a mixed cell population for immediate delivery onto a prepared wound surface.

When an injury, such as a burn, results in loss of skin epithelium, healing and re-epithelialisation must proceed from residual cells at the wound edge. This process may take a considerable time and exposes the individual to risks of infection, scarring and hypopigmentation. It is widely acknowledged that a wound that takes in excess of 21 days to heal is more likely to be left with a hypertrophic scar[1]. Split skin grafting (SSG), taking epithelium from healthy skin elsewhere in the body, may speed this process but is limited by the availability of suitable donor sites and is prone to resulting in poor aesthetic outcomes and large donor site scars. Another key issue is the available area for donor sites. If burns are extensive, a mesh graft can be used – this process allows expansion of the grafted skin to cover an area of up to 6 times the original donor area.

An alternative strategy is to culture sheets of keratinocytes from a biopsy of the patient's own skin. This circumvents the problem of available donor skin area, as there is no theoretical limit to the quantity of cells that can be produced. However, cell culture requires specialist laboratory facilities, is expensive and may take several weeks to yield sufficient cells to allow wound closure.

The ReCell device allows a small (up to 4 cm^2), thin (0.15-0.20mm) split thickness shave biopsy to be physically and enzymatically broken down, yielding a viable suspension of mixed keratinocytes, fibroblasts and

melanocytes that can be immediately sprayed or dripped on to the de-epithelialised area. The process is rapid – around 30 minutes – and does not require specialist skills or facilities to carry out. A cell suspension derived from a 1 sq cm biopsy is sufficient to treat an area of around 80 sq cm, making it particularly valuable for patients with limited available healthy donor sites.

The other key advantage of ReCell is the presence of viable melanocytes in the harvested cells. This means that an excellent skin colour match can be achieved. Given that only a small area of biopsy is required (unlike SSG), it is usually not difficult to source this from close to the wound site, thereby optimising the chances of a good aesthetic result.

3 Clinical context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

Although ReCell has been used in a wide range of conditions requiring re-epithelialisation, for the purposes of the current guidance, only the management of burns is considered.

In England in 2011-12 there were 11,830 admissions with a burns-related diagnosis (ICD-10 categories T20.0 – T31.9: excluding corrosions). Of these, 8,744 were classified as emergencies and therefore are likely to reflect admissions for the acute management of flame burns and scalds [2]. Not all of these admissions will have been to specialist Burns Units or Burns Centres, as specified by the scope. Data from the International Burn Injuries Database (IBID) showed that, in 2007 (the most recent year for which data have been published), there were 5,086 qualifying admissions to specialist burns services in England and Wales, in addition to a further 2,837 cases managed as outpatients [3].

Severity of burns – and therefore the modes of treatment adopted – is assessed by a combination of factors related to the burn itself (depth, extent,

location) and the patient (age, comorbidities). Burns severity is an important measure as it is a major determinant of the length of hospital stay, which itself is a key driver of ultimate cost of care.

Mean length of stay by burns severity [3]

- Minor 0.9 days
- Moderate 8.8 days
- Moderate severe 15.3 days
- Severe 13.6 days
- Severe complex 35.2 days

The IBID results show that, out of 27,083 patients with a burn severity recorded over the period 2003-07, 43% were rated as moderate severity, while 17% were moderate severe, severe or severe complex. Patients with minor burns are likely to heal with simple conservative dressing strategies. Those at the higher severity levels (moderate and above) are more likely to be candidates for surgical intervention and therefore are potential users of ReCell.

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

A wide range of potentially relevant sources of clinical guidelines were searched – no pertinent guidance was found:

- NICE – no relevant guidelines
- Scottish Intercollegiate Guidelines Network – no relevant guidelines
- British Burn Association – no relevant guidelines
- European Burn Association - European Practice Guidelines for Burn Care issued in 2002 and updated in 2011[4]. Principally concerned with

service provision standards. No clinical guidance of relevance to this scope

- American Burn Association – Practice Guidelines for Burn Care issued in 2001[5]. Clinical guidance on a range of aspects of burns service provision and principles of care. No relevant content for this scope
- International Society for Burn Injuries – no relevant guidelines

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

We have been unable to identify any published general clinical pathways for the management of burns and the following is therefore based on information provided to us by clinicians involved in the management of burns. Specific treatment strategies will vary considerably according to individual clinical circumstances and the preferences and policies of the individual burns consultants. The strategy outlined here, therefore, should only be regarded as an expression of general principles of care.

Step 1 (0-2 days): Most patients with anything other than minor burns will be taken to theatre for cleaning and assessment of depth of injury under anaesthetic.

- Superficial dermal wounds thought likely to heal without specific intervention will be debrided and dressed according to local protocols (conventional dressing)
- Full-thickness burns will be dermabraded and early SSG applied
- Partial thickness injuries (including those of indeterminate depth) will be cleaned and debrided. Biological dressing (Biobrane) or conventional dressing applied with a view to reassessment at 7-10 days.

Step 2 (2-10 days): Patients generally remain on ward. Conventional dressings usually redressed daily. Depending on age of patient and extent of injury this redressing may be carried out under anaesthetic. In grafted patients, donor sites also actively managed.

Step 3 (10-12 days): Wound reassessed. If insufficient wound healing progress has been made, delayed skin grafting will take place at this stage. In patients with extensive wounds, limitations regarding the extent of available donor sites may mean that coverage has to be achieved in multiple stages once previous donor sites have healed sufficiently to allow further graft tissue to be taken.

Step 4 (3 months – 2 years): Post-discharge scar assessment. Aesthetic and functional status assessed. Remedial surgical intervention including further grafting may be scheduled at this stage to improve texture and colour of the scar.

3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

The use of early grafting varies considerably by unit, especially where wound depth is uncertain. Laser Doppler assessment of depth is used in some units, although practical issues make this technology difficult to implement particularly with young children.

Burn care is highly individualised, based on the characteristics of the injury and the patient themselves. There are often complicating factors. Use of ReCell is a shift towards early intervention which is disruptive to the procedures many surgeons have been undertaking since qualification. For 30 years surgeons have operated one way, now we are recommending another pathway.

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

ReCell can be used at three distinct stages in the burns management process.

For patients with partial thickness burns, or those of indeterminate depth, harvested cells can be applied using ReCell at step 1, in order to maximise the chances of a wound re-epithelialising. This may result in excellent wound healing progress at step 2, or alternatively a lesser area of unhealed wound that requires delayed grafting. If ReCell is applied at step 1, dressings are left undisturbed until the reassessment at step 2. This incurs savings in terms of re-dressing costs and the requirement for associated anaesthetic/analgesics. Additionally, where the patient's condition is otherwise stable and social circumstances permit, a continued stay on the ward is not required and

patients can be discharged, with the 10-12 day reassessment taking place as an outpatient. This is both preferable to the patient and incurs substantial savings. Experience at Pinderfield's Hospital in Wakefield suggests that approximately 60% of patients not requiring early grafting can be treated in this way, with approximately 75% being discharged for subsequent outpatient management [personal communication Mr Jeremy Rawlins].

ReCell can also be used (at step 1 or 2) in combination with conventional mesh grafting for patients with areas of burn injury lacking confluent dermis. Mesh skin grafting involves mechanical perforation of a continuous sheet of harvested skin to result in a net-like appearance. The resulting mesh can then be stretched over the de-epithelialised area, with subsequent healing taking place due to migration of keratinocytes across the small interstices of the mesh. The mesh pattern may be retained in the final scar, yielding a cosmetically compromised result. Expansion of 2-3 times is clinically typical. In circumstances of limited donor availability wider (4:1, 6:1) may be used, which exacerbates the aesthetic issue and increases risk of graft loss/failure. By using ReCell to spray harvested autologous epithelial cells over the mesh network at the time of application, a thinner graft may be taken without incurring the usual additional risk of graft failure. The combination of thin graft and cell suspension together mitigate the persistence of the mesh-pattern scar, and also enables more routine use of widely meshed graft (and corresponding decrease to donor site area and morbidity).

Use of ReCell results in newly formed epithelium that can require up to approximately two weeks from initial closure to become mature and robust. This must be accounted for in the planning of post-operative care in terms of staff and patient education. Generally, this poses no cause for concern, however if there are clinical concerns relating to the patient's understanding of the post-operative care needed for a ReCell-treated burn injury area and the need for protecting the area from insult while the new skin matures, the short-term risk of re-injury may be mitigated by temporarily increasing use of protective dressings or by proactively combining ReCell with conventional graft (versus ReCell alone) in those areas which may be susceptible to

contact injury due to size or location (e.g. distal extremities, joints) and anticipated patient activity.

Thirdly, at step 4, where the healed scar is hypertrophic or hypopigmented, dermabrasion and application of colour-matched epithelial cells using ReCell can improve the final aesthetic result.

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

Earlier patient discharge will result in less need for nursing care on the wards. The number of dressing changes will also be reduced and performed in outpatients instead of inpatients. Training of the nursing team will be required to ensure they do not continue to change dressings on a daily basis as with other burn treatment options, and that appropriate care is taken of the newly regenerated skin whilst it fully matures.

The cell separation process using ReCell takes around 30 minutes once the skin biopsy has been taken. When use of ReCell is first put into practice, the procedure will add time to the surgery, however as surgical teams become more experienced with ReCell, the procedure will be incorporated in a parallel fashion with minimal impact on surgical time. In fact, once established, use of ReCell alone (in place of mesh skin grafting, as appropriate) saves on the length of time in surgery which has been shown as an independent predictor of length of stay[6].

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

None.

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

None

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

It is unlikely that ReCell will completely remove the need for any related technologies, although where cell culture facilities are currently used, it is possible that these can be scaled down.

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

Where cell culture is used, these are normally provided by commercial providers on a per patient basis. A reduction in use would therefore result in a simple decline in demand for this service, with no formal disinvestment strategy required.

4 Regulatory information

4.1 Provide PDF copies of the following documents:

- instructions for use
- CE mark certificate or equivalent UK regulatory approval such as EC declaration of conformity
- quality systems (ISO 13485) certificate (if required).

PDF copies of these documents should be submitted at the same time as section A.

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes. Authorisation under Directive 93/42/EEC on medical devices, Annex II (excluding Section 4) granted on 18 March 2005. Current certificate valid until 23 January 2017

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

Currently approved for use in: Australia, Canada, China, Croatia, European Member States, Hong Kong, Israel, Kuwait, Macau, New Zealand, Poland, Switzerland, Singapore, Taiwan and Turkey

4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

n/a

4.5 If the technology has been launched in the UK provide information on the use in England.

ReCell is widely used within the NHS in both burns units and plastic surgery departments. The English centres with the greatest use are:

- Chelsea and Westminster Hospital, London – Burns and Plastics
- Guy's and St Thomas' Hospital, London - Plastics
- Broomfield Hospital, Chelmsford– Burns and Plastics
- Pinderfields Hospital, Wakefield– Burns and Plastics
- Queen Elizabeth Hospital Birmingham and Birmingham Children's Hospital – Burns and Plastics
- Nottingham University Hospitals, Nottingham – Burns and Plastics
- Frenchay Hospital, Bristol – Burns and Plastics
- Alderhey Children's Hospital, Liverpool – Burns and Plastics

5 Ongoing studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

A study of ReCell Spray-On Skin for restoration of pigment in hypopigmented burn scars. Randomised controlled study (pilot), 20 patients, expected completion date is May 2014. Primary objective is to assess repigmentation with ReCell versus control at 3 and 6 months. Secondary objective, patient satisfaction levels.

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

We are not aware of any other planned assessments

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

Skin grafting in people with darker skin may result in a poorer colour match in the grafted area compared with normal skin. The ReCell Spray-On Skin system may result in better colour matching of the resulting skin.

The trypsin enzyme used to disaggregate the skin cells from the biopsy during the ReCell process is derived from pigs. This means that the treatment may be unacceptable to people from religious and cultural backgrounds that forbid contact with porcine material.

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

None known

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

The issue of skin pigmentation is an important aspect of the assessment of the aesthetic result of burns wound treatment. As ReCell is able to ameliorate this problem, it will be fully addressed in the submission.

The issue of porcine origin of biological elements that are integral to ReCell is well recognised. Biological dressings such as Biobrane – the other treatment modality specifically mentioned in the scope – also has porcine components and is therefore subject to the same limitation. We have spoken to consultants using both ReCell and Biobrane and we understand that individual patients and their families, once made aware of the situation, are comfortable making their own decision as to both products' use that is acceptable to their beliefs. We do not feel that formal NICE guidance on this issue is either practical or desirable and therefore we have not addressed it further in our submission.

Section B – Clinical evidence

7 Published and unpublished clinical evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of studies

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in section 10, appendix 1.

Search sources

The following sources were used:

- Electronic databases: MEDLINE (including Medline In Process); EMBASE; Cochrane Library. Detailed search strategy listed in section 10, appendix 1.
- Manufacturer's database of known research projects.

- Hand search of abstracts lists for burns-related conferences over the past 5 years: British Burn Association; European Burn Association; American Burn Association; International Society for Burn Injuries.
- Hand search of reference lists from studies identified in the previous searches.

Search terms:

For the electronic database searches, the following strategy was used, suitably adapted to suit each database. The strategy was kept deliberately broad, as it was expected that the number of qualifying studies would be small, and therefore relatively easy to filter manually:

Burns [Subject Heading] OR (Burn* [Textword] OR Scald* [Textword])

AND

ReCell [Textword] OR (Autologous NEAR Cell NEAR Harvest*) [Textwords]

Time frame:

ReCell was developed in the late 1990s but its use has only become widespread over the past 5 years. In order to capture all possible publications, a time limit of 1995-present was used for all databases.

Subsidiary literature search – skin pigmentation

As one of the key claimed benefits of ReCell is its ability to yield an improved skin colour match compared with conventional treatments, a subsidiary literature search was carried out to identify published data specifically relating to the effect of ReCell on skin pigmentation. For this search, studies in clinical areas other than burns were included, in order to capture this element adequately. Although these studies fall outside the scope, we believe that this information is relevant to burns patients and is therefore worth capturing.

Search sources

The following sources were used:

- Electronic databases: MEDLINE (including Medline In Process); EMBASE; Cochrane Library. Detailed search strategy listed in section 10, appendix 1.
- Manufacturer's database of known research projects.
- Hand search of reference lists from studies identified in the previous searches.

Search terms:

For the electronic database searches, the following strategy was used, suitably adapted to suit each database:

Hypopigmentation [Subject Heading] OR Vitiligo [Subject Heading]

AND

ReCell [Textword] OR (Autologous NEAR Cell NEAR Harvest*) [Textwords]

Time frame: 1995 to present

Unpublished studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Search sources:

- Manufacturer's database of known research projects.
- Personal contact with researchers responsible for meeting abstracts identified in the search for published studies

As electronic databases were not involved, no formal search strategy was required

7.2 Study selection

Published studies

7.2.1 Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B1a Selection criteria used for published studies

Inclusion criteria	
Population	Adults and children undergoing treatment for flame burns and scalds
Interventions	Autologous skin cell harvesting (ReCell) used either alone or in combination with other treatments
Outcomes	i. Speed of healing ii. Number of dressings iii. Length of stay per % TBSA iv. Wound infection rates v. Scarring: aesthetic and functional outcomes vi. Pigmentation: aesthetic and functional outcomes vii. Re-admission rates for scar management viii. Transfusion rates during skin grafting ix. Number and size of donor sites x. Growth rate in children xi. Surgical procedure and theatre time xii. Device-related adverse events xiii. Analgesic/anaesthetic use xiv. Other resource utilisation outcomes not specified above xv. Other patient-relevant outcomes not specified above
Study design	Systematic reviews with quantitative outcomes, Randomised controlled trials, non-randomised observational studies, comparative or non-comparative case series
Language restrictions	Any language
Search dates	1995 - 2013
Exclusion criteria	
Population	Patients undergoing treatment for indications other than flame burns or scalds
Interventions	Treatments not involving autologous skin cell harvesting
Outcomes	None explicitly excluded
Study design	Narrative reviews not including direct patient effectiveness data, single patient case reports, animal studies, in vitro studies
Language restrictions	None
Search dates	Pre 1995

7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure 1: PRISMA diagram for main search - burns

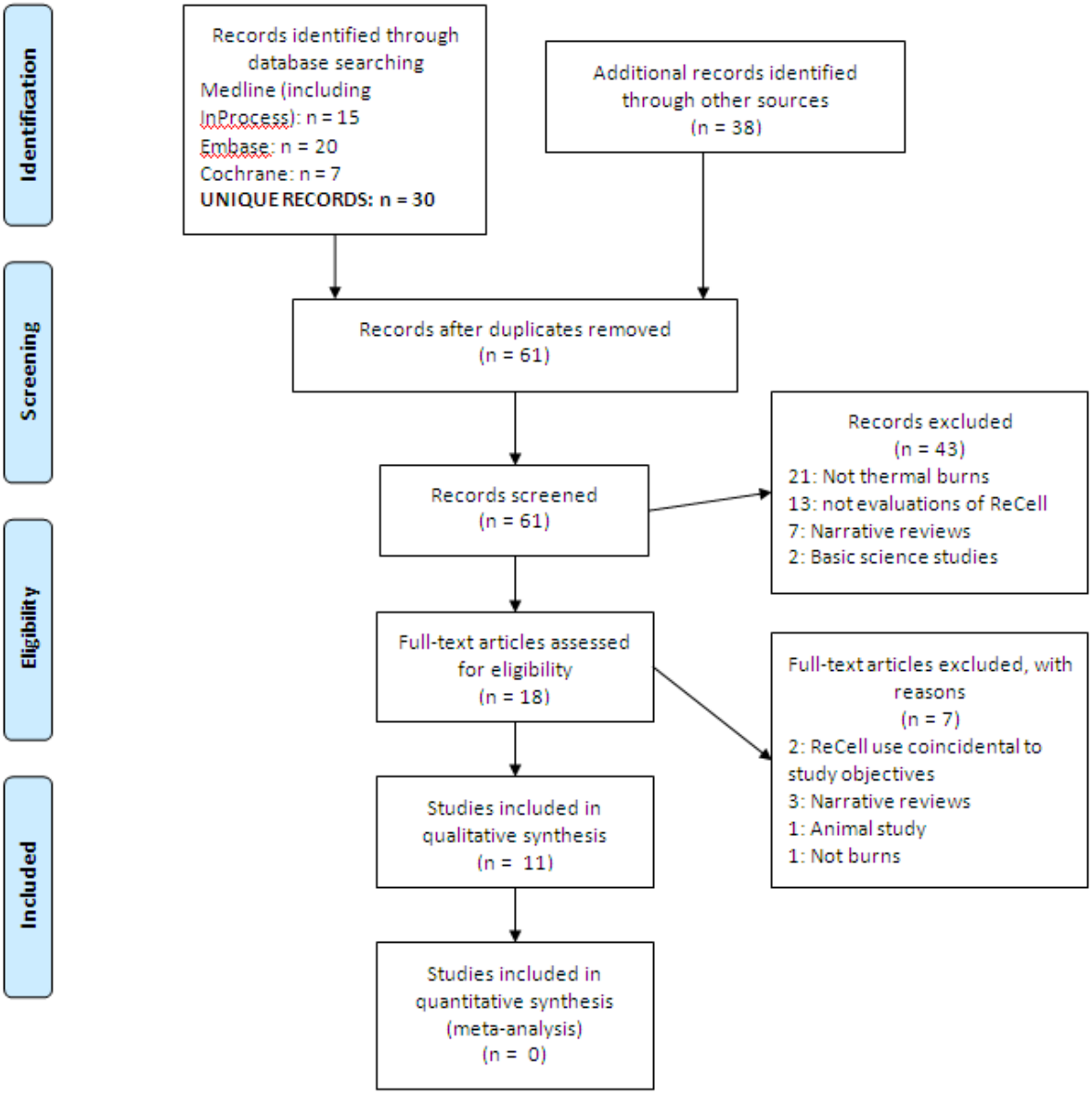


Table B1b Selection criteria used for published studies (subsidiary search)

Inclusion criteria	
Population	Adults and children undergoing treatment with ReCell for any reason
Interventions	Autologous skin cell harvesting (ReCell) used either alone or in combination with other treatments
Outcomes	Effect of treatment on pigmentation
Study design	Systematic reviews with quantitative outcomes, Randomised controlled trials, non-randomised observational studies, comparative or non-comparative case series.
Language restrictions	Any language
Search dates	1995 - 2013
Exclusion criteria	
Population	None
Interventions	Treatments not involving autologous skin cell harvesting
Outcomes	Anything other than effect on pigmentation
Study design	Narrative reviews not including direct patient effectiveness data, single patient case reports, animal studies, in vitro studies
Language restrictions	None
Search dates	Pre 1995

Figure 2: PRISMA diagram for subsidiary search – hypopigmentation

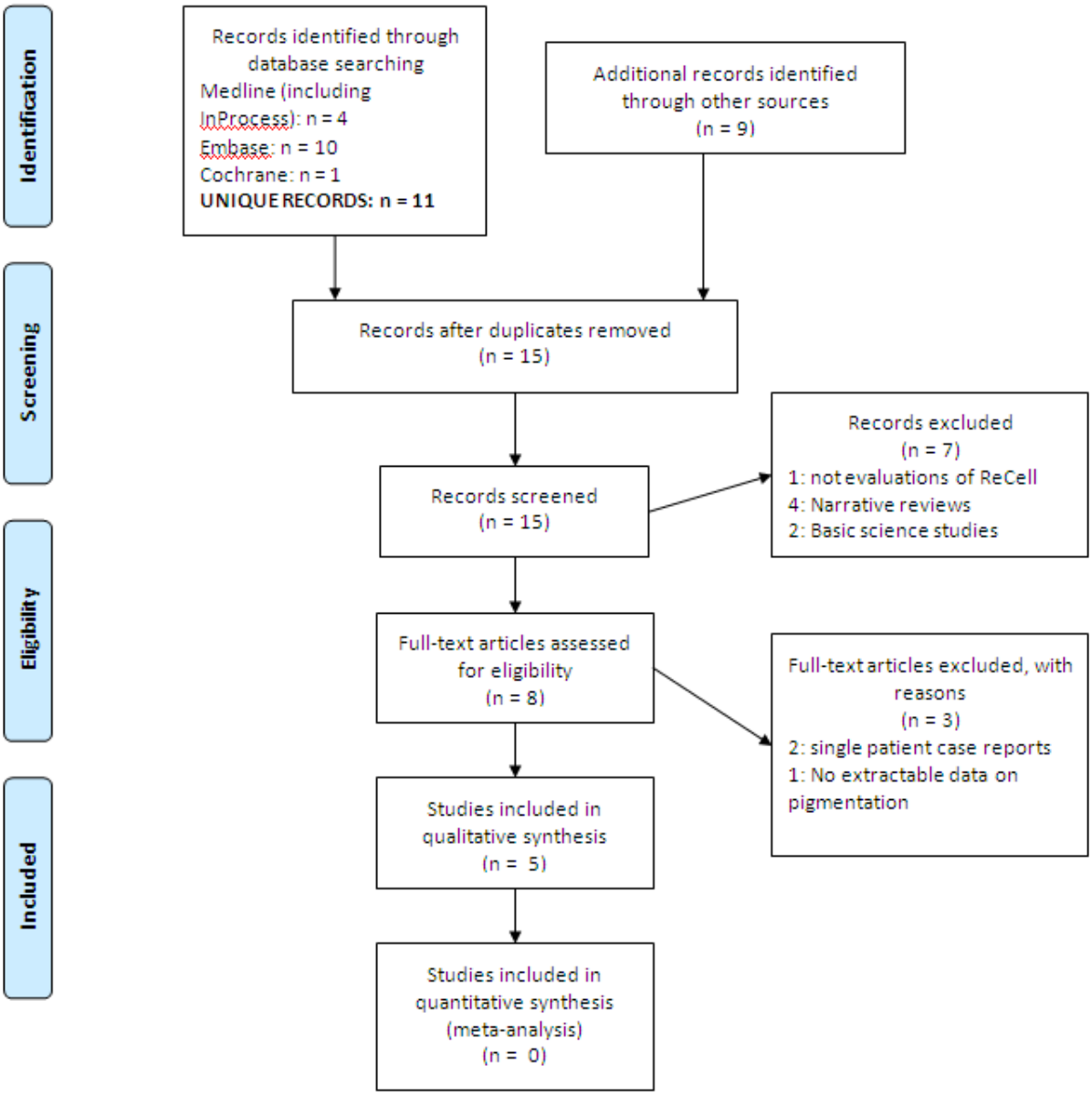


Table B2 Selection criteria used for unpublished studies

Inclusion criteria	
Population	Adults and children undergoing treatment for flame burns and scalds
Interventions	Autologous skin cell harvesting (ReCell) used either alone or in combination with other treatments
Outcomes	i. Speed of healing ii. Number of dressings iii. Length of stay per % TBSA iv. Wound infection rates v. Scarring: aesthetic and functional outcomes vi. Pigmentation: aesthetic and functional outcomes vii. Re-admission rates for scar management viii. Transfusion rates during skin grafting ix. Number and size of donor sites x. Growth rate in children xi. Surgical procedure and theatre time xii. Device-related adverse events xiii. Analgesic/anaesthetic use xiv. Other resource utilisation outcomes not specified above xv. Other patient-relevant outcomes not specified above
Study design	Systematic reviews with quantitative outcomes, Randomised controlled trials, non-randomised observational studies, comparative or non-comparative case series.
Language restrictions	Any language
Search dates	1995 - 2013
Exclusion criteria	
Population	Patients undergoing treatment for indications other than flame burns or scalds
Interventions	Treatments not involving autologous skin cell harvesting
Outcomes	None explicitly excluded
Study design	Narrative reviews not including direct patient effectiveness data, single patient case reports, animal studies, in vitro studies
Language restrictions	None
Search dates	Pre 1995

7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

One unpublished abstract of case series was identified within the main burns indication.

