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

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0.1	05/02/2020	Iain Willits	Initiation of first draft
0.2	05/02/2020	Iain Willits	First draft to NICE
1.1	14/02/2020	Iain Willits	Second draft to NICE
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1.3	25/02/2020	Helen Cole	EAC Oversight
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This medical technology guidance was published in November 2014.

All medical technology guidance is reviewed 3 years after publication.

This review report summarises new evidence and information that has become available since this medical technology guidance was published, and that has been identified as relevant for the purposes of this report. This report will be used to inform NICE's decision on whether this guidance needs to be updated at this time.

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1. Original objective of guidance

To assess the clinical and cost effectiveness of the ReCell spray-on skin system for treating skin loss, scarring and depigmentation after burn injury.

2. Current guidance recommendations

"1.1 The ReCell Spray-On Skin system shows potential to improve healing in acute burns. However, there is insufficient evidence on its use in clinical practice, particularly in relation to which patients might benefit most from its use, to support the case for its routine adoption in the NHS.

1.2 Research is recommended to address uncertainties about the claimed patient and system benefits of the ReCell Spray-On Skin system. Clinical outcomes should include time to 95% healing, length of hospital stay, cosmetic appearance of the scar and function of the burned area, compared with standard care. As relevant databases and registers are available, the research might include analysis of data generated from these. NICE will explore the development of appropriate further evidence, in collaboration with the technology sponsor and with clinical and academic partners, and will update this guidance if and when new and substantive evidence becomes available".

3. Methods of review

The NICE guidance Information Services (gIS) identified 1066 records following the literature search (detailed in Appendix C), reduced to 779 after deduplication. These records were sifted by a single reviewer (IW) to identify records that met the criteria for inclusion according to title and/or abstract (reported in Table 3.1). The same reviewer retrieved full papers where accessible, and performed a second sift of these. Full peer reviewed papers of primary studies that met the scope were included regardless of methodology with the exceptions of case reports and small case series ($n \leq 5$) where outcome data were not aggregated. Secondary studies, such as letters, editorials, and non-systematic reviews were excluded. Systematic reviews with meta-analyses were included, and systematic reviews without meta-analyses were included for bibliography searching ("snow balling").

The EAC took a broad approach to study inclusion to maximise sensitivity, with 26 references selected for full retrieval. A further 51 abstracts were reported by the company, of which five were considered to fit the decision problem. However, in general, the abstracts were poorly reported (sometimes not reporting the year of presentation), and it was not always possible to ascertain whether the patients or data reported in these studies were unique.

Included studies were categorised into study publication type and then into method type (comparative, non-comparative, or economic). Result were reported in tabular form on a study by study basis, and reported narratively by outcome. The key results of interest were time to healing, length of hospital stay, cosmetic appearance of the scar and function of the burned area, based on the research recommendations of MTG21 (NICE, 2014) made in Section 1.2 of the guidance.