One unpublished manuscript of a case series was identified for the hypopigmentation subsidiary search.

7.3 Complete list of relevant studies

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables B1 and B2.

Table B3 List of relevant published studies

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Gravante 2007 [7]		Adults with deep partial thickness burns	ReCell	Split thickness skin graft (SSG)
Wood 2012 [8]		Children with scalds	ReCell + Biobrane	Biobrane
Park 2013 [9]		Patients undergoing surgery for burns	Multivariate regression analysis: Use of ReCell, SSG and SSG+ReCell explored as covariates	
Dunne 2012 [10]		Children with scalds	ReCell + Biobrane	1. Biobrane 2. SSG
Rawlins 2013 [11]		Children with burns	ReCell	SSG
Rawlins 2011 [12]		Adults with deep flame burns	ReCell + Biobrane	SSG
Echlin 2012a [13]		Patients with deep partial thickness burns of face	ReCell after failed SSG	No comparator
Echlin 2012b [14]		Burns patients with SSG donor sites at risk of poor healing	ReCell	No comparator
Palombo 2012 [15]		Children with scarring following scalds	ReCell	No comparator
Sen 2012 [16]		Patients requiring dermal grafts after initial SSG	ReCell with dermal graft	No comparator
De Angelis 2009 [17]		Mixed group of patients including acute burns patients	ReCell	Unclear
Subsidiary search: hypopigmentation				
Cervelli 2009a [18]		Mixed group of patients with dyspigmented or hypertrophic scars	ReCell	No comparator
Cervelli 2009b [19]		Patients with stable vitiligo	ReCell	No comparator
Mulekar 2008[20]		Patients with stable vitiligo	ReCell	Melanocyte-keratinocyte transplant
Daniel 2011		Patients with stable	ReCell	Minigrafting

[21]		vitiligo		

*Studies identified with highlighting indicate that this paper directly relates to the comparisons defined in the decision problem.

Table B4 List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator
Philp 2013 abstract submitted [22]		Patients requiring dermal graft after SSG	ReCell with dermal graft	No comparator
Cui 2013 working manuscript [23]		Patients with dyspigmented scars from burns, trauma and surgery	ReCell	No comparator

7.3.2 State the rationale behind excluding any of the published studies listed in tables B3 and B4.

De Angelis 2009 [17] (table B3) was excluded on the grounds that insufficient data were available in the abstract on both methods and results to draw meaningful conclusions. Having contacted the original authors it was established that the study had never been fully published and that the data was not available to use. It was therefore decided to exclude the study.

7.4 Summary of methodology of relevant studies

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

Table B5a Summary of methodology for randomised controlled trials

Study name	**Gravante 2007** [7]
Objectives	Comparison of split thickness skin grafting (SSG) with ReCell in adults with deep partial thickness burns
Location	Burns centre, S. Eugenio Hospital in Rome, Italy
Design	Randomised controlled part-blinded trial
Duration of study	Two year study with 6 months follow-up for each

	participant
Sample size	100 enrolled; 82 randomised
Inclusion criteria	Adults with deep partial thickness burns Requirement for surgical debridement and epidermal replacement Maximum burn size 320 sq cm
Exclusion criteria	Pre-existing local or systemic infection Pre-existing medical conditions that would interfere with healing: eg diabetes, malignancy, autoimmune disease Renal failure (GFR<60ml/min) Medications that would interfere with wound healing Antibiotics (non-prophylactic) for more than 48 hours prior to treatment Hypersensitivity to trypsin or Hartmann's solution High anaesthetic risk necessitating postponement of surgery
Method of randomisation	Allocated according to controlled-sampling chart to ensure homogeneity between groups for age, gender, type of burns and total bone surface area (TBSA)
Method of blinding	Part-blinded study Blinding of surgeon and patient not possible owing to distinct nature of procedures Assessment of aesthetic result carried out by independent clinician unaware of treatment allocation
Intervention(s) (n =) and comparator(s) (n =)	ReCell: n = 42 SSG: n = 40
Baseline differences	No significant differences in terms of age, gender, height, weight, burns area treated or concomitant disease prevalence
Duration of follow-up, lost to follow-up information	All patients followed up for at least six months. None lost to follow-up.
Statistical tests	Descriptive statistics for continuous quantitative variables by mean and standard deviation, following normality testing. Between-groups comparison by Student's t-testing apart from the area of skin harvested, which was compared using Mann-Whitney test, as variances were unequal. Descriptive statistics for qualitative categorical variables by frequencies, with chi-squared test and Fisher's exact test being used for comparison All p-values considered significant if <0.05
Primary outcomes (including scoring methods and timings of assessments)	a) Time for complete epithelialisation of both treated and biopsy site (days): Patients assessed by clinician at 1, 2, 3 and 4 weeks b) Aesthetic and functional quality of the epithelialisation using simplified version of the Vancouver scar scale and active and passive range of movements across relevant affected

	joints: Patients assessed at 3 and 6 months. Final measure reported.
Secondary outcomes (including scoring methods and timings of assessments)	Skin area harvested (sq cm): Assessed by clinician at time of procedure Skin area treated (sq cm): Assessed by clinician at time of procedure Duration of procedure (min): Assessed by clinician at time of procedure Post-operative pain (visual analogue scale): Time of assessment not specified Adverse events (including infections/inflammation): assessed throughout follow-up period

Table B5b Summary of methodology for randomised controlled trials

Study name	**Wood 2012** [8]
Objectives	Pilot study to compare Biobrane alone, Biobrane + ReCell and standard dressings in children with scald injuries
Location	Royal Perth Hospital, Perth, Australia
Design	Randomised controlled trial
Duration of study	One year study with 6 months follow-up for each participant
Sample size	13 patients
Inclusion criteria	Children with scald injury Minimum TBSA 2% Anticipated not to heal spontaneously within 10 days and therefore eligible for surgery
Exclusion criteria	Wound not initially dressed according to protocol (Acticoat + Duoderm) Unsuitable for anaesthetic at 48 hours post injury Known contraindications, allergies or sensitivities to dressing products used in the trial Late presentations No informed consent Declined to participate
Method of randomisation	Sealed, opaque, identical, serially numbered envelopes prepared by an independent third party
Method of blinding	No formal blinding of study. Check assessment of wound healing carried out by blinded third party. Process outcomes derived retrospectively from hospital database
Intervention(s) (n =) and comparator(s) (n =)	Standard treatment: n = 4 Biobrane alone: n = 4 Biobrane + ReCell: n = 5
Baseline differences	Generally similar. Patients in the Biobrane + ReCell

	group were younger than those in the other two groups (mean 1.3 vs 5.0). Scald size was larger in the Biobrane alone group (mean TBSA 8% vs 4.5% vs 5.2%). Small number meant that statistical significance could not be meaningfully estimated)
Duration of follow-up, lost to follow-up information	Intended follow-up was 6 months. 1 patient in the Biobrane + ReCell arm lost to follow-up after 6 weeks, so not included in long term assessments.
Statistical tests	Descriptive analyses only, owing to small sample size. Data presented as either mean + sd or median + IQR for continuous variables or number (%) for binary outcomes.
Primary outcomes (including scoring methods and timings of assessments)	Proportion of patients undergoing surgery 10 days post randomisation. Decision to operate made on clinical grounds and recorded as a binary measure (yes/no)
Secondary outcomes (including scoring methods and timings of assessments)	Time to healing: number of days post-burn until dressings no longer required (clinical assessment) Healing rate: Digital objective wound size assessment (Visitrak) carried out at 2, 10 and 21 days post burn. Results at 10 and 21 days expressed as % healing relative to 2 day baseline reading Total length of hospital stay: Based on all episodes of in-patient care, including both index and re-admissions, over the 6 months following the burn Pain at dressing changes: assessed using age-appropriate assessment tool (CHIPPS for age < 2 years, FLACC for age 2-7, Revised Faces Pain Scale for age 8+) Resource utilisation: Dressing costs, analgesic costs, theatre costs, overall admission costs, scar management costs Long term scar outcomes assessed at 6 months using Vancouver Scar scale

Table B5c Summary of methodology for randomised controlled trials

Study name	**Daniel 2011 (Abstract)** [21]
Objectives	Pilot study to compare ReCell with minigrafting in patients with stable vitiligo
Location	St George Hospital, Sydney, Australia
Design	Randomised controlled trial with intra-patient controls (paired lesions in each patient randomised for treatment)
Duration of study	12 months
Sample size	14 patients (interim report)
Inclusion criteria	Not stated in abstract
Exclusion criteria	Not stated in abstract

Method of randomisation	Not stated in abstract
Method of blinding	Pre- and post-procedure photographs assessed by independent blinded investigator
Intervention(s) (n =) and comparator(s) (n =)	Intra-patient control, therefore both treatments used in all 14 patients
Baseline differences	Thanks to internal control, there should be perfect matching
Duration of follow-up, lost to follow-up information	Primary outcome assessed at 12 months. No losses to follow-up
Statistical tests	No statistical analysis given in abstract
Primary outcomes (including scoring methods and timings of assessments)	Percentage pigmentation at 12 months for each treatment. Assessed by direct measurement of photographs
Secondary outcomes (including scoring methods and timings of assessments)	Percentage pigmentation at 3 and 6 months Cosmetic outcome of donor and recipient sites, assessed by investigators and subjects

Table B6a Summary of methodology for observational studies

Study name	**Park 2013** [9]
Objective	Assess impact of skin replacement technique used on risk of infection, graft failure and length of hospital stay
Location	Royal Perth Hospital, Perth, Australia
Design	Retrospective multiple regression analysis
Duration of study	8 years
Patient population	All burns patients treated with surgical re-epithelialisation between 2004-11
Sample size	770 patients
Inclusion criteria	Patients undergoing surgical treatment for burns (SSG or other skin replacement surgery)
Exclusion criteria	Patients confirmed to have burn wound infection or community acquired infection on admission or in the pre-surgical period Admissions for subsequent surgery for reconstruction or scar revision Patients with positive sputum, urine or blood microbiology culture
Intervention(s) (n =) and comparator(s) (n =)	SSG alone: n = 387 ReCell alone: n = 73 SSG + ReCell: n = 264 Cultured epithelial cells +/- SSG: n = 46
Baseline differences	Treatment allocation reflected clinician view at the time of admission and was not randomised. However, as the primary analysis was a multiple regression, relevant

	baseline differences will have been corrected for in the results
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Hospital records (RPH Burns Minimum Dataset) accessed to ascertain details of in-hospital wound infections, graft loss and length of stay. Longer term outcomes not presented in this analysis
Statistical tests	Multivariate logistic regression analysis
Primary outcome (including scoring methods and timings of assessments)	Risk of burn wound infection, defined as the frequency of a confirmed infection in the post-surgical period that was not present prior to surgery. Diagnosis was defined by the presence of greater than 100,000 bacteria on wound swabs taken at the time of dressing change (or when indicated clinically)
Secondary outcomes	Frequency of graft loss in the post-operative period – binary assessment (yes/no) as assessed by clinician Length of hospital stay (days) for the index admission

Table B6b Summary of methodology for observational studies

Study name	**Dunne 2012 (Abstract)** [10]
Objective	Evaluation of a dynamic treatment algorithm for paediatric scalds, escalating from Biobrane alone, to Biobrane + ReCell to early SSG according to burn depth
Location	Pinderfields General Hospital, Wakefield, UK
Design	Descriptive case series
Duration of study	18 months approx
Patient population	All paediatric scalds patients admitted to the burns unit
Sample size	40 patients
Inclusion criteria	Children with scalds, suitable for surgical management
Exclusion criteria	Injuries considered likely to heal spontaneously
Intervention(s) (n =) and comparator(s) (n =)	Superficial dermal burn: clean/debridement + Biobrane (n = 20) Mid and deep dermal burn: clean/dermabrasion + ReCell + Biobrane (n = 13) Full thickness: clean/dermabrasion + early split skin graft (n = 7)
Baseline differences	Treatments allocated according to depth of wound, therefore groups not equivalent
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of	Standard follow-up in accordance with burns centre policy and individual clinical need

follow-up, participants lost to follow-up	
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Length of stay Requirement for skin grafting Long term scar assessment Speed of wound healing Donor site morbidity Analgesic requirement Dressing costs Details of scoring methods and timings not described

Table B6c Summary of methodology for observational studies

Study name	**Rawlins 2013 (Abstract)**[11]
Objective	Comparison of ReCell and split-thickness skin grafts (SSG) in management of paediatric burns
Location	Pinderfields General Hospital, Wakefield, UK
Design	Descriptive case series
Duration of study	12 months
Patient population	All paediatric burns patients admitted to the burns unit requiring surgical intervention
Sample size	26 patients
Inclusion criteria	Burns requiring surgical intervention
Exclusion criteria	None described
Intervention(s) (n =) and comparator(s) (n =)	SSG: n = 15 ReCell: n = 11
Baseline differences	Patients allocated according to consultant preference. TBSA geater in the ReCell cohort compared with SSG (mean 6.5% vs 2.9%)
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Standard follow-up in accordance with burns centre policy and individual clinical need. Formal wound assessment made at 4 months post-injury
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Visual analogue scale of burns healing assessed by 5 independent clinicians based on pictures taken 4 months post injury (Range: 0=normal skin – 10=poor scar) Operative time Requirement for physiotherapy

	Incidence of wound infection

Table B6d Summary of methodology for observational studies

Study name	**Rawlins 2011 (Abstract)** [12]
Objective	Comparison of ReCell + Biobrane and split-thickness skin grafts (SSG) for deep flame burns
Location	Pinderfields General Hospital, Wakefield, UK
Design	Descriptive case series
Duration of study	Not stated
Patient population	Patients aged 17-59 undergoing surgical treatment of deep flame burns 48-72 hours post injury
Sample size	15 patients
Inclusion criteria	Not specified
Exclusion criteria	Not specified
Intervention(s) (n =) and comparator(s) (n =)	SSG: n = 10 ReCell: n = 5
Baseline differences	Mean TBSA 15%. No differences between ReCell and SSG groups described
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Standard follow-up in accordance with burns centre policy and individual clinical need. Formal wound assessment made at 6 months post-injury
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Time to wound healing Analgesia requirements Vancouver scar assessment at 6 months

Table B6e Summary of methodology for observational studies

Study name	**Echlin 2012a (Abstract)** [13]
Objective	Use of ReCell on patients with deep partial thickness burns of face
Location	Chelsea & Westminster Hospital, London, UK
Design	Descriptive case series
Duration of study	Not stated
Patient population	Patients with mid to deep dermal scalds or flame burns of the whole face
Sample size	5 patients

Inclusion criteria	Patients initially treated with allograft and when assessed at 9-11 days considered unlikely to heal within 21 days
Exclusion criteria	Not specified
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: all treated with ReCell
Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Assessed for adequacy of healing over 7 days post-operatively
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Time to wound healing

Table B6f Summary of methodology for observational studies

Study name	**Echlin 2012b (Abstract)** [14]
Objective	Use of ReCell on skin graft donor sites in burns patients
Location	Chelsea & Westminster Hospital, London, UK
Design	Descriptive case series
Duration of study	Not stated
Patient population	Patients with SSG donor sites that were either extensive or considered at risk of delayed healing
Sample size	11 sites on 9 patients
Inclusion criteria	Patients at risk of delayed healing of donor site Patients with large burns which would require multiple grafting from the same donor site
Exclusion criteria	Not specified
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: all treated with ReCell
Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Standard care over duration of healing process up to 29 days
Statistical tests	None

Primary outcomes (including scoring methods and timings of assessments)	Time to wound healing

Table B6g Summary of methodology for observational studies

Study name	**Palombo 2012 (Abstract)** [15]
Objective	Use of ReCell in children with burns scarring
Location	S Eugenio Hospital, Rome, Italy
Design	Descriptive case series
Duration of study	Not stated
Patient population	Children with scarring following scalds
Sample size	6 patients
Inclusion criteria	Children with hypertrophic scarring causing aesthetic or functional problems
Exclusion criteria	Not specified
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: all treated with ReCell
Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Standard follow-up over 3 months post-procedure
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Time to wound healing Skin pigmentation at 3 months Scar texture at 3 months

Table B6h Summary of methodology for observational studies

Study name	**Sen 2012 (Abstract)** [16]
Objective	Use of ReCell with split thickness dermal graft in patients with extensive burns
Location	The St. Andrew's Centre for Burns and Plastic Surgery, Chelmsford, UK
Design	Descriptive case series
Duration of study	Not stated
Patient population	Patients with extensive burns requiring dermal grafts after initial conventional SSGs

Sample size	5 patients
Inclusion criteria	Patients with burns >50% TBSA All possible donor sites already used for SSG
Exclusion criteria	Not specified
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: split thickness dermal graft taken from base of SSG donor site. Both donor and recipient sites treated with ReCell
Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Short term report on healing
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Time to wound healing assessed by two independent observers

Table B6i Summary of methodology for observational studies

Study name	**Cervelli 2009a** [18]
Objective	Evaluation of ReCell in patients with hypopigmented post-traumatic scarring
Location	University Tot Vergata, Rome, Italy
Design	Descriptive case series
Duration of study	2 years. Minimum individual follow-up 1 year
Patient population	White adults with dyspigmented or hypertrophic scars unresponsive to previous treatments
Sample size	30 patients
Inclusion criteria	Age 20-50 White ethnicity: skin phototypes II or III Non-smoking Post traumatic scars resistant to previous treatments Affected area <320sq cm
Exclusion criteria	Presence of local or systemic infection Medical conditions or medication that could interfere with healing Use of antibiotics for >48hrs pre procedure Hypersensitvity to trypsin or Hartmann's solution High anaesthetic risk
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: All scars treated with ReCell

Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Active follow-up weekly for 1 month, then at months 3,6,12 and 24. Data for all patients available to 12 months. None lost to follow-up
Statistical tests	Descriptive data only
Primary outcomes (including scoring methods and timings of assessments)	1. Time for complete epithelialisation – assessed by clinician 2. Aesthetic and functional qualities of new scar – assessed by clinician, patient and family using modified Vancouver Scar scale

Table B6j Summary of methodology for observational studies

Study name	**Cervelli 2009b** [19]
Objective	Evaluation of ReCell in patients with stable vitiligo
Location	University Tot Vergata, Rome, Italy
Design	Descriptive case series
Duration of study	1 year. Minimum individual follow-up 6 months
Patient population	Adults and adolescents with stable vitiligo
Sample size	15 patients
Inclusion criteria	Age 10+ Stable vitiligo with no progression in past year Affected area <320sq cm
Exclusion criteria	Extensive depigmentation Concomitant serious systemic disease Keloidal or bleeding tendency
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: All patients treated with ReCell
Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Photographs used to document pigmentation pre-surgery and at 1, 3 and 6 months post surgery
Statistical tests	Descriptive data only
Primary outcomes (including scoring	1. Repigmentation assessed using visual analogue scale and 6-point ordinal global assessment.

methods and timings of assessments)	Both assessments carried out by both clinician and patient 2. Overall cosmetic result using four point ordinal scale carried out by clinician, patient, family members and close friends

Table B6k Summary of methodology for observational studies

Study name	**Mulekar 2008** [20]
Objective	Evaluation of ReCell in patients with stable vitiligo
Location	National Centre for Vitiligo and Psoriasis, Riyadh, Saudi Arabia
Design	Comparative case series
Duration of study	4 months
Patient population	Adults with stable vitiligo
Sample size	5 patients
Inclusion criteria	Patients with stable vitiligo At least two lesions in the same anatomical location
Exclusion criteria	None specified
Intervention(s) (n =) and comparator(s) (n =)	Internally controlled by paired lesions: All patients (n=5) treated with both ReCell and melanocyte-keratinocyte transplantation
Baseline differences	None
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	All patients attended for lesion photography at baseline and 4 months. No losses to follow-up
Statistical tests	Descriptive data only
Primary outcomes (including scoring methods and timings of assessments)	Percentage area of repigmentation in test lesions at four months compared to pre-surgery. Assessed using direct measurement of photographs by two independent clinicians.