Table 3.1. *Criteria for study inclusion.*

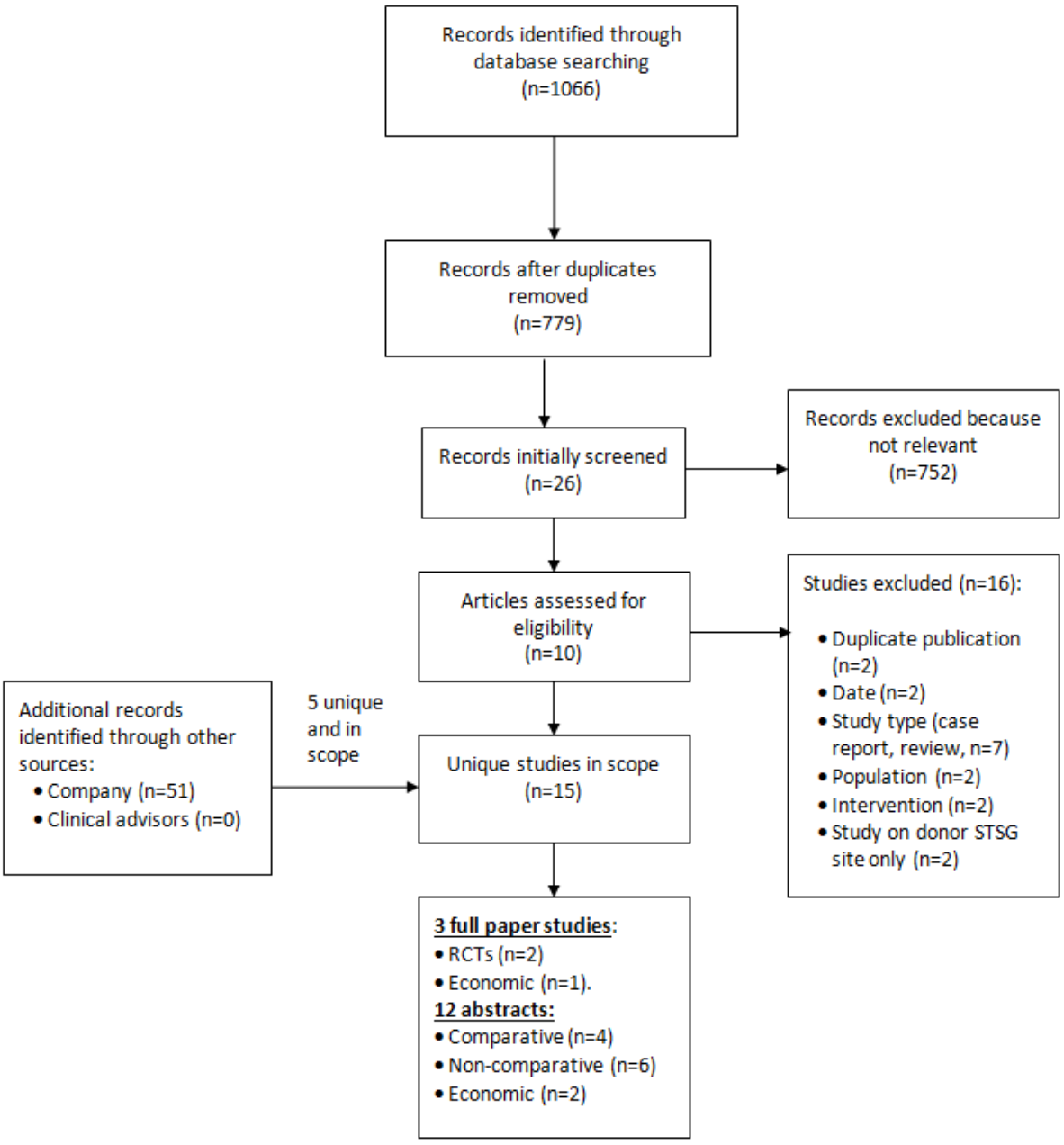
	Original scope issued by NICE	**Comment**
Population	Adults or children treated in Burns Units or Centres for: • Partial thickness burns including scalds caused by hot water where mesh grafting is not required • Large area burns; full thickness or deep partial thickness burns including where mesh grafting is required	The 2 populations were classified as "group A" and "group B" by CEDAR EAC*. It was noted by CEDAR that this classification was largely inadequate to describe the complex nature of people presenting with burns. In particular, there were issues with the heterogeneity of patient condition; the definitions using referral criteria for specialised burn services [in the NHS]; definitions using burn depth and requirement for meshed grafts; and heterogeneity of patient populations in the clinical evidence [matters of generalisability].
Intervention	For the population of "Partial thickness burns including scalds caused by hot water": • ReCell Spray-on skin alone, or in combination with biosynthetic or standard dressings For the population of "Large area burns and full or deep partial thickness burns where mesh grafting is required": • skin mesh graft in combination with ReCell Spray-on skin.	It is noted that ReCell is frequently used as an adjunct to other treatments, such as mixed skin grafts. This adds complexity to the analysis of clinical effectiveness.
Comparator(s)	For the population of "Partial thickness burns including scalds caused by hot water": • Biosynthetic dressings • Standard dressings For the population of "Large area burns; full or deep partial thickness burns where mesh grafting is required": • Skin mesh graft alone • Skin mesh graft plus biosynthetic dressing.	For the purposed of this review, all comparators and none were included.
Outcomes	The outcome measures to consider include: • Speed of healing, including standard criteria such as number of days to full or	All listed outcomes were included if quantitative data were reported. For this review, there was a focus on time to healing, length of hospital stay, cosmetic

	Original scope issued by NICE	Comment
	95% healing • Number of dressings to the wound with or without anaesthesia • Length of hospital stay per % of burn surface area • Wound infection rates • Degree of scarring including aesthetic and functional outcomes • Degree of pigmentation including aesthetic and functional outcomes • Re-admission to hospital for management of scarring • Transfusion rates during skin grafts • Number and size of donor sites • Growth rate in children • Surgical procedure and theatre time • Device-related adverse events.	appearance of the scar and function of the burned area, which were evidence gaps or research recommendations in the original guidance (November 2014) and which informed the inputs to the original economic model.
Cost considerations		Only “population A”* (Adults or children treated in Burns Units or Centres for partial thickness burns including scalds caused by hot water) were considered in the cost analysis.
Subgroups to be considered	None identified	People with burns represents a very heterogeneous population, with consideration to age (children and adults); site and size of burn; type of burn; and co-interventions used.
* From the original Assessment Report (Peirce and Carolan-Rees, 2013).		

Study identification, sifting, and selection are illustrated as a PRISMA diagram (Moher et al., 2009) in Figure 4.1. The EAC considered 10 studies from the gIS search were within the scope of the decision problem. These were supplemented by 5 studies identified by the company. No systematic reviews or meta-analyses were identified. Only three studies were reported in full in peer reviewed journals, whilst 12 studies were available in abstract form only. Studies were categorised as being comparative (n = 7), non-comparative (n = 5), or economic (n = 3). All these studies were included for analysis. An

overview of the fully published studies is reported in Table B1. An overview of the abstracts is reported in Table B2.

Figure 4.1. *PRISMA flow diagram illustrating study selection.*



4. New evidence

4.1. Changes in technology

The ReCell system has been changed such that each kit has a significantly increased coverage area. The company states:

> "RECELL® has been modified to increase the coverage area from 320cm^2 to 1,920cm^2. The device and instructions for use have been modified to allow for processing of the larger volume of cell suspension as described below.
>
> The updated RECELL® Device (referred to internally as RECELL® 1,920) allows for processing up to four (4) 3 cm x 2 cm skin samples, with each process yielding approximately 6 mL of cell suspension (24 ml total) which can be used to treat an area of approximately 1,920cm^2. The expanded, 1,920, version of RECELL® was granted CE Mark in March 2015".

The updated ReCell system involves an increase in the volume of buffer solution and some ancillary equipment such as syringes, needles, and nozzles. It is functionally equivalent to the predecessor system in all aspects except the area covered, with the company stating:

> "The new model performs the exact same function and uses the same mode of action as the technology described in MTG21. Since the initial RECELL® NICE review (MTG21) additional information has been published concerning the RECELL® Autologous Skin Cell Suspension (ASCS) mechanism of action as it relates to the epidermal healing process".

There are cost implications regarding the latest version of the device. These are discussed in Section 4.6.

4.2. Changes in care pathways

There are no NICE guidelines on the management of burns. The EAC did not identify any national guidelines on the management of burns. Treatment of severe burns is a specialised competency (NHS England, 2013). The National Network for Burn Care have produced referral guidance for burns (NBBC, 2012). This guidance was referred to in the original Assessment Report (Peirce and Carolan-Rees, 2013) and has not been updated since.

4.3. Results from MTEP MTG review

Following the publication of MTG21, two research facilitation projects were initiated by NICE. CEDAR EAC was commissioned to design and facilitate a

pragmatic RCT in people undergoing therapy with ReCell compared with those receiving standard care for healing, graft skin sparing and scar outcome. It is understood from the ReCell initial review that the RCT was cancelled in October 2018 due to withdrawal of company financial and material support.