Table B6l Summary of methodology for observational studies

Study name	**Cui 2013 (Draft manuscript)** [23]
Objective	Evaluation of ReCell in patients with dyspigmented scars
Location	Peking Union Medical College Hospital, Beijing, China

Design	Descriptive case series
Duration of study	12 months
Patient population	Adults and adolescents with dyspigmented scars due to injury, disease or surgery
Sample size	12 patients (9 following burns)
Inclusion criteria	Age 15-50 Chinese Non-smoking Dyspigmented scar Affected area <320sq cm
Exclusion criteria	Presence of local or systemic infection Medical conditions or medication that could interfere with healing Use of antibiotics for >48hrs pre procedure Hypersensitvity to trypsin or Hartmann's solution High anaesthetic risk
Intervention(s) (n =) and comparator(s) (n =)	No comparative: all patients received ReCell
Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Active follow-up weekly for 1 month, then at months 3,6 and12. Photographs taken at each visit. Data for all patients available to 12 months. None lost to follow-up
Statistical tests	Descriptive data only
Primary outcomes (including scoring methods and timings of assessments)	Qualitative assessment of pigmentation assessed at 12 months using modified Vancouver Scar Scale. Assessment carried out by both patient and clinician

Table B6m Summary of methodology for observational studies

Study name	**Philp 2013 (Submitted abstract)** [22]
Objective	Use of ReCell with split thickness dermal graft in patients with extensive burns
Location	The St. Andrew's Centre for Burns and Plastic Surgery, Chelmsford, UK
Design	Descriptive case series
Duration of study	Not stated
Patient population	Patients requiring dermal grafts after initial conventional SSGs
Sample size	10 patients
Inclusion criteria	Not specified

Exclusion criteria	Not specified
Intervention(s) (n =) and comparator(s) (n =)	Single arm observational series: split thickness dermal graft taken from base of SSG donor site. Both donor and recipient sites treated with ReCell. Recipient site dressed with Biobrane or Telfa
Baseline differences	n/a
How were participants followed-up (for example, through pro-active follow-up or passively). Duration of follow-up, participants lost to follow-up	Graft sites inspected every 2 days until healed. Otherwise standard of care
Statistical tests	None
Primary outcomes (including scoring methods and timings of assessments)	Time to healing at graft site Time to healing at donor site Long term scar assessment

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Philp 2013 [22] reports on 10 patients undergoing dermal grafting. These patients include the five for whom preliminary data were reported in Sen 2012[16], in addition to five new patients.

7.4.3 Highlight any differences between patient populations and methodology in all included studies.

There are significant differences in baseline characteristics of patients included in the identified studies. This reflects that the studies are small and the samples described are drawn from an extremely heterogeneous population. Outcomes in burns patients are very susceptible to individual factors, such as age, extent, depth and location of burns and the presence of co-morbidities or adverse social circumstances. Thus, within the studies identified, age ranges from 9 months (Dunne 2012a [10]) to 80 years (Echlin 2012b [14]). TBSA ranged from <2% (Gravante 2007 [7]) to >50% (Sen 2012 [16]).

This degree of between-studies variation precludes meta-analysis and makes qualitative generalisation of results difficult to achieve. In some ways, however, this is less of a disadvantage than might be the case in some other disease areas. Burns management is highly individualised – as highlighted by the lack of published clinical guidelines and its exclusion from the Payment by Results tariff. This means that the use of ReCell will always be tailored to the clinical circumstances of the individual patient, rather than based on any population-level estimates of efficacy.

7.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

No sub-group analyses described

7.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

CONSORT diagrams below for the two published randomised controlled trials (Gravante 2007 [7] and Wood 2012 [8]). Insufficient data are available from the abstract of the third RCT (Daniel 2011) [21] to provide these details.

Figure 3: CONSORT diagram for Gravante 2007 [7]

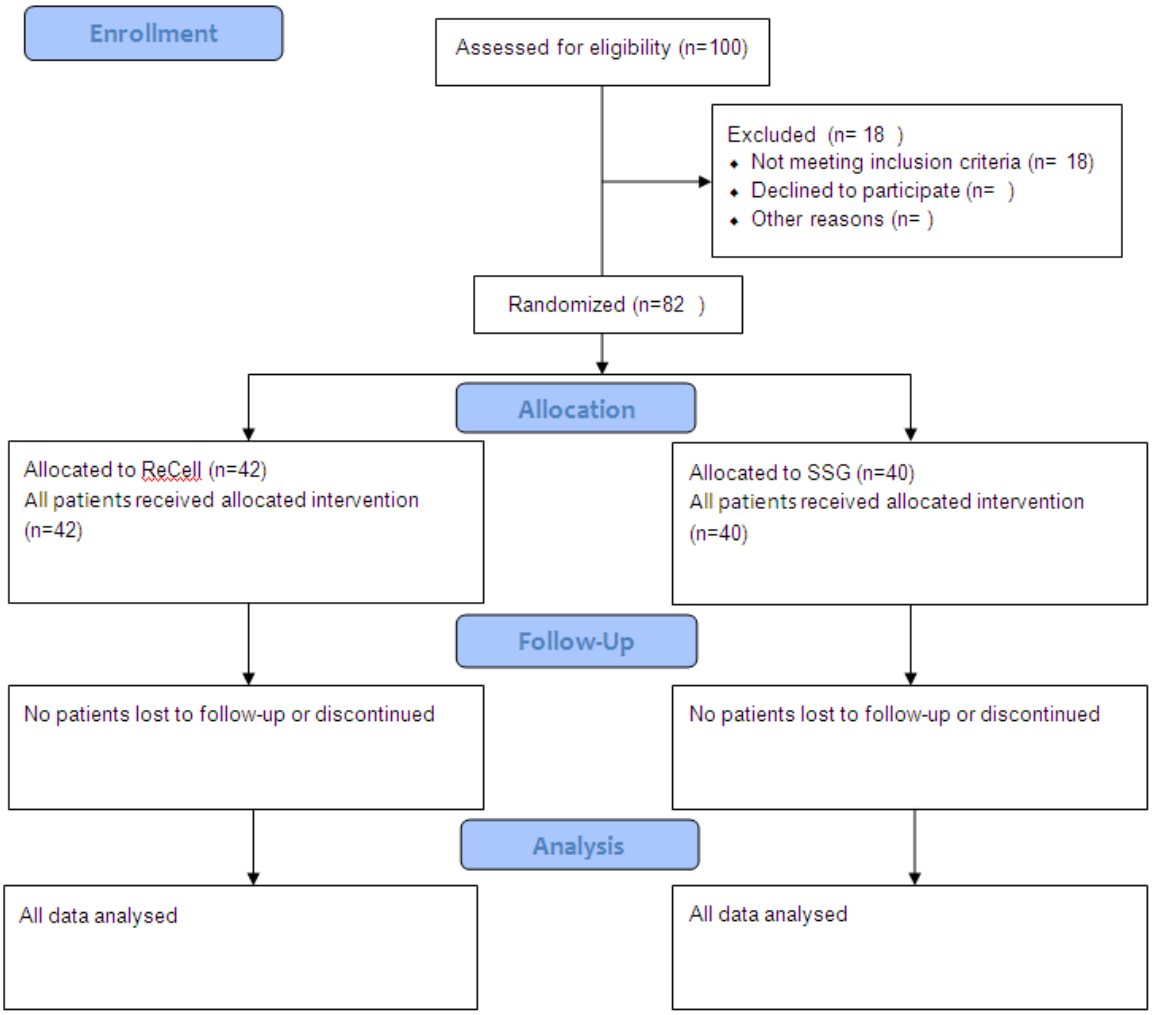
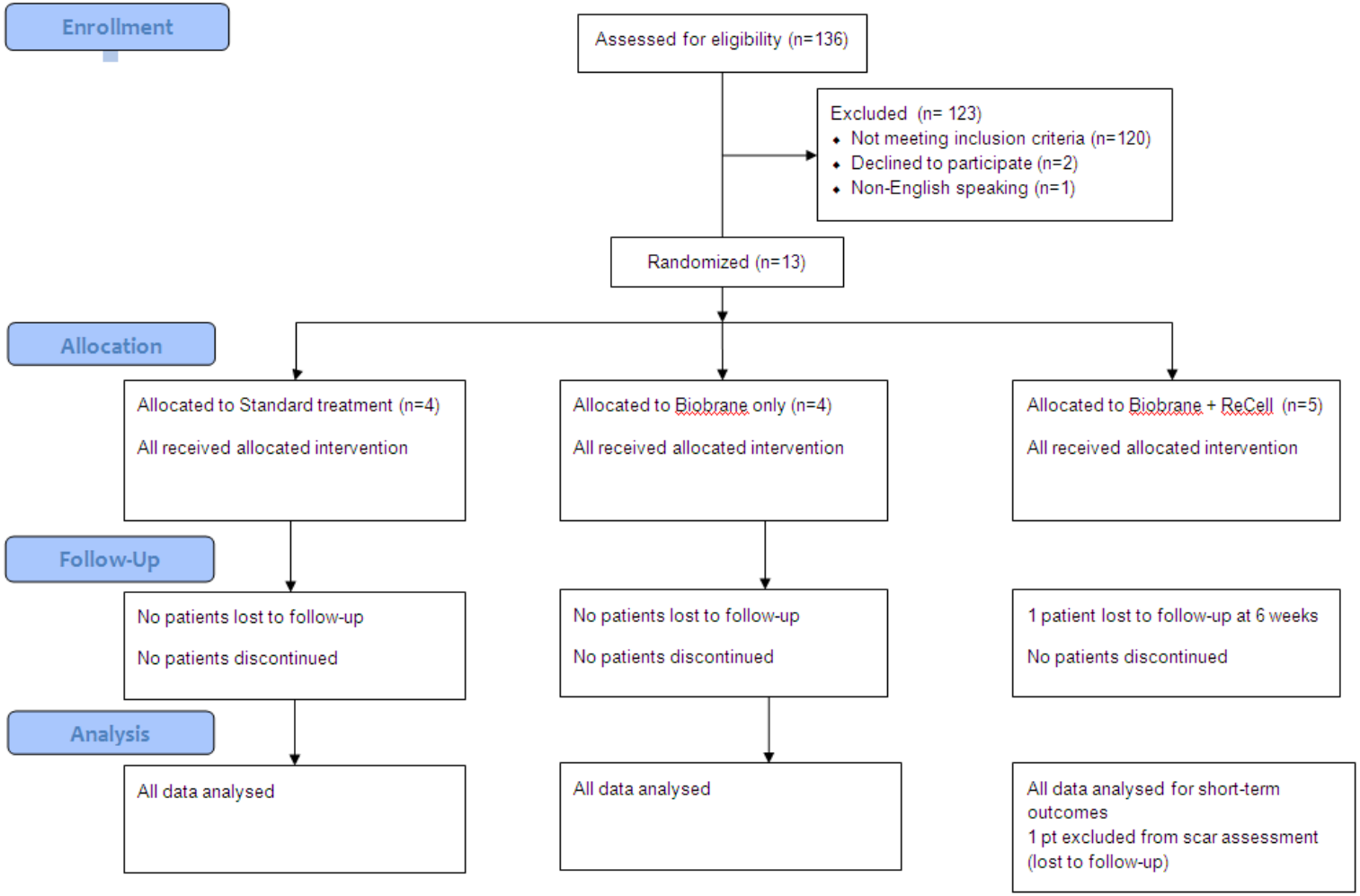


Figure 4: CONSORT diagram for Wood 2011 [8]



7.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

One patient in the Biobrane + ReCell arm of Wood 2012[8] was lost to follow-up at six weeks post randomisation. No further details are given in the paper. All data for the in-hospital outcomes were included in the analysis for this patient, but they were excluded from the long term scar outcome analysis, as they did not attend for this assessment.

7.5 Critical appraisal of relevant studies

7.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables B7 and B8.

Table B7a Critical appraisal of randomised control trials

Study name	**Gravante 2007** [7]	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Not clear	The authors describe a process of controlled sampling to match patient groups but it is not clear whether this was a randomised process
Was the concealment of treatment allocation adequate?	Not clear	
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Relatively tight inclusion/exclusion criteria + between groups matching for age, gender, type of burns and TBSA ensure good comparability
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of	Care providers: No Patients: No Assessors: Mixed	The differing nature of the two interventions made blinding of patients and assessors impossible. However, as the short term outcomes assessed were largely numerical and objective (healing time, operative duration, area treated) this should not have introduced bias. One subjective measure (post operative pain) may have been open to bias due to lack of patient blinding. Long term assessment of scar quality was

bias (for each outcome)?		carried out by one unblinded and one blinded assessor, while functional atatus was assessed by a physical therapist whose blinding status is unknown. Thus there has been an attempt to mitigate the effect of lack of blinding but it is unclear to what extent this has been achieved
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No dropouts reported
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	As all patients randomised received their allocated treatment and there were no dropouts, the data presented represent the ITT population
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B7b Critical appraisal of randomised control trials

Study name	**Wood 2012** [8]	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Yes	Sealed, opaque, identical, serially numbered envelopes prepared by a third party
Was the concealment of treatment allocation adequate?	Yes	
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No	Given the small patient numbers recruited, between-groups differences were inevitable. Most marked difference is in age, with Biobrane + ReCell patients being markedly younger than the other two groups

Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Care providers: No Patients: No Assessors: Mixed	As for the previous study, the differing nature of the two interventions made blinding of patients and assessors impossible. Some of the outcome were numerical and objective (Requirement for surgery, healing time, number of dressing changes) and therefore resistant to the effect of bias. One subjective measure (post operative pain) may have been open to bias thanks to lack of patient blinding. Assessment of healing was validated by a blinded independent assessor using photographs
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	Only one dropout in the Biobrane + ReCell group
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	All data available were presented, which was effectively an ITT analysis for all except the final scar assessment, which excluded the missing patient. However, as the number of patients were so small, no attempt at statistical analysis was made, so the distinction of ITT vs PP is probably moot.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B7c Critical appraisal of randomised control trials

Study name	**Daniel 2011 (abstract)** [21]	
Study question	**Response (yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was randomisation carried out appropriately?	Not clear	
Was the concealment of treatment allocation	Yes	All patients treated with both interventions, hence treatment allocation inherently unbiased

adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Intra-patient control, hence matching will be perfect
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Care providers: No Patients: No Assessors: Yes	The differing nature of the interventions makes blinding of patients and clinicians impractical. Assessment of outcomes carried out by independent blinded assessor
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	All patients followed up. Internal control means that balance will be inherently maintained in the event of drop-outs
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	n/a	Interim report only – formal analysis not presented at this stage
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Table B8 Critical appraisal of observational studies

Study name Park 2013 [9]		
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort	Yes	All patients undergoing surgery for burns in a

recruited in an acceptable way?		large regional burns unit over an 8 year period were included
Was the exposure accurately measured to minimise bias?	Yes	Source of data was a dedicated burns dataset on which detailed records had been entered at the time of the original admission. Variables used in the analysis were derived from this and not subject to retrospective alteration
Was the outcome accurately measured to minimise bias?	Yes	Of the three outcomes assessed, two (wound infection and length of stay) were explicitly defined and recorded at the time of admission. The third outcome (graft loss) was a clinical opinion and therefore potentially prone to bias, but the data was recorded at the time of the original admission and not retrospectively altered
Have the authors identified all important confounding factors?	Unclear	The authors identified a number of factors that were thought likely to influence the outcomes of interest. It is possible that other confounders exist that were not recorded in the dataset that forms the basis of this analysis
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Univariate analysis was first carried out for each of the potential confounders, in order to identify the covariates that should be included in the multivariate logistic regression analysis
Was the follow-up of patients complete?	Yes	48 patients were excluded from the analysis, on grounds of pre-existing signs of wound or systemic infection. All other patients are included in the analysis
How precise (for example, in terms of confidence interval and p values) are the results?		Results for each variable in each of the three regression analyses are presented as odds ratio, 95% CI and p-value. All figures are quoted to two decimal places
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

As all the other published observational studies identified were simple case series, methodological critical appraisal is inappropriate and data are therefore not presented here.

7.6 *Results of the relevant studies*

7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table B9.

Table B9a Outcomes from published and unpublished studies – results reported for primary outcomes and secondary outcomes relevant to decision problem

Study name		**Gravante 2007** [7]
Size of study groups	**Treatment**	42
	Control	40
		Formal sample size estimation not defined in paper
Study duration	**Time unit**	2 years total. 6 months follow-up for each individual
Type of analysis	**Intention-to-treat/per protocol**	Intention to treat
Primary Outcome	**Name**	Time for complete epithelialisation
	Unit	Days
Effect size	**Value**	Mean 13 days in ReCell group (sd = 2) Mean 12 days in SSG group (sd = 2) Mean difference = 1 day
	95% CI	Not specified in paper. Our estimated confidence interval for the mean difference, based on the provided data is 0.12 – 1.88
Statistical test	**Type**	Student's t-test
	p value	Not significant
Second primary outcome	**Name**	Aesthetic result
	Unit	Score on modified Vancouver Scar Scale (ordinal value between 0-5)
Effect size	**Value**	Values not reported in paper
	95% CI	
Statistical test	**Type**	Chi squared test
	p value	Reported as no significant difference
Other outcome	**Name**	Area harvested
	Unit	Sq cm
Effect size	**Value**	Mean 2.2 in ReCell group (sd = 1) Mean 110 in SSG group (sd = 50) Mean difference = 107.8 sq cm
	95% CI	Not specified in paper. Our estimated confidence interval for the mean difference, based on the provided data is 92 – 123

Statistical test	**Type**	Student's t-test
	p value	<0.001
Other outcome	**Name**	Procedure duration
	Unit	minutes
Effect size	**Value**	Mean 59 in ReCell group (sd = 4) Mean 20 in SSG group (sd = 6) Mean difference = 39 minutes
	95% CI	Not specified in paper. Our estimated confidence interval for the mean difference, based on the provided data is 36.8 – 41.2
Statistical test	**Type**	Student's t-test
	p value	<0.001
Other outcome	**Name**	Post-operative pain
	Unit	Visual analogue scale (range 0-10; high = worse)
Effect size	**Value**	Mean 3.3 in ReCell group (sd = 1.6) Mean 6.8 in SSG group (sd = 1.2) Mean difference = 3.5
	95% CI	Not specified in paper. Our estimated confidence interval for the mean difference, based on the provided data is 2.9 – 4.1.
Statistical test	**Type**	Student's t-test
	p value	0.03

Table B9b Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		**Wood 2012** [8]
Size of study groups	**Treatment**	5 (Biobrane + ReCell)
	Control	4 (Biobrane alone)
		4 (Standard treatment)
Sample size		Sample size was calculated as 45 patients, based on the expected incidence of qualifying childhood scalds over the planned 12 month duration of the study. Reductions in the expected incidence and extent of presenting scalds meant that only 16 qualifying patients could be identified, of which 13 were randomised
Study duration	**Time unit**	1 year total. 6 months follow-up for each individual
Type of analysis	**Intention-to-treat/per protocol**	Intention to treat for primary outcome and most secondary outcomes. Loss of one child to follow-up meant that the final scar assessment was effectively a per protocol analysis
Primary outcome	**Name**	Requirement for surgery after 10 days
	Unit	Number of patients
Effect size	**Value**	3 / 4 patients in standard treatment arm 1 / 4 in Biobrane only arm 0 / 5 in Biobrane + ReCell arm
	95% CI	Small numbers recruited meant that statistical analysis would have been of doubtful validity. Consequently, only descriptive data are presented.
Statistical test	**Type**	
	p value	
Other outcome	**Name**	Time to healing
	Unit	Clinician assessment of first day on which full healing was observed Quantitative assessment of unhealed wound size using Visitrak compared at 10 and 21 days versus baseline assessment at 2 days (% healed)
Effect size	**Value**	Standard treatment arm. • Mean time to heal: 34.25 days (sd 14.39) • Median time to heal: 36.5 days (IQR 18.5-47.7) • % healed at 10 days: 71.2% • % healed at 21 days: 90.1% Biobrane alone treatment arm. • Mean time to heal: 17.75 days (sd 4.99) • Median time to heal: 16.0 days (IQR 14.25-23.0) • % healed at 10 days: 83.2% • % healed at 21 days: 97.7%

		Biobrane + ReCell treatment arm. • Mean time to heal: 15 days (sd 3.54) • Median time to heal: 16 days (IQR 11.5-18) • % healed at 10 days: 95% • % healed at 21 days: 100%
	95% CI	Small numbers recruited meant that statistical analysis would have been of doubtful validity. Consequently, only descriptive data are presented
Statistical test	**Type**	
	p value	
Other outcome	**Name**	Dressing changes
	Unit	Number over course of treatment until wound healed
Effect size	**Value**	Standard treatment arm. • Mean dressing changes: 11.5 (sd 4.79) • Median dressing changes: 12.5 (IQR 8-15) Biobrane alone treatment arm. • Mean dressing changes: 7.5 (sd 2.64) • Median dressing changes: 7 (IQR 5.5-9.5) Biobrane + ReCell treatment arm. • Mean dressing changes: 4.8 (sd 1.30) • Median dressing changes: 5 (IQR 4-6)
	95% CI	Small numbers recruited meant that statistical analysis would have been of doubtful validity. Consequently, only descriptive data are presented
Statistical test	**Type**	
	p value	
Other outcome	**Name**	Pain assessment
	Unit	Numerical score from one of three age-appropriate pain assessment tools
Effect size	**Value**	Standard treatment arm. • Median pre-op score: 4.5 • Median post-op score: 5.5 • Median difference: +1.0 Biobrane alone treatment arm. • Median pre-op score: 4.0 • Median post-op score: 2.0 • Median difference: -2.0 Biobrane + ReCell treatment arm. • Median pre-op score: 4.0 • Median post-op score: 3.0 • Median difference: -1.0
	95% CI	Small numbers recruited meant that statistical analysis would have been of doubtful validity.
Statistical	**Type**	

test	**p value**	Consequently, only descriptive data are presented
Other outcome	**Name**	Scar outcomes
	Unit	Vancouver Scar Scale: a four item assessment yielding an ordinal value in the range 0-13 (high = worse)
Effect size	**Value**	Standard treatment arm. • Scores: 0, 6, 5, 6 Biobrane alone treatment arm. • Scores: 3, 9, 3, 2 Biobrane + ReCell treatment arm. • Scores: 5, 3, 0, 6 (+ 1 lost to follow-up)
	95% CI	Small numbers recruited meant that statistical analysis would have been of doubtful validity. Consequently, only descriptive data are presented
Statistical test	**Type**	
	p value	