Newcastle and York EAC was commissioned to conduct an exploratory study into using existing data sources to provide informing data. The International Burn Injury Database (iBID) was identified as a potential retrospective data source to estimate the clinical effectiveness of ReCell. However, it was found that it would not be feasible to draw any conclusions on clinical outcomes associated with ReCell using iBID data (Cole and Willits, 2015).

4.4. New studies

4.4.1. *Overview of included studies*

Comparative studies

Two randomised controlled trials (RCTs) were published fully in peer reviewed journals. Although these were both by the same research group, they had different study protocol identifications, and it is likely they were carried out on different patients (see Table B1).

The larger multicentre study enrolled 101 adult patients with an acute deep partial-thickness burn, with a total burn surface area (TBSA) ranging from 1% to 20% (Holmes *et al.*, 2018b). This was an open label within-patient trial, with independent burn sites on the patient randomised to receive the control (meshed split-thickness skin grafts [STSG]) or the intervention (autologous skin cell suspension [ASCS], i.e. ReCell). Two primary endpoints were reported; the incidence of ReCell-treated area closure compared to control at 4 weeks at the treatment site (non-inferiority analysis), and the incidence of complete donor site healing at 1 week (100% re-epithelialisation, superiority analysis). Secondary endpoints concerned pain, visual appearance, and scarring at the treatment site. Final outcomes were reported at 52 weeks follow up, with most outcomes analysed using a modified *per protocol* (MPP), with patients excluded if they had received confounding treatments post procedure (n = 83). Overall, the RCT was clearly reported, although attention should be made concerning the intervention and comparator, and the analysis employed.

The smaller study enrolled 30 children and adults who generally had more severe burns, with a TBSA of 5% to 50% (Holmes *et al.*, 2018a). These patients were selected from an eligible population of 1,029 people. The study had a similar design compared with the larger study, with subjects acting as

their own controls. However, in this study ReCell was used in combination with STSG in the intervention arm, with the STSG being more widely meshed. The control arm was STSG alone, using a narrower mesh. Thus the aim was to evaluate whether the use of ReCell could reduce the area of donor skin used in this patient group. The dual primary outcomes were confirmed treatment area closure (healing) prior to or at week 8, and a comparison of the actual expansion ratios, computed as the ratio of measured treated area to measured area of the donor site. The area of the donor site included donor skin for the initial treatment and retreatments. Secondary endpoints were analysed at weeks 12, 24, 36, and 52 using *per protocol* analysis. These included patient satisfaction and the Patient and Observer Scar Assessment Scale (POSAS). This study appears to be of similar reporting quality and have the same issues with generalisability as the larger study.

Four studies were nominally comparative but only reported as abstracts (see Table B2). One study was a prospective within-patient comparison of ReCell compared with STGS, but was limited to 10 patients and was difficult to interpret (Sood *et al.*, 2015). One UK based study (Othman *et al.*, 2016) compared five different modalities; conventional dressings, Biobrane®, Recell®, Recell® with Biobrane combined with STGS in 100 consecutive patients. Reported outcomes were limited to scarring, dyspigmentation, and itching. There was insufficient detail reported to fully interpret the results. The two other abstracts were identified by the company and have not been independently identified by the EAC. Holmes *et al.* and Platt *et al.* used historical controls and reported on mortality and length of stay.

Non-comparative studies

Six non-comparative studies were identified as abstracts, four in the main literature search (Carter *et al.*, 2019, Craig *et al.*, 2019, Hickerson *et al.*, 2019, Walker *et al.*, 2018) and two by the company (Molnar *et al.* and Sood *et al.*). Single-armed observational studies offer only weak inference of causality, and require either explicit comparisons with uncontrolled data sources, such as historical data, or implicit extrapolation for their interpretation (e.g. before and after effect). This, coupled with the inevitably poor quality of reporting associated with abstracts, made interpretation very challenging. There is therefore a very low level of confidence in the veracity of the results reported by these studies. Limited details of these studies are reported in Table B2.

Economic studies

Three economic studies were identified, one of which was published as a full paper in a peer-reviewed journal. This study was described as a cost-effectiveness study, although it did not report on clinical effectiveness or quality of life (Kowal *et al.*, 2019). The study was from the perspective of a

specialist burns hospital in the United States. The study utilised a decision analytic model (decision tree) by simulating the pathway of 200 burn patients' "profiles" comparing ReCell with standard care. Monte Carlo analysis was used in sensitivity analysis. Results were reported as aggregated differential costs between the treatment modalities. Additionally, a budget impact analysis was performed.

The main limitation of the model appears to be related to the poor quality evidence informing the inputs. Often, these were from small observational studies or expert opinion (eight clinicians surveyed). The study also lacked generalisability to the NHS in many ways. These included the perspectives the patient pathways adopted, use of American costs, use of American burns registries and databases, and the currency (US dollars) results were reported in.

The other two studies were available as abstracts only. One study, identified in the literature search, was described as a cost-effectiveness study (Foster *et al.*, 2018). It is probable that this reported the same data as the Kowal *et al.* (2019) study, who was a co-author. Another study by Foster *et al.*, identified by the company, was described as a budget impact study. Again, it is likely this study was reporting results based on the same model as Kowal *et al.* Neither abstract reported quantifiable cost data that could be generalised to the NHS.

4.4.2. *Results of included studies*

Overall, the reporting of results in the included studies was poor, particularly in the abstracts, where it was difficult to contextualise the data. All results should therefore be considered bearing in mind the limitations of the informing studies. Key results of the comparative studies are reported in Table B3. Key results of the single-armed studies are reported in Table B4.

Healing at burns wound site

The best evidence for healing at the treatment site was reported in a within patient RCT of 101 subjects (Holmes *et al.*, 2018b). This study reported that nearly all (97.6%) the burns wounds treated with ReCell had achieved ≥ 95% re-epithelialisation at 4 weeks. This was non-inferior to the skin control (STSG, 100% re-epithelialisation). Another RCT reported very similar rates (non-inferior) of wound closure between ReCell combined with STSG compared with a finer mesh of STSG alone at 4 and 8 weeks. No other comparative data on treatment site healing was available. Data from single-armed studies was difficult to interpret due to the heterogeneity of the populations and interventions used, outcome definition, and poor reporting. Studies reported over 90% healing rate (wound closure or re-epithelialisation)

at 8 weeks using the ReCell technology (Carter *et al.*, 2019, Craig *et al.*, 2019, Hickerson *et al.*, 2019, Sood *et al.*, 2015).

Healing at donor site

Healing at the donor site is superior with ReCell compared with STSG because ReCell has a greater expansion ratio (typically 1:80), hence the donor area is considerably smaller, and would be expected to heal faster. This was evidenced in the RCT by Holmes *et al.* (2018b), who reported significantly more rapid healing of the ReCell donor site than the graft donor site. Additionally, an RCT reported that ReCell could reduce the size of the graft donor site when combined with STSG (Holmes *et al.*, 2018a).

Length of hospital stay

Length of hospital is a key economic driver, as there can be considerable savings made by discharging burns patients earlier. Neither of the RCTs reported this outcome (Holmes *et al.*, 2018a, Holmes *et al.*, 2018b). An observational study, presented as an abstract, reported significantly reduced hospital stay with ReCell compared with historical norms (Holmes *et al.*, date unknown). Similarly, Platt (abstract, details unknown) reported length of stay was reduced from 55 days from data reported in a burns registry, to 24 days with ReCell. It is not possible to interpret what this means in practice.

Scarring and depigmentation

An RCT reported that there was no significant difference between ReCell and control groups in the Patient and Observer Scar Assessment Scale (POSAS) at weeks 12, 24, 36, and 52 (Holmes *et al.*, 2018b). One abstract of a comparative observational study reported that ReCell was associated with a 25% rate of scarring which was less than the comparators (conventional dressing, STSG, Biobrane). It is not possible to contextualise this information with the limited data reported. This was also the case for the single-armed studies that reported this outcome.