Table B9c Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		**Daniel 2011 (Abstract)** [21]
Size of study groups	**ReCell**	14 patients with intra-patient control – all received both treatments
	Minigrafting	
Study duration	**Time unit**	12 months
Type of analysis	**Intention-to -treat/per protocol**	ITT – data from all patients presented
Primary Outcome	**Name**	Percentage repigmentation at 12 months
	Unit	%
Effect size	**Value**	ReCell: 15% Minigrafting: 12%
	95% CI	Interim report: descriptive data only
Statistical test	**Type**	
	p value	
Secondary outcome	**Name**	Percentage repigmentation at 3 months
	Unit	%
Effect size	**Value**	ReCell: 27% Minigrafting: 11%
	95% CI	Interim report: descriptive data only
Statistical test	**Type**	
	p value	

Table B9d Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Park 2013 [9]
Size of study groups	ReCell alone	73
	ReCell + SSG	264
	SSG alone	387
	Cell culture +/- SSG	46 (this category relates to a cell culture technology that is no longer available, so data relating to this group are not presented below)
Study duration	Time unit	8 years total. Each individual followed up until discharge
Type of analysis	Intention-to-treat/per protocol	Not relevant to retrospective regression analysis
Primary Outcome	Name	Frequency of new burn wound infection
	Unit	Hazard ratio for infection associated with each surgery type vs SSG alone (reference) in multivariate logistic regression analysis
Effect size	Value	SSG alone: 1.00 ReCell alone: 0.78 ReCell + SSG: 1.23
	95% CI	ReCell alone: 0.34 – 3.42 ReCell + SSG: 0.45 – 4.52
Statistical test	Type	Not specified
	p value	ReCell alone: 0.98 ReCell + SSG: 0.97
Second primary outcome	Name	Frequency of graft loss
	Unit	Hazard ratio for graft loss associated with each surgery type vs SSG alone (reference) in multivariate logistic regression analysis
Effect size	Value	SSG alone: 1.00 ReCell alone: 0.89 ReCell + SSG: 1.56
	95% CI	ReCell alone: 0.45 – 2.32 ReCell + SSG: 0.56 – 3.21
Statistical test	Type	Not specified
	p value	ReCell alone: 0.09 ReCell + SSG: 0.67

Other outcome	**Name**	Length of stay
	Unit	Hazard ratio for increased length of stay associated with each surgery type vs SSG alone (reference) in multivariate logistic regression analysis
Effect size	**Value**	SSG alone: 1.00 ReCell alone: 0.70 ReCell + SSG: 0.98
	95% CI	ReCell alone: 0.57 – 0.82 ReCell + SSG: 0.88 – 1.10

Table B9e Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		**Dunne 2012 (Abstract)** [10]
Size of study groups	**ReCell + Biobrane**	13
	Biobrane alone	20
	Early SSG	7
Study duration	**Time unit**	18 months approx
Type of analysis	**Intention-to -treat/per protocol**	Not relevant: descriptive case series
Outcome	**Name**	Requirement for skin grafting
	Unit	N (%)
Effect size	**Value**	ReCell + Biobrane: 5 (38%) Biobrane alone: 6 (30%) Early SSG: 2 (29%)
	95% CI	Descriptive data only
Statistical test	**Type**	
	p value	
	Minigrafting	
Statistical test	**Type**	
	p value	

Table B9f Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Rawlins 2013 (Abstract) [11]
Size of study groups	ReCell	11
	SSG	15
Study duration	Time unit	4 months
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive case series
Outcome	Name	Scar outcome
	Unit	VAS (mean)
Effect size	Value	ReCell: 3.9 SSG: 3.9
	95% CI	ReCell: 2.8 – 4.9 SSG: 3.3 – 4.5
Statistical test	Type	Not stated
	p value	P=0.97
Outcome	Name	Operative time
	Unit	Minutes
Effect size	Value	ReCell: 87 mins SSG: 58 mins
	95% CI	Not stated
Statistical test	Type	Not stated
	P value	P=0.05
Outcome	Name	Mean duration of physio follow-up
	Unit	Days
Effect size	Value	ReCell: 21 days SSG: 40 days
	95% CI	Not stated
Statistical test	Type	Not stated
	P value	P=0.29

Table B9g Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Rawlins 2011 (Abstract) [12]
Size of study groups	ReCell + Biobrane	5
	SSG	10
Study duration	Time unit	4 months
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive case series
Outcome	Name	Mean time to wound healing
	Unit	Days
Effect size	Value	ReCell: 18 days SSG: 48 days
	95% CI	Not stated
Statistical test	Type	Not stated
	p value	Not stated

Table B9h Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		Echlin 2012a (Abstract) [13]
Size of study groups	ReCell	5
Study duration	Time unit	Not specified
Type of analysis	Intention-to-treat/per protocol	Not relevant: descriptive case series
Outcome	Name	Mean time to wound healing
	Unit	Days
Effect size	Value	ReCell: 5 days
	95% CI	Not stated
	Type	Not relevant
Statistical test	p value	Not relevant

Table B9i Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		**Echlin 2012b (Abstract)** [14]
Size of study groups	**ReCell**	11 sites in 9 patients
Study duration	**Time unit**	Not specified
Type of analysis	**Intention-to-treat/per protocol**	Not relevant: descriptive case series
Outcome	**Name**	Mean time to wound healing (donor site)
	Unit	Days
Effect size	**Value**	ReCell: 9 days
	95% CI	Not stated
	Type	Not relevant
Statistical test	**p value**	Not relevant

Table B9j Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		**Palombo 2012 (Abstract)** [15]
Size of study groups	**ReCell**	6 patients
Study duration	**Time unit**	Not specified
Type of analysis	**Intention-to-treat/per protocol**	Not relevant: descriptive case series
Outcome	**Name**	Time to complete re-epithelialisation
	Unit	Days
Effect size	**Value**	ReCell: All patients healed by 10 days
	95% CI	Not stated
	Type	Not relevant
Statistical test	**p value**	Not relevant

Table B9k Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		**Sen 2012 (Abstract)** [16]
Size of study groups	**ReCell**	5 patients
Study duration	**Time unit**	Not specified
Type of analysis	**Intention-to-treat/per protocol**	Not relevant: descriptive case series
Outcome	**Name**	Time to healing
	Unit	Not specified
Effect size	**Value**	ReCell: "Epithelialisation appeared complete in all cases and in times comparable to conventional graft and donor site healing"
Statistical test	**95% CI**	Not stated
	Type	Not relevant
	p value	Not relevant

Table B9l Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		**Philp 2013 (Submitted abstract)** [22] **NOTE: Extended data relating to previous abstract (Sen 2012** [16]**)**
Size of study groups	**ReCell**	10 patients (2 died – results for 8 survivors presented)
Study duration	**Time unit**	Not specified
Type of analysis	**Intention-to-treat/per protocol**	Not relevant: descriptive case series
Outcome	**Name**	Time to healing
	Unit	Days
Effect size	**Value**	ReCell: 12 days (graft) 14 days (donor)
	95% CI	Not stated
	Type	Not relevant
Statistical test	**p value**	Not relevant

Table B9m Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		**Cervelli 2009a** [18]
Size of study groups	**ReCell**	30 patients
Study duration	**Time unit**	2 years (minimum follow up 1 year)
Type of analysis	**Intention-to-treat/per protocol**	Not relevant: descriptive case series
Outcome	**Name**	Patient assessment of outcome
	Unit	Categorical N (%)
Effect size	**Value**	Excellent: 18 (60%) Good: 8 (27%) Fair: 1 (3%) Poor: 3 (10%)
	95% CI	Not stated
Statistical test	**Type**	Not relevant
	p value	Not relevant
Outcome	**Name**	Surgeon assessment of outcome
	Unit	Categorical N (%)
Effect size	**Value**	Excellent: 18 (60%) Good: 6 (20%) Fair: 3 (10%) Poor: 3 (10%)
	95% CI	Not stated
Statistical test	**Type**	Not relevant
	P value	Not relevant
Outcome	**Name**	Pigmentation grading
	Unit	Categorical N (%)
Effect size	**Value**	Normal: 18 (60%) Slight: 9 (30%) Moderate: 3 (10%)
	95% CI	Not stated
Statistical test	**Type**	Not relevant
	P value	Not relevant

Table B9n Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		**Cervelli 2009b** [19]
Size of study groups	**ReCell**	15 patients
Study duration	**Time unit**	1 years (minimum follow up 6 months)
Type of analysis	**Intention-to-treat/per protocol**	Not relevant: descriptive case series
Outcome	**Name**	Extent of pigmentation
	Unit	Ordinal N (%)
Effect size	**Value**	100%: 0 (0%) 76-99%: 12 (80%) 51-75%: 0 (0%) 25-50%: 3 (20%) 1-25%: 0 (0%)
Statistical test	**95% CI**	Not stated
	Type	Not relevant
	p value	Not relevant
Outcome	**Name**	Patient assessment of outcome
	Unit	Categorical N (%)
Effect size	**Value**	Excellent: 10 (67%) Good: 5 (33%) Fair: 0 (0%) Poor: 0 (0%)
	95% CI	Not stated
Statistical test	**Type**	Not relevant
	P value	Not relevant

Table B9o Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

Study name		**Mulekar 2008** [20]
Size of study groups	**ReCell**	5 patients with intra-patient controls so all patients received both treatments
	M-K transplant	
Study duration	**Time unit**	4 months
Type of analysis	**Intention-to -treat/per protocol**	Not relevant: descriptive comparative case series
Outcome	**Name**	Percentage repigmentation at 4 months
	Unit	%
Effect size **Statistical test**	**Value**	Pt 1: ReCell – 100%; MKT – 100% Pt 1: ReCell – 40%; MKT – 30% Pt 1: ReCell – 0%; MKT – 0% Pt 1: ReCell – 65%; MKT – 100% Pt 1: ReCell – 100%; MKT – 100%
	95% CI	Not stated
	Type	Not relevant
	p value	Not relevant

Table B9p Outcomes from published and unpublished studies – results reported for primary outcome and secondary outcomes relevant to decision problem

[redacted]		[redacted] 23
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]

7.6.2 Justify the inclusion of outcomes in table B9 from any analyses other than intention-to-treat.

7.7 Adverse events

In section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The original literature search described in section 7.1 above also captured studies reporting adverse events. The following studies specifically reported adverse event rates:

Gravante 2007 [7]; Wood 2012 [8]; Park 2013 [9]; Rawlins 2013 [11]

7.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table B10.

Because the majority of the data relating to ReCell are derived from observational studies that did not collect adverse event data using formal MedDRA criteria, these results are presented in narrative format in the table below:

Table B10 Adverse events described in studies

Study	Populations						Events		
	Treatment 1		Treatment 2		Treatment 3		Treatment 1	Treatment 2	Treatment 3
	Type	N	Type	N	Type	N			
Gravante 2007 [7]	ReCell	42	SSG	44			No intra-operative or post-operative events reported	No intra-operative or post-operative events reported	
Wood 2012 [8]	Conventional	4	Biobrane	4	Biobrane + ReCell	5	1 graft loss (25%) + 1 overgranulation (25%)	1 wound infection (25%)	1 wound infection (20%) + 1 sepsis (20%) [same patient]
Park 2013 [9]	SSG	387	ReCell	73	SSG + ReCell	264	91 patients (11.8%) had a new wound infection. No significant difference between groups (SSG: HR=1.00, ReCell: HR=0.78, SSG+ReCell: HR=1.32) 116 patients (15.1%) experienced graft loss. No significant difference between groups (SSG: HR=1.00, ReCell: HR=0.89, SSG+ReCell: HR=1.56)		
Rawlins 2013 [11]	ReCell	11	SSG	15			2 wound infections (18%)	2 wound infections (13%)	

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

In accordance with European regulations, any event which meets all three basic reporting criteria listed below is considered an incident and is reported to the relevant National Competent Authority by Avita Medical Ltd:

1. *An event has occurred such as:*
    - *A malfunction or deterioration in the characteristics or performance (failure to perform in accordance with intended use, when used in accordance with the instructions for use)*
    - *Unanticipated adverse reaction or unanticipated side effect*
    - *Degradation/destruction of the device (i.e. fire)*
    - *Inaccuracy of the labelling, instructions for use or promotional materials*
2. *Avita Medical's device is suspected to be a contributory cause of the incident*
3. *The event led, or might have led to the following:*
    - *Death of a patient, user or other person*
    - *Serious deterioration in the state of health of a patient, user or other person*

No such event has been reported since ReCell has been granted CE recognition (March 2005) and so there are no data to list in this paragraph

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope.

The ReCell device itself is associated with an inherently low risk of adverse events, as the device itself at no point comes into contact with the patient. Trypsin and sodium lactate are used in the processing of the patient's own cells, which are then re-applied to the patient's wound. Although, in theory, sensitivity or allergy to either of these two components could result in an adverse event, in clinical practice this has never been reported.

Adverse events reported within clinical trials and observational studies tend therefore to be related to the surgical procedure and the immediate post-operative management process. The most important of these are wound infections, sepsis and graft loss – events that are familiar complications of burns management and which are associated with established mechanisms for identification and treatment.

The retrospective analysis of 770 patients treated with various surgical interventions at a single burns unit in Australia carried out by Park et al [9] offers the best perspective on the relative risk of these adverse events with a range of treatment modalities. In this series, 50.3% of patients were treated with SSG, 9.5% with ReCell alone and 43.3% with SSG and ReCell combined. 11.8% of patients had microbiologically proven wound infections and 15.1% experienced graft loss (not mutually exclusive). After correcting for age, type and extent of injury and co-morbid diabetes, there was no significant effect of intervention type on the risk of either outcome (see table B9c).

Studies carried out in other indications for ReCell (principally vitiligo and venous leg ulcers) have not demonstrated any other adverse event signal not demonstrated in these burns studies.

These data, combined with the lack of reportable adverse events reported from clinical practice, offer strong reassurance that the use of ReCell is not currently associated with any significant risk of device-related adverse events, nor with an increase in the expected level of procedure-related complications.

7.8 Evidence synthesis and meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Not appropriate

7.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

The identified studies relating to ReCell are a mixture of comparative randomised controlled trials, comparative case series and non comparative case series. The comparative studies have been carried out in widely varying patient populations and evaluate ReCell – either alone or in combination with other treatments – against a variety of comparator treatments. Although there is some degree of consistency in terms of outcomes measured, the degree of heterogeneity in patient populations, interventions and study methodology precludes conventional meta-analysis. Furthermore, the lack of cross-over in characteristics between the studies means that mixed treatment comparison is also inappropriate. For these reasons we have elected to carry out a narrative review of studies carried out in burns patients in addition to a supplementary review of studies in a broader patient population relating to the management of dyspigmentation.

Randomised controlled trials in burns

Gravante 2007 [7]

This is the largest published randomised controlled trial of ReCell, carried out in patients with deep partial thickness burns and was intended to investigate the use of ReCell vs early SSG – all interventions were carried out between days 3-5 post injury. Outcomes relevant to the procedure itself, healing times and long term aesthetic outcome were assessed. Patients were explicitly matched for age, gender, type and extent of burns, to ensure that any observed differences reflected the treatments used, rather than the population evaluated.

The area of burn treated was the equivalent for both groups (176 sq cm vs 180 sq cm; p=ns) while the mean size of donor site, was significantly smaller in ReCell treated patients (2.2 sq cm vs 110 sq cm; $p<0.001$), reflecting the fundamental difference in the treatment modalities. Mean duration of the primary operative procedure was significantly longer with ReCell (59 mins vs 20 mins; $p<0.001$).

The mean time to wound healing was comparable in the two groups (13 days vs 12 days; p=ns). Mean post-operative pain score was significantly lower in the ReCell group (3.3 vs 6.8; p=0.03). Long term aesthetic results with regard to pigmentation and vascularity were equivalent between the two groups (scores not reported). There were no interoperative or postoperative adverse events reported in either group.

Overall, this study demonstrates equivalence between ReCell and SSG with regard to wound healing and ultimate result in patients with deep partial thickness burns, although post-operative pain and donor site size were significantly better in the ReCell-treated group.

Wood 2012 [8]

This is a pilot RCT that provides a useful insight into the relative value of Biobrane, ReCell + Biobrane or SSG in a paediatric scald population. The

numbers involved were small – 4 patients each for SSG and Biobrane alone and 5 for Biobrane + ReCell – so formal statistical analysis was not carried out. Despite this limitation, the study gives us a perspective on clinical outcomes that is informative.

The four patients allocated to SSG were expected to undergo the procedure on day 10 of the injury and all but one did so. Of the patients allocated to Biobrane alone, one required grafting, while none of the patients to Biobrane + ReCell. Median time to healing was the same in both the Biobrane and Biobrane/ReCell groups (16 days) – less than half that observed in the SSG group (36.5 days). Post-intervention pain scores also appeared lower (5.5, 2.0, 3.0 respectively). Long term scar outcomes were similar between groups.

The study also assessed healthcare costs. Although it is possible to identify potential areas of saving for some elements with ReCell (dressing costs, theatre costs, admission costs), the huge variation in individual patient expenditure, largely reflecting length of stay, make it difficult to draw any clear conclusions.

Overall, the study provides some reasonable data, suggesting once again that both Biobrane and Biobrane/ReCell can offer equivalent outcomes to SSG, while allowing healing to take place more quickly and allowing reduced expenditure in some care elements.

Observational studies in burns

Park 2013 [9]

This large retrospective observational study evaluated 770 burns patients treated with either SSG alone (n=387), ReCell + SSG (n=264), ReCell alone (n=73) or cultured epithelial cell +/- SSG (n=46). The latter group relates to a technology that is no longer available and is therefore not considered further.

The study assessed the impact of treatment type on the risk of burn wound infection, graft loss and length of hospital stay by means of a multivariate

logistic regression analysis, comparing the impact of both ReCell-containing regimens versus SSG alone. After correction for potential confounders, there was found to be no significant difference between SSG and ReCell alone (HR = 0.78; p=0.98) or ReCell + SSG (HR 1.23; p=0.97) for the wound infection outcome. Similarly, there was no significant difference in the risk of graft loss for either ReCell (HR=0.89; p=0.09) or ReCell + SSG (HR=1.56; p=0.67). With regard to length of hospital stay, ReCell patients had a significantly lower length of stay (HR=0.70; p<0.01), while there was no significant difference with ReCell + SSG (HR=0.98; p=0.85).

It should be borne in mind that the patient groups were not matched a priori in this retrospective analysis, and it is possible that the decision to use one treatment modality over another may have been governed by factors that were not controlled for in the regression analysis. Nonetheless, this study provides good evidence that the risk of wound infection or graft loss associated with ReCell is at least as good as that seen with SSG and that, when used alone, ReCell-treated patients are able to be discharged from hospital significantly earlier than those undergoing SSG (whether with or without ReCell).

There were three other comparative case series identified in the literature search:

- ***Dunne 2012*** [10]
- ***Rawlins 2013*** [11]
- ***Rawlins 2011*** [12]

Dunne 2012 [10] reported on 40 children with scalds treated using an escalating clinical pathway (Biobrane alone => ReCell + Biobrane => SSG) according to the depth of the scald. All treatments were instituted within the first 48 hours of treatment, with the intention of achieving early healing. 71% of full thickness burns, 62% of mid and deep dermal burns and 70% of superficial dermal burns were successfully healed without further grafting using this strategy.

Although this study does not allow a direct comparison of treatments to be carried out, as the populations for each modality were different, it nonetheless demonstrates that ReCell can be successfully integrated into a standard treatment pathway in a burns unit.

Rawlins 2013 [11] reported on 26 children with burns managed with either ReCell or SSG. Patients were treated according to the preference of the consultant in charge, meaning that patients with smaller burns tended to undergo SSG (mean TBSA: 2.9%) while children with larger burns were more likely to be treated with ReCell (mean TBSA: 6.5%). Burns outcome was evaluated by five independent clinicians using a VAS at four months, and showed no difference between treatments (mean score 3.9 for both groups). Mean duration of physiotherapy follow-up was shorter for ReCell treated patients (21 days vs 40 days) while duration of the initial operative procedure was longer (87 minutes vs 58 minutes).

This study, once again, is subject to the limitations of the non-randomised design, but supports the hypothesis that ReCell is at least as effective as SSG, while potentially offering savings in long term treatment support.

The third comparative series, Rawlins 2011 [12], compares outcomes in 5 patients with deep flame burns treated with ReCell + Biobrane and 10 matched controls treated with SSG. The abstract does not detail which criteria were used for matching patients with controls. Mean TBSA was 15% (range 9-24%).

ReCell + Biobrane was associated with a considerably shorter healing time (18 days vs 48 days; p value not given) and analgesic requirements were less (numerical data not given). At six months, the quality of scar, as assessed by the Vancouver Scar Assessment, was also better in the ReCell + Biobrane group (numerical data not given).

Although there is limited data given in this abstract, the information supplied supports the use of ReCell with Biobrane in patients with larger, deep dermal burns, where SSG would ordinarily be the treatment of choice.

Below is a brief review of five further non-comparative case series that can complement our understanding of the role of ReCell in burns:

- ***Cui 2013 (unpublished)***[23]
- ***Echlin 2012a*** [13]
- ***Echlin 2012b*** [14]
- ***Palombo 2012*** [15]
- ***Sen 2012/Philp 2013*** [16,22]

[redacted]

Echlin 2012a[13] presents data on 5 patients with mid to deep dermal burns affecting the whole face, who had been primarily treated with allografts 0-2 days post burn but who were found to have unhealed burns at day 9-11 in four cases and at 23 days in one case. The four patients treated at day 9-11 were all healed by day 7 post surgery (mean time to healing 5 days) while the late-presenting patient showed improvement but required a further small allograft to complete the healing.

Echlin 2012b[14] describes 9 patients with 11 donor sites used to provide skin grafts. 8 of the 9 were burns patients and had a mean skin loss of 10% on the donor sites. All sites healed by day 14 (mean time to healing day 9) and in two patients, the donor sites were able to be further harvested on days 14 and 20 respectively. In two patients, there were two or more donor sites only one of which was treated with ReCell. In one patient the ReCell treated site was healed within 7 days while the untreated site took until day 29 to heal. In the second patient, the treated site was healed within 13 days, but the untreated site was not healed until day 20.