Adverse events

None of the studies reported significant adverse events related specifically to the use of ReCell.

Pain

One RCT reported that ReCell was associated with a reduction in pain at the donor site compared with the control (Holmes *et al.*, 2018a). One comparative study reported that ReCell was associated with increased post-procedural

pain at the treatment site compared with STSG; however, after 2 weeks pain was similar for both groups (Foster *et al.*, 2019).

Surgical re-intervention

Several single-armed studies reported on rates of re-operation. However, it is not possible to interpret this data in the absence of a comparator and due to small sample sizes.

Other clinical and procedural outcomes

No data were identified that reported on other outcomes included in the scope, namely: number of dressings to the wound with or without anaesthesia; wound infection rates; re-admission to hospital for management of scarring; transfusion rates during skin grafts; number and size of donor sites; growth rate in children; surgical procedure and theatre time.

4.4.3 *Results of economic studies*

The study by Kowal *et al.* (2019) reported that the Use of ReCell was approximately cost saving or cost neutral (≤ 2% difference) in all the scenarios simulated. This was driven by reduced length of hospital stay associated with ReCell and reduction in regrafting procedures. The authors estimated that introduction of ReCell could lead to a 14.0 to 17.3% annual reduction in overall costs for the burns centre. Conservatively, this was $5.3 million per centre or $26,600 per patient. The EAC has noted the issues with uncertainty regarding the model inputs and the lack of generalisability of the data to a UK setting.

The other economic studies were published as abstracts only (Foster *et al.*, 2018; Foster *et al.*, unknown). None were set in the UK. In the opinion of the EAC, the reporting of these studies was insufficient to draw conclusions.

4.5 Ongoing trials

The EAC sifted the results of the gIS search for on-going trials (n = 19) and protocols identified by the company (n = 6). Six of the ongoing studies identified by the gIS search were considered to be in scope; however 2 of these were the protocols for the RCTs by Holmes *et al.*, namely NCT01138917 (Holmes *et al.*, 2018b) and NCT02380612: (Holmes *et al.*, 2018a). All 4 of the study protocols identified by the company that were in scope (2 being out of scope on population) were also identified by the gIS search. Ten ongoing studies were excluded because they reported on the wrong population (e.g. vitiligo, diabetic foot ulcer), 1 ongoing study was in the wrong intervention, and 2 were excluded because they focussed on the treatment of donor sites only.

Therefore 4 ongoing studies were identified as being unique and within scope of the decision problem. The protocols of these studies are summarised in Table B5. One study (NCT03626701) is described as a parallel RCT comparing ReCell in combination with specialised dressing with a polyurethane foam dressing (Mepilex). This study is planned to recruit 210 children with partial-thickness burns; however it has not started recruitment yet and it is unclear if the study is proceeding. The other study protocols describe observational studies, with 2 protocols describing continued access schemes (NCT03626701 and NCT02994654) and one enrolling patients with life-threatening burns, as an adjunctive to grafting (NCT02992249). It is unclear whether these studies have contributed to data published in conference abstracts.

4.6 Changes in costs

Newcastle EAC has previously undertaken a review of the changes in costs associated with ReCell treatment (Keltie *et al.*, 2019), summarised in Table 4.1.