Palombo 2012[15] gives brief details of 6 children with hypertrophic scars following burn injuries. After dermabrasion and ReCell, complete re-epithelialisation was achieved by day 10 in all patients. Satisfactory skin pigmentation and texture was reported in all cases by 3 months post-operatively.

Sen 2012[16] and Philp 2013[22] present data from the same sequence of patients with extensive burns, who underwent dermal skin grafting. In these 10 patients there was a shortage of viable donor skin to achieve coverage of burn injuries. After all available sites had been harvested for standard SSGs, a second dermal skin graft was obtained from the base of the donor site. After application to the wound, ReCell was used to colonise both dermal graft and the donor site with epithelial cells.

Two of the 10 patients died as a result of their burns. Amongst the 8 survivors, Average time to healing was 12 days for the burn sites and 14 days for the donor sites. Ultimate scar appearance was assessed as being no worse than would have been expected for a conventional SSG and donor site.

These case series, while lacking the robustness of a randomised controlled trial, give a clear impression of the benefits that can be achieved with ReCell in a broader range of clinical situations than is defined in the scope: long term scar management, donor site healing and making dermal skin grafting a possibility. The Echlin 2012b abstract[14] is particularly compelling with regard to donor site healing, especially as it includes two within-patient comparisons of healing times for ReCell-treated donor sites with untreated sites.

[redacted] This aspect of ultimate scar aesthetics is a particularly important outcome for patients, especially those with darker skins, where depigmented scars are particularly obvious. In order to understand this aspect of ReCell's benefit further, we undertook a supplementary literature search for studies investigating this outcome. While much of the data

identified relates to patients with conditions other than burns, the technology and means of application is identical to that used with burns injuries and we believe it is therefore reasonable to use this data to inform our understanding of ReCell.

Studies in dyspigmentation

Cui 2013 (draft manuscript)[23]

The findings of this paper have already been discussed in the burns section of the narrative review above.

Cervelli 2009a[18]

This paper presents the results of 30 adult patients with post-traumatic scars with unacceptable aesthetic appearance that had proved resistant to previous treatment with intralesional steroids, chemical peeling, laser therapy, microdermabrasion or dermabrasion. 11 patients had hypopigmentation, 2 had hyperpigmentation, 3 had hypertrophy or keloid formation and 14 had skin contracture. Surgery was performed 15-16 months post injury. After dermabrasion, ReCell was used to re-epithelialise the affected area.

All patients completed at least one year's follow-up and were assessed for cosmetic result. Histological examination identified pigmented melanocytes as being present is 18 patients (60%) at 5 weeks post operatively and in 28 patients (93%) by 7 weeks. Subjective assessment of scar pigmentation was carried out at 1 year, using a modified version of the Vancouver Scar Scale, with scars being assessed as being normal or slightly, moderately or severely abnormal. 18 patients (60%) rated their pigmentation as being normal, with the remainder rating the pigmentation as being slightly (n=9; 30%) or moderately (n=3; 10%) abnormal. No patient rated their pigmentation as being severely abnormal.

Surgeons rated the overall functional and cosmetic result as good or excellent in 24 cases (80%) while patients scored a similar rating in 26 cases (87%).

Cervelli 2009b[19]

This study presents the effect of ReCell on skin pigmentation in 15 adult patients with stable vitiligo, carried out over a 2 year period. Three weeks after ReCell was used, 6 patients (40%) had visible repigmentation, rising to 9 patients (60%) by five weeks. When assessed at six months, 80% of patients had greater than 75% repigmentation in the treated area, with the remaining 20% having 25-50% repigmentation. 10 patients (67%) rated the result as excellent, while 5 (33%) patients rated it as good. No patients rated their result as fair or poor.

Mulekar 2008 [20]

This pilot study compared two modalities of autologous cell treatment in 5 patients with stable vitiligo. Each patient had two lesions in the same anatomical location treated, one with ReCell and another with melanocyte-keratinocyte transplantation (MKT). The latter procedure involves a similar process of separation of the epidermal cells from a thin shave skin biopsy, although in this case the sample requires overnight processing in a laboratory.

4 months after the procedure, the pigmentation results were assessed. In two cases, 100% repigmentation was achieved using both techniques; in one case neither intervention was able to achieve any repigmentation. Of the two remaining patients, in one case ReCell was more successful (40% vs 30%) while in the second, MKT was more effective (65% vs 100%). The author concluded that the repigmentation was similar with the 2 methods.

Daniel 2013 [21]

This is an abstract describing an interim report of a randomised controlled trial comparing ReCell and SSG (minigrafting) in the management of vitiligo. 14 patients with paired lesions were treated with both technologies and the degree of repigmentation assessed at 12 months. Limited data are available, but the authors report 15% of patients with full repigmentation with ReCell at 12 months, compared to 12% with minigrafting.

Although these studies have been carried out across a range of different pathologies, the consistent finding from 4 of the five studies is that treatment with ReCell can deliver good or excellent repigmentation in around 60-80% of patients treated, even where multiple previous treatments have failed. In the fifth study (Daniel 2013 [21]) data on this outcome were not provided in this form in the abstract.

The disruption of normal melanocyte presence and function within wounded skin results in dyspigmentation, highlighting the presence of otherwise less noticeable scars, and in the case of hypopigmentation, leaving the skin without normal protection from ultraviolet radiation and the associated risk of skin malignancy [24, 25]. It is well documented that the undesirable aesthetics of scars can lead to profound psychological implications [26,27].

Although it is difficult to directly extrapolate these results to patients suffering acute burns, similar levels of effectiveness may well be achievable and the evidence provides support for the successful transplantation of pigment producing cells (functioning melanocytes) with ReCell.

7.9 Interpretation of clinical evidence

7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

There is good evidence from both prospective and retrospective studies that the use of ReCell is at least as effective as SSG in achieving wound healing in the acute management of partial thickness burns in both adults and children and achieves comparable cosmetic and functional scar results.

This benefit is not associated with any known device-related adverse events and patients who undergo treatment with ReCell have no greater risk of wound infection or graft loss than patients treated with SSG.

The addition of ReCell to SSGs and dermal grafts allows more rapid epithelialisation of the burn site than would have been achieved with SSG alone.

The use of ReCell with biological dressings such as Biobrane is well established. This combination offers comparable benefits to SSG but is associated with more rapid healing, lower costs and shorter length of hospital stay. There is insufficient evidence to quantify any incremental benefit of this combination over either component used alone.

ReCell can be used to treat donor sites for SSGs and allows more rapid healing. In patients with large burns, this approach is advantageous, as it allows skin to be re-harvested from the site more quickly than would otherwise be the case.

When used to reprofile or repigment established burns scars, ReCell yields high rates of improvement in the final aesthetic result. This beneficial result on pigmentation is backed up by similarly positive results in patients with vitiligo treated with ReCell.

7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

There is one large randomised controlled trial [7] and one large retrospective regression analysis [9] of ReCell that underlie its safety and efficacy in the acute management of burns. The remaining evidence derives from two small randomised controlled trials[8,21] and a number of case series – both comparative and non-comparative. Inevitably, the lack of multiple randomised controlled trials means that making robust comparisons of different treatment modalities is challenging. Clearly the design of a retrospective case series does not include the advantages of randomisation and few of the measures described can be appropriately analysed from a statistical standpoint.

This limitation is compounded by the inherent heterogeneity of burns patients. Differences in age, depth, location and extent of burns mean that burns management is not readily amenable to standardised management protocols – a fact reflected by the lack of clinical guidelines highlighted in section A.

These combine to mean that the results presented are probably best understood in qualitative rather than quantitative terms. For instance, we can say with some confidence that ReCell is at least as effective as SSG in partial thickness burns and that length of hospital stay is likely to be less. Converting this comparison into an estimate of the number of days involved, however, would extend beyond the limits of the study designs and would, in any case be highly dependent on the patient populations being treated.

On the positive side, the wide range of patient types and treatment strategies evaluated in the case series, and the absence of adverse events, gives us a degree of confidence that the results seen are likely to be applicable and safe across a broad range of patients.

7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

The scope requires that evidence should address a) patients with partial thickness burns and scalds not requiring SSG and b) patients with large area burns, whether full thickness or deep partial thickness, where SSG may be required. Both these patient groups have been adequately addressed by the evidence presented, with acute management of the burn, donor site management and late scar revision being covered. Although not a study, additional cases of ReCell combined with SSG may be seen illustrated in O'Neill 2012 [28].

Secondly, the scope asks that the interventions considered should be either a) ReCell alone or in combination with biosynthetic or standard dressings or b) skin mesh graft in combination with ReCell. Once again, both these interventions have been covered within the presented evidence, either alone or in comparison with each other

Thirdly, we are asked to consider comparisons with either biosynthetic or standard dressings alone for partial thickness burns or SSG with or without biosynthetic dressing in large area burns. These comparators have all been covered by the presented evidence, although all possible permutations have not been addressed – for instance there is insufficient evidence to state how ReCell combined with biosynthetic dressings compares with ReCell combined with standard dressings.

Fourthly, there is a range of twelve outcomes that we are asked to consider. Most of these have been covered for some of the scenarios investigated although not all are covered for all combinations. Thus, for instance, we have good data on wound infection rates for ReCell alone, ReCell + SSG and SSG alone in a range of different burn types, but data on surgical procedures and theatre time is not available for all of these three options. No data are available for some outcomes (growth rate in children, and transfusion rates). Partial data exists for others: for instance we can describe the impact of the

different treatment options on length of hospital stay, but this cannot be expressed as length of stay per % TBSA.

Finally, we are asked to consider special issues relating to the porcine origin of trypsin in ReCell and the impact of ReCell on skin pigmentation. We have presented extensive data on skin pigmentation, derived from both burns and non-burns patients. Regarding the porcine origin, we are not able to offer any information on the acceptability of the technology to individuals with religious prohibitions relating to pigs.

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

The critical issue regarding external validity relates not to the technology and the study results presented but to the inherent heterogeneity of burns patients. As already discussed, management strategies for burns are essentially individualised and it is very difficult to define standard patterns of care. Whilst general principles as to the areas where ReCell may be most advantageously used can be inferred from the evidence, it will never be possible, regardless of the future extent of the evidence, to draw firm lines and define protocols.

Data from Wakefield (Dunne 2012 [10]) have shown how ReCell can be effectively implemented into a general care pathway, but the actual treatment used will always depend on the individual medical, social and cultural characteristics of the individual patient.

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

ReCell as an adjunct to the existing care pathway is suitable for all burn surgeries, ranging from donor site treatment [14] to burn injury treatment alone and in combination with conventional skin grafting. It has been shown to be particularly well suited for mixed (including indeterminate) depth burns[10], darker skin patients[23], facial burns [13], paediatric scalds [8,10] and those with extensive burns [16, 22].

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

The review of the economic evidence should be systematic and transparent and a suitable instrument for reporting such as the PRISMA statement ([redacted]).

A PDF copy of all included studies should be provided by the sponsor.

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

The search strategy set out to identify studies in one of three qualifying groups:

1. Economic evaluations of ReCell in the acute treatment of burns
2. Economic evaluations of biological or other dressing types in the acute treatment of burns
3. Cost impact studies in acute burn management, regardless of intervention used

Electronic databases searched were: MEDLINE (including In Process), EMBASE and NHS Economic Evaluations Database. A broad search strategy was used to maximise the number of potential studies, as prior experience had led us to expect a relatively small number of studies would be identified. Details of the search terms used are given in Appendix 3.

After preliminary screening of abstracts for likely inclusion, full text versions of the studies were obtained. In addition to formal inclusion/exclusion assessment of these studies, reference lists were manually searched in order to identify possible further qualifying studies.

As the availability of full data is a necessary requirement for use of economic studies, no hand search of abstracts presented at medical meetings was carried out.

Finally the manufacturer was consulted in order to identify any further potentially qualifying unpublished studies.

Search dates: As cost data are time-sensitive, a decision was made to limit the search to the past 10 years (Jan 2003 – July 2013)

Perspective: We ideally wished to identify studies evaluating UK NHS expenditure. However, the expected paucity of published data meant that no strict geographical limitation was placed on the search, although any UK studies identified will be given greater weight in any subsequent use within this submission.

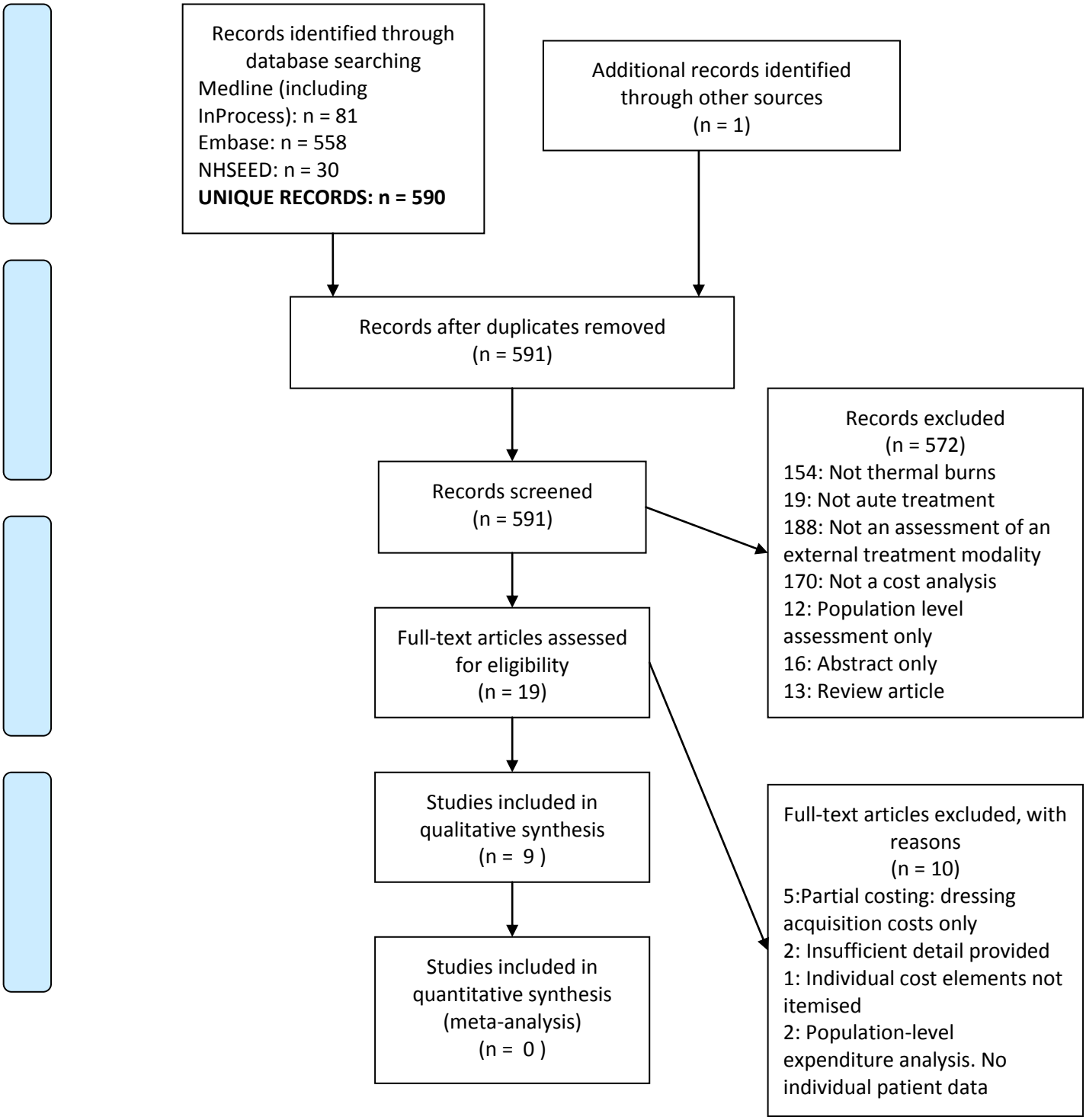
8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table C1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Adults and children undergoing treatment for flame burns and scalds of at least partial thickness
Interventions	Any specified external wound management strategy including, but not limited to ReCell and biosynthetic dressings
Outcomes	Cost of care (expenditure and/or reimbursement), cost benefit, cost utility, budget impact
Study design	Cost effectiveness analyses, cost of care analyses, budget impact analyses, other economic assessments.
Language restrictions	None
Search dates	January 2003 – July 2013
Exclusion criteria	
Population	Patients undergoing care for any injury other than flame burns and scalds
Interventions	Surgical strategies, oral or parenteral therapies, any treatment not given at the time of acute burn management
Outcomes	Non cost-based outcomes, population-level assessments (ie not based on individual patient care costs), partial cost assessment (ie insufficient to compare overall costs of care for the element assessed)
Study design	Epidemiological assessments, non-quantitative review articles
Language restrictions	None
Search dates	Published before January 2003

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure 5 – PRISMA flow chart for economic literature search



8.1.4 Description of identified studies

Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

The search identified three qualifying cost effectiveness analyses, all evaluating two types of dressing [Carayanni 2011[29], Caruso 2006[30], Silverstein 2011[31]. There were no formal economic evaluations of ReCell or biological dressings.

All remaining studies were cost of care analyses, which were used to inform the costings and transition probabilities for the de novo model

Table C2 Summary list of all evaluations involving costs

Study name (year)	**Location of study**	**Summary of model and comparators**	Patient population (key characteristics, average age)	Costs (intervention and comparator)	Patient outcomes (clinical outcomes, utilities, life expectancy, time to recurrence for intervention and comparator)	Results (annual cost savings, annual savings per patient, incremental cost per QALY)
Carayanni 2011[29]	Burn centre in Athens, Greece	Cost effectiveness analysis of oil-based vs povidone iodine based dressings	211 patients undergoing acute treatment of burns not requiring surgery Mean age was 42.6 in oil group and 42.7 in iodine group 109 had superficial	Hospital stay cost Staff time costs Dressing costs Laboratory costs Medication costs	Two main indicators of effectiveness: 1. For deep partial burns effectiveness defined by a reduced length of stay in one group compared to the other 2. For superficial burns (outside scope) the time to achieve a 50%	Mean total cost of care per patient was lower in the oil-based group: €529.66 vs €566.21 (all) €579.83 vs €582.15 (deep) Oil based dressings were associated with a

			partial thickness burns (Outside scope) 102 had deep partial thickness burns. Mean TBSA was 9.89% and 10.26% in the two groups	All measured in 2006 Euros	reduction in transepidermal water loss defined effectiveness Data on pain, qualitative wound evaluation and complication rates were also collected	mean reduction in length of stay of one day Oil based dressings consequently dominated povidone iodine based dressings
Comment: This study evaluated a group of patients who were explicitly not expected to require surgery. This implicitly excludes those with indeterminate burns depth and therefore only covers the milder end of the scope-defined patient group						
Caruso 2006[30]	8 Burn Centres in USA	RCT of two types of dressing (Aquacel or silver sulfadazine [SS]) with cost effectiveness analysis	82 patients with burns of varying depths, excluding those likely to require grafting. Mean age 29.4 in Aquacel group and 24.0 in SS group Mean TBSA was 12.0% and 10.8% in the two groups	Costs of care included: Dressing acquisition costs Staff time costs Medication costs Hospital stay costs were not included All costs in 2004 US$	The primary endpoint was the cost effectiveness of Aquacel vs SS, based on a primary effectiveness endpoint defined as a comparison of the proportion of patients achieving full re-epithelialisation within 21 days Data were also collected for redressing pain, comfort and safety	Mean total cost of care was $1040.00 for Aquacel vs 1180.80 for SS Re-epthelialisation was achieved at 21 days in 73.8% of Aquacel patients vs 60.0% of SS patients Aquacel therefore dominated SS
Comment: This study, like the previous one, excluded patients with indeterminate wound depth and therefore only applies to a subset of the scope population. Additionally, hospital stay cots were not incorporated in the analysis						
Silverstein	10 burns	RCT	100 patients aged	Acquisition	Proportion with 100% re-	78.3% of Silicone

2011[31]	centres in the USA	comparing two types of dressing: Silver-containing soft silicone foam dressing (Silicone) and Silver sulfadiazine cream (SS). Cost data were collected as a secondary outcome in a subset of 40 patients (100 total). Data used to estimate cost effectiveness (cost per healed burn)	5+ with a second degree (partial thickness) burn area of 2.5% - 20%. Mean age 37.0 (Silicone) and 39.2 (SS) Mean TBSA treated 5.64% (Silicone) and 4.93% (SS)	cost of dressings Cost of staff time to change dressings Analgesia cost All costs in 2009 US$	epithelialisation at 20 days post burn Dressing and analgesic costs Primary outcome was defined as incremental cost effectiveness, based on the two outcomes above, although cost data were only gathered from 40% of patients Data also collected on % healed at 1 and 2 weeks post burn, mean length of stay, pain, ease of use, microbiological colonisation and safety	patients healed by 21 days vs 66.2% of SS patients. Mean total cost was $309 in Silicone group and $514 in SS group Silicone therefore dominated SS
Comment: This study only collected direct costs associated with the dressings tested and does not therefore yield an overall cost of care figure						
Fong 2005[32]	Burn Centre in Perth, Australia	Audit reporting clinical results obtained with two different dressing types: Acticoat	Four pairs of burns patients matched for TBSA and burn depth.	The following costings were documented for the 8 patients: Hospital stay	The primary endpoint for this costing sub-audit was the total cost of care for the four patients on each dressing type excluding antibiotic, surgery, cultured epithelial autograft	Average total cost of care per patient was $19,726 in the Acticoat group and $27,339 in the Silvazine group. Dressing acquisition

		and Silvazine. Within the data is a detailed cost comparison for four matched pairs of patients receiving treatment with one or the other dressing type		costs Dressing costs All costs in 2002 US$ Note: although table 5 in this paper quotes Aus$, in all other sections, the results are said to be US$	and staff costs.	costs accounted for $946 and $1533 per patient respectively , the remainder being due to hospital costs.
Comment: Although this study is limited by the exclusion of certain cot elements, the level of detail provided make this a useful contribution to the understanding of true costs of care in burns						
Pellatt 2010[33]	Paediatric burns centre in Bristol, UK	Assessment of cost of care for major paediatric burns	3 patients with major burns (30-40% TBSA) – mixed partial and full thickness Patients aged 3, 4, and 12 years	Fully detailed costing including: Staff time Theatre time Consumables Ward costs Invasive procedures Medications Laboratory Imaging + 20% uplift for overheads	Main outcome was descriptive analysis of the costs in each case	Total costs ranged from £55,355 to £74,494 (mean £63,157) Largest clinical components were ward costs (ICU/HDU + standard ward) and theatre time. Dressing costs accounted for 5% of total costs

				All costs in 2009 £		
Comment: Although this study is very small and included only severely burned children, this paper is a valuable source of information on NHS unit costs to validate the assumptions used in our de novo model						
Hemington-Gorse 2008[34]	Welsh Burns Centre, Swansea	Assessment of cost of care for major burns: comparison between actual expenditure and HRG costing	Records from 409 patients admitted over 2005/6 were used to generate unit costings for all elements of care. These values were applied to three patients to produce individual costings. Patient ages were 35, 31, and 45. TBSA were 27-48%	Detailed costing (as for Pellatt above). Staff costs, drugs, consumables and indirect costs were assessed for each area to generate a cost per unit time for: ITU Theatre Dressing room Low dependency ward. Individual high cost items were separately accounted for. All expressed as 2005/6	Narrative description of cost of for each of the three patients. Parallel assessment of payment accrued using HRG tariff	Cost of care ranged from €121,496 - €761,205. Theatre time and ITU stay were the most expensive components. HRG-based costings were 39%, 49% and 6% less than this for the three patients assessed

				Euros		
Comment: Once again, a small study with severely burned patient but, like Pellat 2010, it provides UK unit costs for use in our model						
Griffiths 2005[35]	Regional burns unit, Bristol, UK	Assessment of cost of care for 3 paediatric scalds	Three patients aged 13 months, 21 months and 2 years with scalds affecting 4%, 2% and 3% TBSA. All partial thickness burns	Comprehensive cost assessment including staff costs for the following elements: Ward costs Theatre visits Dressings Medications All costs expressed as 2004 £.	Narrative description of costs incurred in the management of the three patients. Comparison made with the equivalent HRG-based tariff	Total costs were £2169, £2063 and £1317 Equivalent HRG costings were 50%, 48% and 35% less than this
Comment: This study provides similar information to the previous two analyses, but this time focussing on more minor burn injuries						
Ahn 2012[36]	Burn centre in Sydney, Australia	Detailed cost of care analysis of 20 adult patients	Random sample of 20 adult patients (mean age 40.5) admitted to burns unit, stratified into four categories by extent of burns: 0-9% TBSA 10-19% TBSA 20-29% TBSA 30% + TBSA.	Comprehensive assessment including the following elements: Ward stay Staff costs Theatre visits Dressings Medications	Costing data were used to estimate: Cost per % TBSA Cost per hospital day Regression analysis to develop equation for estimation of total costs based on TBSA	Total cost of care was $2.45million ($122,456 per patient). By group: Gp 1: $3,884 per pt Gp 2: $16,536 per pt Gp 3: $28,312 per pt Gp 4: $49,233 per pt Overall cost per % TBSA was $6,264

			Overall mean TBSA was 19.6%. In the four groups it was 3.1%, 13.2%, 22.6% and 39.3% respectively	Lab tests Imaging Fluid and nutritional support All costs in 2008 AUS $		As costs per TBSA was not a linear function, a regression formula to estimate the cost more accurately was presented
Comment: the methodology here is similar to that used in Rawlins (unpublished) which is described below and was used to generate costings for our own model. It therefore helps to validate the model.						
Rawlins 2013[37] Unpublished data – content provided as spreadsheet	Burns centre in Wakefield, UK	[redacted]	[redacted]	[redacted]All costs reported in 2011 £	Primary objective was to describe costs associated with each patient. [redacted]	[redacted]
Comment: This work is not yet completed, but it provides a good insight into the costs of current UK practice across a wide range of burns severity and is therefore included here.						

8.1.5 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

Table C3 Quality assessment of health economic studies

Study name Carayanni 2011[29]		
Study design		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Generated within this study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	As above
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	

13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/A	
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Stated as 2006 Euros
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	No discount in base case because time horizon <1year. Sensitivity analysis explored discounting on basis of economic contraction
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	Only discount rate was explored
29. Were the ranges over which the parameters were	Yes	

varied stated?		
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Caruso 2006[30]		
Study design		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	

7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Generated within this study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	As above
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Stated as 2004 US dollars
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	

22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	No	21 day study, so discounting not justfied
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Silverstein 2011[31]		
Study design		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Generated within this study
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	Yes (see above)
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	

15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	US$ 2009
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	n/a	
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	
32. Were major outcomes	Yes	

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

Study name Fong 2004[32]		
Study design		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	No	Cost outcomes were secondary to the clinical objectives of the study
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost of care analysis only
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	n/a	No CER generated
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	No	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported	n/a	

separately?		
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Stated as 2002 AUS$
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	n/a	
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	

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

Study name Pellat 2010[33]		
Study design		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	n/a	Descriptive cost of care analysis
5. Were the alternatives being compared clearly described?	n/a	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	n/a	No CER generated
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported	n/a	

separately?		
15. Was the relevance of productivity changes to the study question discussed?	No	Paediatric population
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	UK £. Assumed date 2009
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	n/a	
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	

32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Hemington-Gorse 2008[34]		
Study design		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	n/a	Descriptive cost of care analysis
5. Were the alternatives being compared clearly described?	n/a	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	n/a	No CER generated
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported	n/a	

separately?		
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Euros. Assumed date 2006
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	n/a	
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	

32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Griffiths 2005[35]		
Study design		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	n/a	Descriptive cost of care analysis
5. Were the alternatives being compared clearly described?	n/a	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	n/a	No CER generated
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported	n/a	

separately?		
15. Was the relevance of productivity changes to the study question discussed?	No	Paediatric population
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	UK £. Assumed date 2004
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	n/a	
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	

32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name Ahn 2012[36]		
Study design		
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	n/a	Descriptive cost of care analysis
5. Were the alternatives being compared clearly described?	n/a	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
8. Was/were the source(s) of effectiveness estimates used stated?	n/a	No CER generated
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported	n/a	

separately?		
15. Was the relevance of productivity changes to the study question discussed?	No	Mentioned in passing in the introduction
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Results presented as 2008 Aus$. Main results also given in US $
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
22. Was the time horizon of cost and benefits stated?	n/a	
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if cost or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	No sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	

32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

No table has been provided for Rawlins 2013[37] as this is uncompleted work, without a full draft of the paper available for assessment.

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

There have been no published economic analyses that allow us to answer the two questions posed in the scope, therefore de novo analyses are required.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

Patients of any age presenting for acute care of partial thickness burns or scalds, where there is no immediate need for mesh grafting. The second patient group (patients requiring meshed graft) has not been modelled – for the rationale please see

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

For the first decision problem, the comparators used in the analysis are as defined in the scope: ReCell +/- biosynthetic dressing (Biobrane) vs conventional dressings or Biobrane alone

For the second decision question defined in the scope, we have not presented a model, as there is insufficient evidence to feed the input parameters.

The main indication for the use of ReCell with a meshed SSG is in patients with extensive burns, in whom a shortage of available unburned skin means that complete epithelial coverage cannot be achieved in a single step. With a traditional or small-mesh graft, part of the burn must be covered first, while waiting for the donor sites to heal sufficiently to allow re-harvesting. With ReCell, a larger mesh graft can be used, with the interstices being seeded with epithelial cell. This reduces the total time required to achieve 100% epithelial coverage (feedback from clinical advisors).

If ReCell is also used to seed the donor sites, the time elapsed before re-harvesting can be carried out is reduced, thereby also reducing the total time to healing (Echlin 2012a[13]). Given that the major drivers of costs in severely burned patients are the length of stay and use of theatre time (Pellat 2010[33]), it seems likely that this strategy will need net savings well in excess of the cost of ReCell.

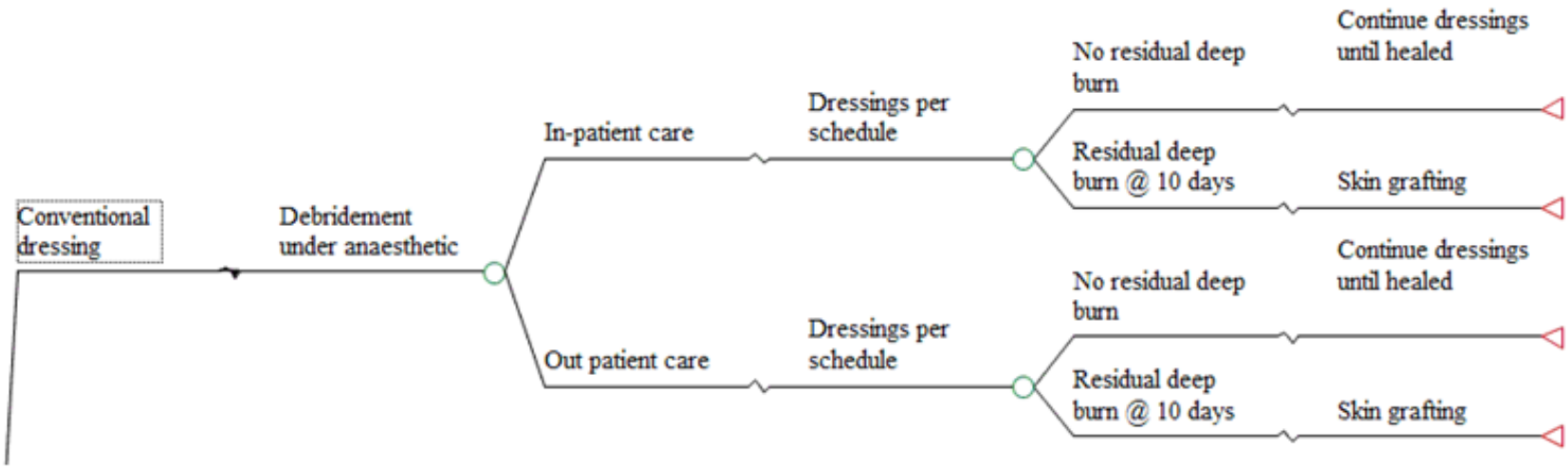
An alternative strategy in this situation is the use of cultured epidermal cells. A biopsy is harvested from the patient's own intact skin and then cultured into sheets of cells in a laboratory. These can then be used to cover the area. This process, however is costly (approximately £2,500) and time consuming – typically 2-3 weeks from the time of harvesting, thereby incurring substantial additional hospital stay costs.

Unfortunately, however, the quantitative data to support these scenarios is lacking and any model devised would be purely speculative.

In the light of our professional advice and the lack of any quantitative sources to fuel our model assumptions, we have therefore been forced to omit a cost analysis for this second decision problem.

Figure 6: Model structure

Provide a diagram of the model structure you have chosen.



9.1.4 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

As discussed in the clinical section, the challenge that presents itself in the modelling of burn care management is that the pathway of care is highly individualised, depending on the precise nature, extent and depth of burn, and the characteristics of the patient being treated. The pathway outlined in section 3.3 therefore represents only broad principles of care, an approximation that is carried over into the model.

There are several distinct stages to consider where the use of ReCell may have a financial impact over one or both of the comparators over and above its acquisition cost:

1. *The requirement to remain in hospital for treatment.* Conventional dressings require regular renewal – this may be carried out daily or on alternate days, depending on the policy in the individual unit (step 2, section 3.3). This process, by exposing the burn, is a potential source of infection and must therefore be carried out in a sterile environment (theatre or sterile dressing room). It is also potentially painful and therefore, especially in children, strong analgesia or general anaesthesia may be required. For ReCell or Biobrane the wound surface is left covered until formal reassessment at day 10-12 (Step 3, section 3.3). Until this point, generally only the secondary superficial dressing requires changing, a process that does not require the use of specialist sterile facility and may be carried out in out-patients, if required. This means that conventionally treated patients are more likely to remain in hospital than those using ReCell and/or Biobrane. This element of the process is captured in the first chance node of the model

2. *Requirement for meshed SSG*. If a wound has an area of full thickness burn, it cannot re-epithelialise from the base but depends instead on migration of cells from the wound edge. Whilst this may be sufficient for

very small areas, in practice an area of any size will require grafting with healthy epithelial tissue from elsewhere on the body. At the initial assessment (step 1, section 3.3) such areas may not be immediately obvious, with the deeply burned area only becoming apparent when it fails to heal over the course of step 2. ReCell, by populating the wound base with both keratinocytes and fibroblasts effectively functions as an early skin graft and reduces the number of patients progressing to SSG at a later stage. Neither conventional dressings nor Biobrane alone can achieve this.

This element of difference is captured at the second chance node of the model.

3. *The time to achieve re-epithelialisation*. Even if SSG is not required, the time required to heal the wound is a major cost driver for burns patients. Especially for in-patients, the daily costs incurred are substantial. ReCell, by populating the wound site with epithelial cells from the outset of treatment, is associated with faster rates of healing than conventional dressings, which rely purely on re-epithelialisation from the wound base. One advisor suggested that, in her experience, this difference results in a 25-50% reduction in healing times with ReCell, an experience matched in the RCT of Wood et al[8], where a reduction of 56% was seen with ReCell + Biobrane. Biobrane alone, by allowing the wound to remain covered and undisturbed, also achieves a reduction in healing times. In the Wood study[8] this effect was not quite as great as that of ReCell and Biobrane combined, although the small numbers of patients involved mean that it is impossible to know if this difference is real.

   This element of the care pathway is captured in the calculation of the payoffs at the end of the non-grafted arms of the model.

An additional point of difference between ReCell and the comparators is the long term aesthetic appearance of the burn scar. Whist it is reasonable to assume that this benefit is likely to yield cost savings in terms of a reduced

requirement for scar revision surgery, a lack of available data to populate the model means that we have restricted our analysis to the acute phase of treatment.

A Markov structure using a daily cycle would have had the potential to capture the day-to-day changes in management (and therefore cost), as in reality, the decisions to discharge or to proceed to skin grafting are not necessarily taken at a fixed time point. However, we have been unable to source sufficiently detailed data to yield daily state transition probabilities and, given the relatively small number of possible care pathways, elected to use the simple decision tree option.

9.1.5 Provide a list of all assumptions in the cost model and a justification for each assumption.

For the base case the following assumptions have been made:

1. At the time of initial treatment the burn is considered to be partial thickness with no definite areas of deep involvement. This is in keeping with the scope

2. The area of burn requiring treatment is 640 sq cm. This represents around 5-10%TBSA depending on the age/size of the patient. There are a number of reasons why this size has been chosen:

    a. This size of burn is sufficiently severe to warrant active intervention in a burn centre where ReCell might be considered an option

    b. Data from cost analyses carried out in both the Australia (30) UK (31) show that costs of care decline rapidly at TBSA <5%

    c. In patients with larger burns – 20%+ TBSA – the costs of intensive care, circulatory support, multiple surgical interventions

and very extended lengths of stay are likely to override any cost differences attributable to ReCell or its comparators.

3. All burns are considered sufficiently severe to warrant initial debridement in theatre. Patients undergoing conventional and Biobrane treatment are assumed to require 20 minutes theatre time at the start of treatment, while those treated with ReCell will require 30 minutes theatre time. This is based on feedback from our clinical advisors

4. All patient will remain as inpatients until day 2, following which those fit for discharge will receive re-dressings either as outpatients or as ambulant visitors to the ward. This is based on feedback from our clinical advisors

5. All patients are assumed to be managed either on a general burns ward or in outpatients, if they have been discharged. ITU treatment has been excluded, as its very high costs (£4,210 per day) would obscure other treatment cost differences.

9.1.6 Define what the model's health states are intended to capture.

As we adopted a decision tree approach, rather than a Markov model, the term "health states" does not strictly apply. However, our model distinguished between the following three mutually exclusive binary states:

- Inpatient treatment vs outpatient treatment
- Requirement for SSG at 10 days vs no requirement for SSG
- Wound 100% epithelialised vs incomplete healing

Each of these three states are associated with different probabilities, according to the treatment method adopted, and each is also associated with cost differences, thereby driving the conclusions of the model.

9.1.7 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table C4 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	21 days	The model explores the acute treatment process of burns management, which ends with complete re-epithelialisation. Clinical trials of conventional dressings yield typical times to re-epithelialisation in patients not requiring graft of 13.4 – 18.3 days in patients with the size of burn we are considering. The IBID (3) has documented the mean llength of stay for burns in the UK. For the categories Moderate-severe, which correspond to our population of interest, mean length of stay ranged from 8.8 days – 15.3 days. 21 days was therefore considered sufficient to capture the majority of patients and further costs were cut off at this point	Caruso 2006[30] Silverstein 2011[31] Fong 2005[32] Cuttle 2012[38] IBID 2007[3]
Discount of 3.5% for	No discounting applied	The time horizon was too short to justify discounting	

costs			
Perspective (NHS/PSS)	NHS	All the costs accounted for were directly incurred by the NHS hospital trust, with no consideration given to indirect or societal costs. This is in accordance with the scope	
Cycle length	n/a	A Markov model was not used, as a simple decision tree structure allowed as to answer the decision problem adequately. Cycle length is therefore not relevant.	
NHS, National Health Service; PSS, Personal Social Services			

9.2 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical evidence section of the submission (section 7). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

Detailed objective data relating to the parameters used in the model are relatively difficult to ascertain, owing to the scarcity of comparative studies in the evidence base. We have used data from both the clinical and costing studies identified in our systematic reviews, in addition to input from four consultant burns surgeons experienced in the use of both ReCell and Biobrane (see paragraph 9.2.5).

Healing times for different treatment modalities. The baseline for these estimates was the expected time to achieve re-epithelialisation using conventional dressings. We identified two studies from our economic review that compared different forms of conventional dressings in patients with burns and a mean TBSA of 5-10%, and provided estimates of the mean time to 100% re-epithelialisation (Caruso 2006[30] and Silverstein 2011[31]). One additional similar study (Cuttle 2007[38]) was identified in the original economic literature search but was excluded from the final results as it did not provide

individual patient level costing data. The six values described in the treatment arms of this study were 16 days, 17 days, 13 days, 17 days, 15 days and 18 days. On his basis, a value of 15 days for time to healing was used..

The impact of ReCell, Biobrane or their combination on these healing rates is not clearly documented in the published literature. In the RCT carried out by Wood et al[8], the median healing time with both Biobrane and ReCell + Biobrane was 16 days, compared with 36.5 days for conventional dressings, representing a 56% reduction. To eliminate outliers, if we look at the interquadrantic range, at the lower quartile the times to healing were 18.5 days, 14.25 days and 11.5 days for Conventional, Biobrane and Biobrane + ReCell respectively, representing reductions of 23% for Biobrane alone and 38% for ReCell + Biobrane. For the upper quadrant, the equivalent times to healing were 47.7 days, 23 days and 18 days, representing reductions of 52% for Biobrane alone and 62% for ReCell + Biobrane.

Another case series described the use of ReCell alone on SSG donor sites (Echlin 2012a[13]. Although not identical to a thermal burn, the presence of de-epithelialised skin represents a good model for observing healing. Two patients had more than one donor site. In these, the use of ReCell was associated with faster healing than the use of conventional dressings. In one case, the ReCell treated site healed within 7 days, while the conventionally treated site took 36 days (80% reduction). In the second case, the ReCell treated site healed in 13 days, while the conventionally treated site took 20 days (35% reduction).

None of these data are sufficiently robust to generate robust estimates of the impact on healing times. As a conservative estimate, we set baseline healing rate reduction for Biobrane and ReCell alone at 30% with the combination of the two at 40%, while testing across the range 0%-50% for all three.

Requirement to be treated as an in-patient

The possibility of discharge and management as an out-patient hinges on a number of factors:

- Extent of dressings and therefore practicality of home management
- Pain associated with dressing change and therefore requirement for analgesia
- Co-existing conditions/injuries with requirement for inpatient management
- Social and geographical issues

A key difference between conventional dressings and ReCell or Biobrane is the type of dressing required. For ReCell and Biobrane, the wound surface itself remains covered, while secondary dressings – largely required to absorb any excess exudate – is all that needs to be changed. This is relatively simple and pain free. For conventional dressings, the exposure of the wound site not only requires more sophisticated sterile dressing facilities but also tends to be associated with considerably more pain. For these reasons, a patient with conventional dressings is more likely to require in-patient management.

We have been unable to identify any clinical studies characterising this difference so, based on advisor input, have adopted arbitrary values of 50% in-patient care for conventional dressings, with 25% for the other modalities.

Probability of requiring skin grafting

An assessment of the burn is made at around 10-12 days. If at this stage there is evidence of areas of full thickness burn and if, in the clinician's opinion, it is felt unlikely that the wound will be fully healed by secondary intention by 21 days - the critical time for achieving a good scar result (Deitch 1983[1]) – then a decision will be made to undertake skin grafting.

We identified data from four clinical trials of conventional dressings with regard to this outcome - two from the economic review ((Caruso 200630, Silverstein 201131) and two from the original search that were excluded on grounds of inadequate costing data (Cuttle 200738 and Ostlie 2012[39]). The

proportion of patients failing to heal within 21 days in the eight conventional dressing arms in these studies were: 15%, 22%, 26%, 26%, 32%, 34%, 36% and 40%. Based on these results, we chose a baseline value for the model of 30%.

There are very limited equivalent data for the three comparators. The study of Wood et al[8] selected a group of patients who were felt likely to need surgery from the outset. Of these, 3/4 treated conventionally went on to grafting, 1/4 treated with Biobrane and 0/4 treated with ReCell + Biobrane. Given the small sample and the inclusion criterion mentioned above, it was felt unlikely that these results could be extrapolated, so we sought the opinion of our expert advisors.

They felt that, although Biobrane allowed the speed of healing to be accelerated, there was no evidence that it would have an impact on the likelihood of an SSG being required. For this arm, therefore, no alteration was made to the baseline assumption. For ReCell-treated patients (with or without Biobrane), it was felt that the risk of requiring SSG was substantially lower, with estimates ranging from <5% at one extreme, to a 25-50% reduction compared to conventional at the other. For the purposes of the baseline model, we used an absolute grafting rate of 10% for both ReCell alone and ReCell + Biobrane, with a broad range explored in the sensitivity analysis.

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

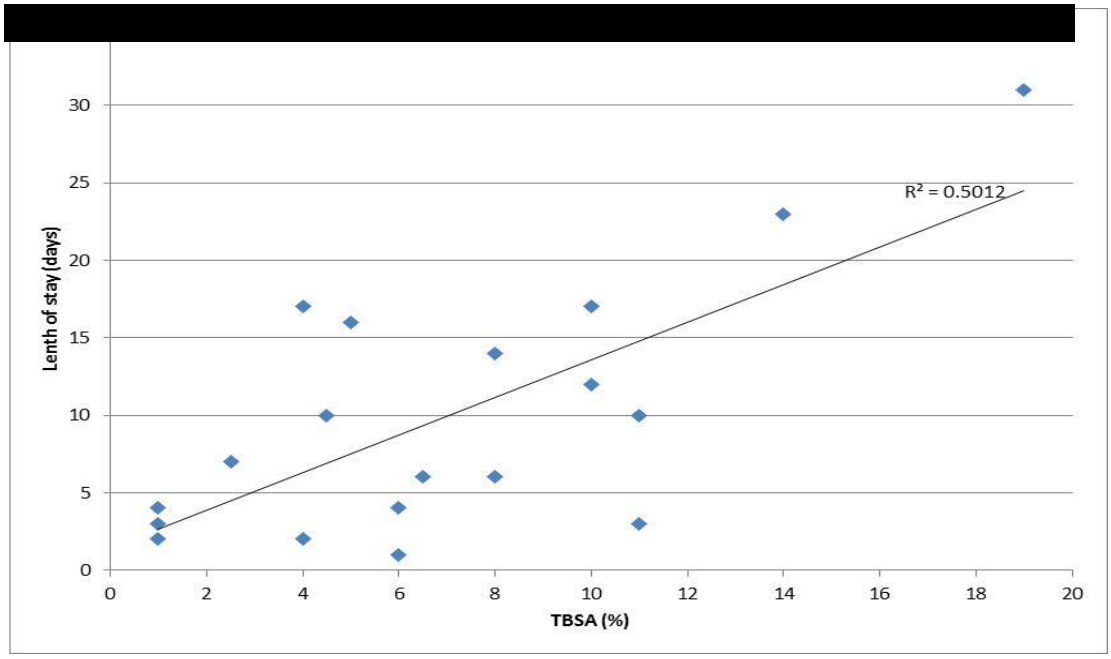
No extrapolation beyond acute phase

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

No intermediate outcomes used in the baseline model.

For the sensitivity analysis, the effect of varying TBSA affected was explored. TBSA is closely correlated to overall admission cost (Ahn 2012[36], Rawlins 2013[37]). This reflects its association with a number of cost variables in our model, including the proportion of patients treated as an in-patient, the proportion of patients requiring CCG and the mean time to healing. We have no detailed data available to map these associations accurately. However, the data in the unpublished Rawlins analysis, allow the exploration of the relationship between TBSA and length of stay. – which is, itself dependent on the same three variables. This demonstrates an approximately linear relationship between the two variables (R^2=0.5), once outliers have been removed (see figure 6). Within the range of TBSA explored, therefore, we applied a linear correction to the values for inpatient care, total healing time and requirement for SSG, subject certain limits of clinical plausibility:

- Proportion in-patient: 10% - 75%.
- Proportion needing SSG: 5% - 50%
- Mean time to heal: 7 days – 28 days



9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Adverse events were not captured in the model, as there is no evidence that the adverse event rates differ between the treatments used.

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

The panel of expert advisers was selected by the manufacturer, on the basis that they were consultant burns/plastics surgeons,, with experience of using ReCell, Biobrane and/or the combination in the type of patients included in the scope.

Five consultants were asked to assist and four provided responses to our questions. Each set of responses was independent of the others, with no intention to arrive at a consensus view. This was to ensure that we were able to grasp the range of opinion for each variable, rather than a single compromise value.

Those participating were:

Mr Jeremy Rawlins – formerly Consultant Plastic Surgeon at the Burns Unit at Pinderfields Hospital, Wakefield UK, now working in the same role at the Royal Perth Hospital, Perth, Australia.

Mr Bruce Philps – Consultant Plastic Surgeon at the St Andrews Centre for Plastic Surgery and Burns at Broomfield Hospital, Chelmsford UK

Miss Isabel Jones – Consultant Plastic Surgeon and Head of the Burns Unit, Chelsea and Westminster Hospital, London UK

Prof Fiona Wood – Head of the Burns Unit at the Royal Perth Hospital, Perth, Australia.

Fiona Wood invented and patented the technology that underlies the ReCell system and has a financial stake in the parent company that owns the patents. She also has more experience in the use of ReCell than anyone else in the world, so her advice was considered essential.

The other three advisors have no financial conflicts of interest.

The background information provided included a summary of the NICE scope and the proposed strategy for economic modelling. The clinical background was familiar to al participants, much of it having been generated in their own units.

Each participant was then given a questionnaire to complete, asking for their views on the most plausible care pathways, transition probabilities and treatment durations for each of the nodes in the baseline model. Opportunity was given for extended comments to explain the context and rationale for their responses.

In addition, a series of more generic questions were posed, in order to understand the clinical decision making process insofar as it relates to the factors determining the choice of treatment for any given situation.

The responses were returned to the health economics team, who then had the opportunity to send follow-up questions to clarify their answers. No formal Delphic process was used and advisors were not aware of each other's responses.

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C5 below.

Table C5 Summary of variables applied in the cost model

Variable + name used in model	Value	Range	Source
Proportion of patients treated as an in-patient			
Conventional (pInpatientConv)	50%	25% - 75%	Expert panel opinion
ReCell (pInpatientRC)	25%	25% - 75%	
Biobrane (pInpatientBio)	25%	25% - 75%	
ReCell + Biobrane (pInpatientComb)	25%	25% - 75%	
Proportion of patients progressing to SSG			
Conventional (pSSGConv)	30%	15%-40%	Based on the range of values seen in four comparative studies: Caruso[30], Siverstein[31], Cuttle[38] and Ostlie[39]. Rationale described in 9.2.1
ReCell (pSSGRC)	10%	5%-20%	Expert panel opinion
Biobrane (pSSGBio)	30%	15%-40%	
ReCell + Biobrane (pSSGComb)	10%	5%-20%	
Mean time to 100% re-epithelialisation			
Conventional (tHealConv)	15 days	13-18 days	Based on the range of values seen in three comparative studies: Caruso[30], Siverstein[31], and Cuttle[38]. Rationale described in 9.2.1

ReCell (tHealRC)	10.5 days	7.5 – 15 days	Calculated by applying a fixed percentage improvement in healing times to the range of baseline values for conventional treatment. Based on Wood[8] and Echlin[13]. Rationale described in 9.2.1
Biobrane (tHealBio)	10.5 days	7.5 – 15 days	
ReCell + Biobrane (tHealComb)	9 days	7.5 – 15 days	
Costs of resources.			
Conventional dressing change(cDressing)	£166	£83-249 (+/- 50%)	Pinderfields Burns Unit cost analysis (Rawlins[37])
ReCell (cReCell)	£950 per 320 sq cm treated	Fixed	
Biobrane (cBiobrane)	£60.80 per 320 sq cm treated	Fixed	
Secondary dressing change (cDressminor)	£25	£12.50-£37.50 (+/- 50%)	Nominal cost based on an assumption of 30 minutes nurse time + consumables
Daily bed cost in burn unit (cBed)	£152 (standard burns unit bed)	£76-£228	Pinderfields Burns Unit cost analysis (Rawlins[37])
Daily staff cost in burn unit (cStaff)	£469 (all professionals involved)	£234.50 - £703.50 (+/-50%)	Pinderfields Burns Unit cost analysis (Rawlins[37])
Hourly cost of theatre time (cTheatre)	£5,411 (per hour of use)	£643.50 - £5,500	Baseline value from Pinderfields Burns Unit cost analysis (Rawlins 37). Other UK studies have shown hourly costs ranging from £643.50 (Pellat[33]) to £5,500 (Hemington-Gorse[34]). The range tested therefore extends to these limits.
Overall cost of SSG – procedure + post-op care (cGraft)	£5,214.50	£1,948 - £6,663.50	Based on 30 minutes theatre time, discharge at 4 days, secondary re-dressing every 2

			days (all expert advice) + fully healed by 11 days (Ostlie[39]). Range tested defined by upper and lower limits of these values for conventional treatment.

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

Acute in-patient burns management is specifically excluded from PbR. For this reason there are no burns-specific codes in HRGv4. Pricing is therefore negotiated on a local basis according to a range of formulas. These contracts are not based on individual patient costings and, as such, often differ significantly from the actual costs incurred.

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

As explained above, OPCS procedure codes are not relevant to this analysis

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

The search strategy we used in section 8 captured studies of NHS resource utilisation within its search terms. We reviewed the original search results to identify any additional studies that might have been excluded as part of the original review. This left four relevant studies examining resource use within the NHS:

- Pellat 2010[33] - costing of a major paediatric burn
- Hemington-Gorse 2008[34] – cost of running the Welsh Burns Service

- Griffiths 2006[35] – cost of a hot drink scald
- Rawlins 2013[37] – cost of a mixed caseload of burns

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[1].

Clinical advisors not formally used to validate costs and resource use, although one of our advisors (Mr Jeremy Rawlins) had carried out one of the analyses and answered specific queries if required.

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

£950 per pack, each of which can treat up to 320 sq cm.

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

n/a

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C6 and C7. Table C7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

When completing tables C6 and C7 the price of the technology should refer to the list price stated in 9.3.4 unless a justification for using an alternative price has been provided in 9.3.5. If a technology is not for single use and consumables are needed to provide a treatment, these must be itemised and a breakdown of prices presented.

For all costs presented a source of the data must be stated.

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Table C6 Costs per treatment/patient associated with the technology in the cost model

Items	Value	Source
Price of the technology per treatment/patient	£950 per 320 sq cm. £1900 for the base case 640 sq cm	Manufacturer
Consumables (if applicable)	Self contained kit – no additional consumables required	
Maintenance cost	None	
Training cost	None (provided by manufacturer)	
Other costs	Use of ReCell adds approximately 10 minutes to the baseline 20 minutes procedure time. This is separately accounted for in the model and is estimated at £901. Renewal of secondary dressing on alternate days costed at £25 – based on 10 days treatment, total cost is £125	Expert opinion
Total cost per treatment/patient	Based on 640 sq cm, total cost is £2,926	

Table C7a Costs per treatment/patient associated with the comparator technology in the cost model (Conventional treatment)

Items	Value	Source
Cost of the comparator per treatment/patient	The cost of initial dressing is absorbed in the theatre cost.	Rawlins 2013[37]
Consumables (if applicable)	n/a (absorbed in dressing cost)	
Maintenance cost	n/a	
Training cost	n/a	
Other costs	Redressings required every 2 days at a cost of £166. Based on 10 days stay, total cost is £830	Rawlins 2013[37]
Total cost per treatment/patient	£830	

Table C7b Costs per treatment/patient associated with the comparator technology in the cost model (Biobrane)

Items	Value	Source
Cost of the comparator per treatment/patient	Prices of Biobrane vary according to dressing size. The mean value is £0.19 per	Manufacturer price list

	sq cm, equating to £121.60 per patient	
Consumables (if applicable)	Standard secondary dressing – absorbed in theatre cost	
Maintenance cost	n/a	
Training cost	n/a	
Other costs	Renewal of secondary dressing on alternate days costed at £25 – based on 10 days treatment, total cost is £125	Expert opinion
Total cost per treatment/patient	£246.60	

Table C7c Costs per treatment/patient associated with the comparator technology in the cost model (ReCell + Biobrane)

Items	Value	Source
Cost of the comparator per treatment/patient	£1900 (ReCell) + £121.60 (Biobrane) for the base case 640 sq cm	Manufacturers
Consumables (if applicable)	No additional consumables required	
Maintenance cost	None	
Training cost	None	
Other costs	Use of ReCell adds approximately 10 minutes to the baseline 20 minutes procedure time. This is separately accounted for in the model and is estimated at £901. Renewal of secondary dressing on alternate days costed at £25 – based on 10 days treatment, total cost is £125	
Total cost per treatment/patient	Based on 640 sq cm, total cost is £3,047.60	

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Health states not used in model

Adverse-event costs

9.3.9 Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

No adverse events included in the model

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

No additional miscellaneous costs

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

More rapid healing and a better result with regard to pigmentation are likely to result in more aesthetically acceptable scarring. It might be anticipate that this will reduce the long term requirement for restorative surgery. Unfortunately there are currently insufficient data to support this claim, however, so it could not be captured in the model

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

- Multiple univariate deterministic analyses
- Multivariate scenario deterministic analyses

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

A deterministic approach was used. Probabilistic sensitivity analyses were not undertaken.

In the field of burns management, individual circumstances determine the course of management to a much greater extent than in many other areas. The data that the model are based on therefore tend to be multimodal and subject to complex, non-normal distributions. This, combined with a lack of rigorous, research-defined data for many of our parameters would make probabilistic analysis essentially meaningless.

For the deterministic ranges, for the same reasons, rather than adopt a mean + 95% CI approach, we have selected either mean +/- 50%, or taken the extremes of estimates available for the parameter in question.

9.4.3 Complete table C10.1, C10.2 and/or C10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table C10.1 Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base-case value	Range of values
Proportion of patients treated as an in-patient		
Conventional (pInpatientConv)	50%	25% - 75%

ReCell (pInpatientRC)	25%	25% - 75%
Biobrane (pInpatientBio)	25%	25% - 75%
ReCell + Biobrane (pInpatientComb)	25%	25% - 75%
Proportion of patients progressing to SSG		
Conventional (pSSGConv)	30%	15%-40%
ReCell (pSSGRC)	10%	5%-20%
Biobrane (pSSGBio)	30%	15%-40%
ReCell + Biobrane (pSSGComb)	10%	5%-20%
Mean time to 100% re-epithelialisation		
Conventional (tHealConv)	15 days	13-18 days
ReCell (tHealRC)	10.5 days	7.5-15 days
Biobrane (tHealBio)	10.5 days	7.5-15 days
ReCell + Biobrane (tHealComb)	9 days	7.5-15 days
Costs of resources.		
Conventional dressing change(cDressing)	£166	£83-249 (+/- 50%)
Secondary dressing change (cDressminor)	£25	£12.50-£37.50 (+/- 50%)
Daily bed cost in burn unit (cBed)	£152 (standard burns unit bed)	£76-£228
Daily staff cost in burn unit (cStaff)	£469 (all professionals involved)	£234.50 - £703.50 (+/- 50%)
Hourly cost of theatre time (cTheatre)	£5,411 (per hour of use)	£643.50 - £5,500
Overall cost of SSG – procedure + post-op care (cGraft)	£5,214.50	£1,948 - £6,663.50

Table C10.2 Variables used in multi-way scenario-based sensitivity analysis. A. Clinical scenarios

Variable	% in-patient	% SSG	Time to heal (days)
Base case	ReCell: 25% ReCell/Bio: 25% Conv: 50% Biobrane: 25%	ReCell: 10% ReCell/Bio: 10% Conv: 30% Biobrane: 30%	ReCell: 10.5 ReCell/Bio: 9.0 Conv: 15 Biobrane: 10.5
TBSA = 320 sq cm	ReCell: 12.5% ReCell/Bio: 12.5% Conv: 25% Biobrane: 12.5%	ReCell: 5% ReCell/Bio: 5% Conv: 15% Biobrane: 15%	ReCell: 7 ReCell/Bio: 7 Conv: 7.5 Biobrane: 7
TBSA = 1,280 sq	ReCell: 50%	ReCell: 20%	ReCell: 21

cm	ReCell/Bio: 50% Convl: 75% Biobrane: 50%	ReCell/Bio: 20% Conventionl: 50% Biobrane: 50%	ReCell/Bio: 18 Conventionl: 28 Biobrane: 21
50% less effect of treatment on all three parameters	ReCell: 37.5% ReCell/Bio: 37.5% Conv: 50% Biobrane: 37.5%	ReCell: 15% ReCell/Bio: 15% Conv: 30% Biobrane: 30%	ReCell: 12.75 ReCell/Bio: 12 Conv: 15 Biobrane: 12.75

Table C10.2 Variables used in multi-way scenario-based sensitivity analysis. B. Cost scenarios

Variable	Bed cost (£)	Staff cost (£)	Theatre cost (£)
Base case	£166	£469	£5411
All costs 25% lower	£124.50	£351.75	£4058.25
All costs 25% higher	£207.50	£586.25	£6763.75

Table C10.3 Variable values used in probabilistic sensitivity analysis

Not carried out

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

The costs of ReCell and Biobrane were considered fixed, as no reliable data are available regarding the level of discounts available

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C11.

Table C11a Base-case results

Treatment	Total per patient cost (£)
ReCell	£7,891.93
ReCell + Biobrane	£7,787.05
Conventional dressings	£9,542.77
Biobrane	£6,397.82

9.5.2 Report the total difference in costs between the technology and comparator(s).

Table C11b Base-case differences in cost:

Comparison	Difference in costs(£)
ReCell vs Conventional dressings	-£1650.84
ReCell+Biobrane vs Conventional dressings	-£1,755.72
Recell vs Biobrane	£1,494.11
ReCell+Biobrane vs Biobrane	£1,389.23

:

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C12.

Table C12a Summary of costs by category of cost per patient (ReCell vs conventional dressings)

Item	Cost *ReCell*	Cost *Conventional dressings*	Increment	Absolute increment	% absolute increment
Technology cost	£2,032.62	£1,120.50	£912.12	£912.12	55.3%
Hospital cost	£5,861.31	£8,422.27	-£2,560.96	£2,560.96	155.3%
Mean total cost per patient	£7,893.93	£9,542.77	-£1,648.84	£1,648.84	100.0%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

NOTE: I HAVE FILLED IN THE % ABSOLUTE INCREMENT COLUMN AS DEFINED IN THE TEMPLATE, ALTHOUGH IN THIS FORMAT THE VALUE OF THIS FIGURE IS UNCLEAR

Table C12b Summary of costs by category of cost per patient (ReCell + Biobrane vs conventional dressings)

Item	Cost *ReCell + Biobrane*	Cost *Conventional dressings*	Increment	Absolute increment	% absolute increment
Technology cost	£2,135.33	£1,120.50	£1,014.83	£1,014.83	57.8%
Hospital cost	£5,651.72	£8,422.27	-£2,770.55	£2,770.55	157.8%
Mean total cost per patient	£7,787.05	£9,542.77	-£1,755.72	£1,755.72	100.0%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table C12c Summary of costs by category of cost per patient (ReCell vs Biobrane)

Item	Cost *ReCell*	Cost *Biobrane*	Increment	Absolute increment	% absolute increment
Technology cost	£2,032.62	£250.97	£1,781.65	£1,781.65	119.2%
Hospital cost	£5,861.31	£6,147.85	-£286.54	£286.54	19.2%
Mean total	£7,893.93	£6,398.82	£1,495.11	£1,495.11	100.0%

cost per patient					
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table C12d Summary of costs by category of cost per patient (ReCell + Biobrane vs Biobrane)

Item	Cost *ReCell + Biobrane*	Cost *Biobrane*	Increment	Absolute increment	% absolute increment
Technology cost	£2,135.33	£250.97	119.2%	£1,884.36	£1,884.36
Hospital cost	£5,651.72	£6,147.85	19.2%	-£496.13	£496.13
Mean total cost per patient	£7,787.05	£6,398.82	100.0%	£1,388.23	£1,388.23
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C13.

N/A

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C14.

N/A

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

The results of the one-way sensitivity analyses are presented in table C13 below:

Table C13a – Results of deterministic one way sensitivity analyses (ReCell)

Variable	Range tested	Total cost per patient	
		Low	High
Proportion of patients treated as an in-patient	25% - 75%	£7,106.82	£9,205.79
Proportion of patients progressing to SSG	5% - 20%	£7,596.84	£8,488.12
Mean time to 100% re-epithelialisation	7.5 – 15 days	£7,439.02	£8,571.33
Costs of resources.			
Conventional dressing change(cDressing)	£83 - 249	£7,850.43	£7,933.43
Secondary dressing change (cDressminor)	£12.50 - £37.50	£7,826.62	£7,957.25
Daily bed cost in burn unit (cBed)	£76 - £228	£7,550.98	£8,236.88
Daily staff cost in burn unit (cStaff)	£234.50 - £703.50	£6,835.75	£8,952.11
Hourly cost of theatre time (cTheatre)	£643.50 - £5,500	£5,271.81	£7,942.88
Overall cost of SSG – procedure + post-op care (cGraft)	£1,948 - £6,663.50	£7,486.78	£7,958.33

Table C13b – Results of deterministic one way sensitivity analyses (ReCell + Biobrane)

Variable	Range tested	Total cost per patient	
		Low	High
Proportion of patients treated as an in-patient	25% - 75%	£7,125.69	£8,889.33
Proportion of patients progressing to SSG	5% - 20%	£7,478.32	£8,404.53
Mean time to 100% re-epithelialisation	7.5 – 15 days	£7,561.62	£8,692.93
Costs of resources.			
Conventional dressing change(cDressing)	£83 - 249	£7,745.55	£7,828.55
Secondary dressing change (cDressminor)	£12.50 - £37.50	£7,730.20	£7,843.94
Daily bed cost in burn unit (cBed)	£76 - £228	£7,469.75	£8,104.36
Daily staff cost in burn unit (cStaff)	£234.50 - £703.50	£6,808.02	£8,766.09
Hourly cost of theatre time (cTheatre)	£643.50 - £5,500	£5,164.93	£7,836.01
Overall cost of SSG – procedure + post-op care (cGraft)	£1,948 - £6,663.50	£7,379.91	£7,851.45

Table C13c – Results of deterministic one way sensitivity analyses (Conventional)

Variable	Range tested	Total cost per patient	
		Low	High
Proportion of patients treated as an in-patient	25% - 75%	£7,757.39	£11,328.14
Proportion of patients progressing to SSG	5% - 20%	£8,872.72	£9,989.47
Mean time to 100% re-epithelialisation	7.5 – 15 days	£8,991.87	£10,369.12
Costs of resources.			
Conventional dressing change(cDressing)	£83 - 249	£8,858.02	£10,227.52
Secondary dressing change (cDressminor)	£12.50 - £37.50	£9,542.77	£9,542.77
Daily bed cost in burn unit (cBed)	£76 - £228	£8,862.57	£10,222.97
Daily staff cost in burn unit (cStaff)	£234.50 - £703.50	£7,443.99	£11,641.54
Hourly cost of theatre time (cTheatre)	£643.50 - £5,500	£7,238.47	£9,585.78
Overall cost of SSG – procedure + post-op care (cGraft)	£1,948 - £6,663.50	£8,321.32	£9,735.97

Table C13d – Results of deterministic one way sensitivity analyses (Biobrane)

Variable	Range tested	Total cost per patient	
		Low	High
Proportion of patients treated as an in-patient	25% - 75%	£5,621.02	£7,695.16
Proportion of patients progressing to SSG	5% - 20%	£5,507.54	£6,993.01
Mean time to 100% re-epithelialisation	7.5 – 15 days	£6,046.55	£6,927.24
Costs of resources.			
Conventional dressing change(cDressing)	£83 - 249	£6,274.32	£6,523.32
Secondary dressing change (cDressminor)	£12.50 - £37.50	£6,334.14	£6,463.51
Daily bed cost in burn unit (cBed)	£76 - £228	£5,996.97	£6,800.67
Daily staff cost in burn unit (cStaff)	£234.50 - £703.50	£5,158.01	£7,638.74
Hourly cost of theatre time (cTheatre)	£643.50 - £5,500	£4,094.53	£6,441.84
Overall cost of SSG – procedure + post-op care (cGraft)	£1,948 - £6,663.50	£5,177.37	£6,592.02

9.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

Table C14 – Results of scenario analyses

Scenario	Total cost per patient				Incremental cost			
	ReCell	ReCell + Biobrane	Conventional	Biobrane	ReCell vs Conventional	Recell + Biobrane vs Conventional	ReCell vs Biobrane	ReCell + Biobrane vs Biobrane
TBSA = 320 sq cm	£5,537.72	£5,534.37	£5,514.31	£4,491.51	£23.41	£20.06	£1,046.21	£1,042.86
TBSA = 1280 sq cm	£14,402.80	£13,870.80	£16,098.92	£10,684.12	-£1,696.12	-£2,228.12	£3,718.68	£3,186.68
All benefits reduced by 50%	£9,311.99	£9,277.16	£9,542.77	£7,433.46	-£230.78	-£265.61	£1,878.53	£1,843.70
Hospital costs reduced by 25%	£7,595.82	£6,530.71	£7,492.70	£5,060.14	£103.12	-£961.99	£2,535.68	£1,470.57
Hospital costs increased by 25%	£9,185.79	£9,041.36	£11,588.35	£7,734.86	-£2,402.56	-£2,546.99	£1,450.93	£1,306.50

9.5.8 Present results of the probabilistic sensitivity analysis described in table C10.3.

N/A

9.5.9 What were the main findings of each of the sensitivity analyses?

The results of the sensitivity analyses demonstrate considerable robustness in the model, with qualitative comparative results remaining consistent across the ranges tested. None of the univariate analyses revealed areas where parameter variation would have yielded different conclusions.

The scenario analyses demonstrated that the cost difference between ReCell and conventional treatment tended to narrow as TBSA was reduced and if the level of overall benefits or hospital costs were lowered. By contrast, an increase in TBSA or hospital costs tended to widen the gap, with consequent increase in savings

9.5.10 What are the key drivers of the cost results?

- Area of TBSA treated exerted a major effect on all treatents
- Proportion of burns treated as in-patient – this was of particular relevance to conventionally treated patients
- Hospital costs in general, particularly the cost of staff time. The latter had the greatest impact on conventional dressings, while the ReCell results were more sensitive to theatre costs

Miscellaneous results

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

None

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

No subgroup analyses performed

9.6.2 Define the characteristics of patients in the subgroup(s).

N/A

9.6.3 Describe how the subgroups were included in the cost analysis.

N/A

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

N/A

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

N/A

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Our baseline model explored the management of burns of 640 sq cm. This is approximately equivalent to 5-10% TBSA, depending on the size of the patient. The results yielded overall costs that ranged from £6,398 to £9,543 per patient.

[redacted] This suggests that our model probably slightly underestimates costs, although the exclusion of complex patients and multiple theatre visits probably accounts for this.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Our literature search identified no other studies that carried out the comparisons identified in the scope. We therefore have no other data against which to benchmark our conclusions.

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

The population chosen had moderately extensive burns (TBSA 5-20%). Although we extended this range to 2.5% - 20% for the purposes of the sensitivity analysis, it would be unsafe to go beyond these boundaries. Smaller burns (<2%) are unlikely to be treated in a hospital setting and, unless there are specific reasons to use it (eg facial burn, visible burn on pigmented skin), ReCell is unlikely to be the treatment of choice.

In patients with more extensive burns, length of stay (and costs) tend rise extremely rapidly. This reflects a number of factors, including a greater likelihood of requiring skin grafting for full thickness injury, greater likelihood of requiring ITU admission, greater likelihood of multiple trips to theatre, the impracticalities of managing a burn of this size as an out-patient. All these factors take the patient out of the scope of this model and, although ReCell undoubtedly has a place in the management plan for these extremely expensive patients, it would require a completely different approach to evaluate its cost impact.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

Strengths:

The model is simple and allows transparent exploration of the cost impacts of various treatments used in acute burns care

Costings are drawn from a recent comprehensive English analysis and are therefore likely to reflect true costs of care for the NICE-influenced population

Sensitivity analysis demonstrates considerable robustness to parameter variation

Weaknesses:

The clinical parameters are based, for the most part, on the results of small studies and case series, or on expert opinion. These estimates are therefore subject to considerable potential error and it has not been possible to generate distributions around the central values

Some of the comparisons made are not necessarily of relevance to normal clinical practice. Biobrane alone, for instance, has its greatest use in patients with smaller or more superficial burns and would less commonly be used in isolation for the types of burns where ReCell might be considered. The apparently lower costs seen with Biobrane alone, therefore, may simply reflect inappropriateness in the comparison

One of the key determinants of burns management is the decision to undertake skin grafting. This depends not primarily on wound size, but depth. Unfortunately there were no data available to incorporate depth in our model, and therefore this element of the analysis may not truly reflect the likely situation. Given that one of the key benefits of ReCell is to reduce the need for (and the size of) skin grafting, we may well have underestimated its benefit.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

With the currently available evidence, there is little opportunity for further modelling in acute burns management. Issues such as the long term impact o ReCell on scar hypertrophy and pigmentation will certainly be worth exploring, once sufficient data become available to support a model.

Appendices

9.9 Appendix 1: Search strategy for clinical evidence (section 7.1.1)

Primary search (Burns indication)

9.9.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

All four databases listed above searched

9.9.2 The date on which the search was conducted.

02 August 2013

9.9.3 The date span of the search.

January 1995 – July 2013

9.9.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

MEDLINE/MEDLINE In-Process

Burns [MeSH] OR (Burn* [Textword] OR Scald* [Textword])

AND

ReCell [Textword] OR (Autologous NEAR Cell NEAR Harvest*) [Textwords]

EMBASE

Burns [Subject] OR (Burn* [Textword] OR Scald* [Textword])

AND

ReCell [Textword] OR (Autologous NEAR Cell NEAR Harvest*) [Textwords]

Cochrane Library

Burn* [Title, Abstract, Keywords] OR Scald* [Title, Abstract, Keywords]

AND

ReCell [Title, Abstract, Keywords] OR (Autologous AND Cell AND Harvest*) [Title, Abstract, Keywords]

9.9.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

- Manufacturer database (Avita Medical Ltd). Manual database of known studies held by manufacturer consulted for all studies using ReCell.

- Hand search of abstracts lists for burns-related conferences over the past 5 years: British Burn Association; European Burn Association; American Burn Association; International Society for Burn Injuries.
- Hand search of reference lists from studies identified in the previous searches.

9.9.6 The inclusion and exclusion criteria.

Inclusion criteria:

- Adults and children undergoing treatment for flame burns and scalds
- Treatment with autologous non-cultured skin harvesting (ReCell) used either alone or in combination with other treatments
- Systematic reviews with quantitative outcomes, randomised controlled trials, non-randomised observational studies, comparative or non-comparative case series
- Outcomes including:
    - Speed of healing
    - Number of dressings
    - Length of stay per % TBSA
    - Wound infection rates
    - Scarring: aesthetic and functional outcomes
    - Pigmentation: aesthetic and functional outcomes
    - Re-admission rates for scar management
    - Transfusion rates during skin grafting
    - Number and size of donor sites
    - Growth rate in children
    - Surgical procedure and theatre time
    - Device-related adverse events
    - Analgesic/anaesthetic use
    - Other resource utilisation outcomes not specified above
    - Other patient-relevant outcomes not specified above

Exclusion criteria

- Patients undergoing treatment for indications other than flame burns or scalds
- Treatments not involving autologous non-cultures skin cell harvesting
- Narrative reviews not including quantitative patient effectiveness data, single patient effectiveness data, single patient case reports, animal studies, in vitro studies

9.9.7 The data abstraction strategy.

Four researchers were involved in the process Jonathan Belsey (JB) and Tricia Dixon (TD) from JB Medical Ltd [Sponsor] and Claire Darby (CD) and Andrew Quick (AQ) from Avita Medical Ltd [Manufacturer].

Search results were initially screened to eliminate duplicates. Preliminary assessment of identified abstracts was carried out by two researchers (JB + CD) working together in order to identify clearly excluded studies. Full-text of remaining abstracts were obtained, where available. For data not yet fully published, meeting abstracts/posters were obtained. Draft manuscript obtained from author for one study.

All studies were scrutinised by two researchers independently (JB + TD) to ascertain whether inclusion/exclusion criteria were satisfied. For included studies, quantitative results were extracted by two researchers independently (JB + CD). Data were captured on Excel spreadsheet, although as meta-analysis was deemed not possible, no further data analysis was undertaken. PRISMA diagram constructed on basis of results.

Narrative review of included studies carried out by one researcher (JB) with comments and approval by two further researchers (JB + CD + AQ)

Secondary search (Hypopigmentation indication)

9.9.8 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

All four databases listed above searched

9.9.9 The date on which the search was conducted.

06 August 2013

9.9.10 The date span of the search.

January 1995 – July 2013

9.9.11 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

MEDLINE/MEDLINE In-Process

Hypopigmentation [MeSH] OR Vitiligo [MeSH]

AND

ReCell [Textword] OR (Autologous NEAR Cell NEAR Harvest*) [Textwords]

EMBASE

Hypopigmentation [Subject] OR Vitiligo [Subject]

AND

ReCell [Textword] OR (Autologous NEAR Cell NEAR Harvest*) [Textwords]

Cochrane Library

Hypopigmentation [Title, Abstract, Keywords] OR Vitiligo [Title, Abstract, Keywords]

AND

ReCell [Title, Abstract, Keywords] OR (Autologous AND Cell AND Harvest*) [Title, Abstract, Keywords]

9.9.12 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

- Manufacturer database (Avita Medical Ltd). Manual database of known studies held by manufacturer consulted for all studies using ReCell.
- Hand search of reference lists from studies identified in the previous searches.

9.9.13 The inclusion and exclusion criteria.

Inclusion criteria:

- Adults and children undergoing treatment with ReCell for any reason
- Treatment with autologous non-cultured skin harvesting (ReCell) used either alone or in combination with other treatments
- Systematic reviews with quantitative outcomes, randomised controlled trials, non-randomised observational studies, comparative or non-comparative case series

- Outcomes reported for effect of treatment on pigmentation

Exclusion criteria

- Treatments not involving autologous non-cultures skin cell harvesting
- Narrative reviews not including quantitative patient effectiveness data, single patient effectiveness data, single patient case reports, animal studies, in vitro studies
- Any outcome other than the effect on pigmentation
-

9.9.14 The data abstraction strategy.

Four researchers were involved in the process Jonathan Belsey (JB) and Tricia Dixon (TD) from JB Medical Ltd [Sponsor] and Claire Darby (CD) and Andrew Quick (AQ) from Avita Medical Ltd [Manufacturer].

Search results were initially screened to eliminate duplicates. Preliminary assessment of identified abstracts was carried out by two researchers (JB + CD) working together in order to identify clearly excluded studies. Full-text of remaining abstracts were obtained, where available. For data not yet fully published, meeting abstracts/posters were obtained. Draft manuscript obtained from author for one study.

All studies were scrutinised by two researchers independently (JB + TD) to ascertain whether inclusion/exclusion criteria were satisfied. For included studies, quantitative results were extracted by two researchers independently (JB + CD). Data were captured on Excel spreadsheet, although as meta-analysis was deemed not possible, no further data analysis was undertaken. PRISMA diagram constructed on basis of results.

Narrative review of included studies carried out by one researcher (JB) with comments and approval by two further researchers (JB + CD + AQ)

9.10 Appendix 2: Search strategy for adverse events (section 7.7.1)

NOTE: AS IT WAS APPARENT THAT THE NUMBER OF STUDIES AVAILABLE WAS LIMITED, IT WAS FELT MORE EFFECTIVE TO INCLUDE ADVERSE EVENTS AS A SPECIFIED OUTCOME WITHIN THE MAIN SEARCH, WITH DATA BEING ISOLATED AT THE EXTRACTION STAGE. NO NEW SEARCH STRATEGY IS THUS REPORTED.

9.11 Appendix 3: Search strategy for economic evidence (section 8.1.1)

The following information should be provided.

9.11.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline + Medline In-Process
- Embase
- NHS EED.

9.11.2 The date on which the search was conducted.

20 August 2013

9.11.3 The date span of the search.

January 2003 – July 2013

9.11.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

MEDLINE/MEDLINE In-Process

Burns [MeSH]

AND

Cost Allocation [MeSH] OR Cost Control [MeSH] OR Cost of Illness [MeSH] OR Cost Benefit Analysis [MeSH] OR Healthcare Costs [MeSH] OR Health Expenditures [MeSH]

EMBASE

Burns [Subject]

AND

Cost [Subject] OR Cost Benefit Analysis Cost [Subject] OR Cost Control [Subject] OR Cost Effectiveness Analysis [Subject] OR Cost Minimization Analysis [Subject] OR Cost of Illness [Subject] OR Cost Utility Analysis [Subject]

NHS EED

Burn* [Title, Abstract, Keywords] OR Scald* [Title, Abstract, Keywords]

[No further limitations applied, owing to dedicated nature of database]

9.11.5

9.11.6 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Consultation with manufacturers (Avita Medical Ltd) regarding any known cost or economic analyses.

Hand search of reference lists from studies identified in the previous searches.

9.12 Appendix 4: Resource identification, measurement and valuation (section 9.3.2)

BASED ON THE LIMITED NUMBER OF PUBLICATIONS IN THE FIELD, THIS ELEMENT WAS DERIVED FROM THE SAME SEARCH AS IS DESCRIBED IN APPENDDIX 3 ABOVE

References

[1] Deitch, E.A., Wheelan, T. M., Rose, M. P., Clothier, J. & Cotter, J. (1983) Hypertrophic Burn scars: analysis of Variables. The Journal of Trauma 23 (10), 895-898

[2] Health and Social Care Information Centre. Hospital episode statistics. Admitted patient care 2011-12: Primary diagnosis. http://www.hscic.gov.uk/catalogue/PUB08288/hosp-epis-stat-admi-prim-diag-4cha-11-12-tab.xls Accessed 10/8/13

[3] UK National Burn Care Group. International Burn Injury Database. UK burn injury data 1986-2007 inclusive. http://www.ibidb.org/downloads/doc_download/4-2008-first-ibid-report Accessed 10/8/13

[4] European Burn Association. European Practice Guidelines for Burns Care. The Hague 2011. http://www.euroburn.org/userfiles/users/36/pdf/guidelines/EBAGuidelinesBurnCareVersion1.pdf Accessed 10/08/13

[5] American Burn Association. Practice guidelines for Burn Care. J Burn Care Rehabil 2001; 22(suppl1):1S-69S

[6] Lim, J., Liew, S., Chan, H., Jackson, T., Burrows, S., Edgar, D.W., Wood, F.M. (2013) Is the length of time in acute burn surgery associated with poorer outcomes? *Article in press* Burns, http://dx.doi.org/10.1016/j.burns.2013.06.005

[7] Gravante, G., Difede, M., Araco, A., Grimaldi, M., Deangelis, B., Arpino, A., Montone, A. (2007). A randomized trial comparing ReCell® system of epidermal cells delivery versus classic skin grafts for the treatment of deep partial thickness burns. Burns, 33(8), 966-972

[8] Wood, F., Martin, L., Lewis, D., Rawlins, J., McWilliams, T., Burrows, S. & Rea,S. (2012). A prospective randomised clinical pilot study to compare the effectiveness of Biobrane® synthetic wound dressing, with or without autologous cell suspension, to the local standard treatment regimen in paediatric scald injuries. Burns 38, 830-839

[9] Park, J. H., Heggie, K. M., Edgar, D. W., Bulsara, M. K. Wood, F. M. (2013) Does the type of skin replacement surgery influence the rate of infection in acute burn injured patients? *Article in press* Burns, http://dx.doi.org/10.1016/j.burns.2013.03.015

[10] Dunne, J. & Rawlins, J. (2012) Early Paediatric Scald surgery – Developing a (cost effective) dermal preserving surgical protocol for all childhood scalds. International Society for Burns Injuries Meeting.

[11] Rawlins, J. M. (2013) ReCell® versus Split-Thickness Skin grafts in the Management of Deep Dermal Paediatric Scalds. Chinese Burns Association

[12] Rawlins, J., Signy, J., Rea, S. & Wood, F. (2011) Dermabrasion, ReCell and Biobrane versus Split Thickness Skin Grafting for deep flame burns – a comparative pilot study. European Burns Association Meeting.

[13] Echlin, K., Way, B. & Jones, I. (2012) Autologous non-cultured epidermal cell suspension to improve healing in deeper partial thickness facial burns. International Society for Burns Injuries Meeting.

[14] Echlin, K., Way, B. & Jones, I. (2012) Autologous non-cultured epidermal cell suspension to accelerate healing of split thickness donor sites. International Society for Burns Injuries Meeting.

[15] Palombo, M., Bruno, A., Santi, G., Anniboletti, T. Moroni, S., Palombo, P. (2012) Our Experience with ReCell: A Panel of Cases. International Society for Burns Injuries Meeting

[16] Sen, S. K., Ives, M., Philp, B., Dziewulski, P. Herndon, D. & Wood, F. (2012) Use of Split thickness dermal grafts in combination with sprayed keratinocytes in burns. International Society for Burns Injuries Meeting

[17] De Angelis, B., Lacarini, L., Montone, A., Cervelli, V. (2009) ReCell: A new device for skin autologous inplants in the treatment of burns and scars. European Burns Association Meeting

[18] Cervelli, V., De Angelis, B., Spallone, D., Lucarini, L., Arpino, A., & Balzani, A. (2009). Use of a novel autologous cell-harvesting device to promote epithelialization and enhance appropriate pigmentation in scar reconstruction. Clinical and Experimental Dermatology, 35(7), 776-780

[19] Cervelli, V., De Angelis, B., Balzani, A., Colicchia, G., Spallone, D., & Grimaldi, M. (2009). Treatment of stable vitiligo by ReCell system. Acta Dermatovenerologica Croatica, 17(4), 273-278

[20]Mulekar, S. V., Issa, A. A., & Eisa, A. A. (2011). Treatment of post-burn leucoderma with non-cultured melanocyte-keratinocyte transplantation (MKTP). Burns, 37(3), 448-452

[21] Daniel B, Venugopal S, Martin L, Agero A, Rhodes L, Frew J, Wittal R, Le Guay J, Murrell D. (2011) A randomised controlled trial assessing the effectiveness of minigrafting vs ReCell in stable vitiligo: preliminary results. International Pigment Cell Conference.

[22] Philp B, Dziewulski P, El-Muttardi N, Shelley O ,Mazurek M Barnes D Ives M, Sen S, Lloyd-Hughes A, Myers S, Herndon D, Wood F (2013) Dermal grafts combined with ReCell – preliminary clinical results. Abstract submitted for presentation

[23] Cui Y, Liu Z, Zeng A, Wang X, Zhu L, Si L, Wang J, Song K. The use of the novel autologous cell-harvesting device, ReCell® to enhance appropriate pigmentation in Chinese patients with dyspigmentation: A preliminary exploratory investigation. Draft manuscript awaiting submission. ACADEMIC IN CONFIDENCE

[24] Tyack, Z.F., Pegg, S., Ziviani, J. (1997) Postburn dyspigmentation: its assessment, management, and relationship to scarring – a review of the literature. J Burn Care Rehabil 18,435-440.

[25] Chadwick, S., Heath, R., Shah, M. (2012) Abnormal pigmentation within cutaneous scars: A complication of wound healing. Indian J Plast Surg 45,403-411

[26] Wisely, J.A., Hoyle, E., Tarrier, N., Edwards, J.(2007) Where to start? Attempting to meet the psychological needs of burned patients. Burns 33,736-746

[27] Zeitlin, R.E. (1007) Long-term psychosocial sequelae of paediatric burns. Burns 23,467-472

[28] O'Neill, T.B., Rawlins, J., Rea, S., Wood, F.M. (2012) Complex chemical burns following a mass casualty chemical plan incident: How optimal planning and organisation can make a difference. Burns 38,713-718

[29] Carayanni VJ, Tsati EG, Spyropoulou GC et al. Comparing oil-based ointment versus standard practice for the treatment of moderate burns in Greece: a trial based cost effectiveness evalualtion. BMC Complement Altern Medicine 2011:11:122

[30] Caruso DM, Foster KN, Blome-Eberwein et al. Randomized clinical study of hydrofiber dressing with silver or silver sulfadiazine in the management of partial-thicknessburns. J Burn Care Res 2006;27:298-309

[31] Silverstein P, Heimbach D, Meites H et al. An open, parallel, randomized, comparative, multicentre study to evaluate the cost-effectiveness, performance, tolerance and safety of a silver-containing soft silicone foam dressing (intervention) vs silver sulfadiazine cream. J burn Care Res 2011;32:617-626

[32] Fong J, Wood F, Fowler B. A silver coated dressing reduces the incidence of early burn wound cellulitis and associated costs of inpatient treatment: comparative patient care audits. Burns 2005:31:562-7

[33] Pellat RAF, Williams A, Wright H, Young AER. The cost of a major paediatric burn. Burns 2010;36:1208-14

[34] Hemington-Gorse SJ, Potokar TS, Drew PJ, Dickson WA. Burn care costing: the Welsh experience. Burns 2009; 35:378-82

[35] Griffiths HR, Thronton KL, Clements TS et al. The cost of a hot drink scald. Burns 2006;32:372-4

[36] Ahn CS, Maitz PKM. The true cost of burn. Burns 2012;38:967-74

[37] Unpublished data. Analysis carried out by team headed by Rawlins J, Pinderfield Hospital Burns Unit, Wakefield. UK (2013). Data supplied as spreadsheet.

[38] Cuttle L, Naidu S, Mill J et al. A retrospective cohort study of Acticoat versus Silvazine in a paediatric population. Burns 2007; 33:701-7

[39] Ostlie DJ, Juang D, Aguayo P et al. Topical silver sulfadiazine vs collagenase ointment for the treatment of partial thickness burns in children: a prospective randomized trial. J Paed Surg 2012; 47:1204-7