Table 4.1: *Variables and parameters related to costs used in original company submission, and updates applied by the Newcastle EAC.*

Variable	Base-case (original submission)	Updated (Newcastle EAC) [source]
Biobrane unit cost, £	Note that prices vary according to dress size however £0.19 per cm^2 was the mean value used which gave a total cost of £121.60 per patient (based on 640 cm^2 base-case scenario)	Mean £0.22 per cm^2 [NHS Supply Chain]; [redacted] which gives a total cost of £140.80 per patient (based on 640 cm^2 base-case scenario)
ReCell unit cost, £	£1900 (per 640 cm^2 which was base-case scenario, i.e. 2 ReCell kits)	£2700 (plus VAT, covers up to 1920 cm^2) [Provided by company]

Secondary dressing change	£25 (including 30 minutes nurse time in ward and £18 arbitrary consumables)	£28.06 [Derivation unknown, original cost inflated to 2018 cost]
Conventional dressing change	[redacted]	[redacted]
Daily bed cost in burn unit (standard burns unit bed), £	[redacted]	[redacted]
Daily staff cost in burn unit (all professionals involved), £	[redacted]	[redacted]
Hourly cost of theatre time, £	[redacted]	[redacted]
Overall cost of SSG procedure + post-op care	[redacted]	[redacted]
[redacted]		

The conclusion of the cost update report (Keltie *et al.*, 2019) was:

> "…..this review of the cost data does not support re-assessment of ReCell on an economic basis alone. It is not possible for the EAC to conclude whether the guidance should be amended, updated, withdrawn, deferred or updated within another programme without a view of the clinical evidence."

The initial submitted economic model that informed MTG21 was performed only on "Group A", namely patients with partial thickness burns or scalds

where mesh grafting is not required (Peirce and Carolan-Rees, 2013). This model was later planned to be updated by CEDAR to assess the economics of two additional subgroups, namely patients with "large area burns which are judged to need wide mesh grafting", and patients with "full thickness or deep partial thickness burns which are judged to need skin grafting" (Peirce and Carolan-Rees, 2014). However, CEDAR reported it was not possible to conduct this analysis because "virtually no quantitative data for clinical benefit or resource saving was obtained from the survey of clinical experts". As CEDAR did not develop did not develop an additional economic model, this is not considered further.

The key clinical parameters used in the initial model included the proportion of patients undergoing in-patient care; the number of dressings per schedule; the proportion of patients requiring skin grafting; and mean healing time. These outcomes were not reported in any of the included studies. The RCT by Homes *et al.* (2018b) did report healing rates, but this was in ReCell compared with STSG, a population not reflective of Group A in the original submission and model. The EAC therefore concludes that there is no new data available to reliably inform the economic model.

4.7 Other relevant information

The company stated in the information request that "AVITA Medical has also received CE Mark for two additional configurations of the RECELL® technology since the previous review - REGENERCELL™ and RENOVACELL™, however company focus is with the expanded RECELL® configuration". The company has indicated that 25 hospital trusts are currently NHS users of ReCell (list supplied in commercial confidence). The company has stated for the time being that sales of ReCell will be restricted to existing customers of the product, and the product will not be actively marketed to new NHS providers.

An expert reviewer stated that "that the only clinical autologous keratinocyte culture service in the UK has recently ceased operating", and "Re-Cell may well be the only available 'next best thing'". The EAC has been unable to identify any specific information on this service and how it might impact on burns patients' pathways. It is noted that cultured grafts were not a comparator and were not subject to review in MTG21.

Other potentially competing products mentioned by two expert advisors included Cellutome, a skin harvesting technology for autologous skin grating. There does not appear to be any clinical evidence to support this technology. The Meek Skin Graft Mesher may lead to procedural improvements in meshed STSG. The EAC is also aware of the existence of biopolymer sprays

such as LQD spray which may be used for similar indications to ReCell in some instances.

5. Conclusion

The evidence base to support the uptake of ReCell since the publication of the original Assessment Report is poor in terms of quality, quantity, and generalisability. Of the studies identified, a within-patient RCT (n = 101) comparing ReCell with STSG in patients with partial thickness thermal burns was probably the most informative (Holmes *et al.*, 2018b). This study demonstrated non-inferiority of ReCell in treatment site healing, with greatly reduced donor site area, and improved skin appearance. However, this was a relatively small open-label study, and might not be generalizable to all burns patients. The study did not provide data to inform the economic analysis of the technology. Another smaller RCT used ReCell combined with STSG (Holmes *et al.*, 2018a). It is unclear if the advantages of ReCell used as an adjunctive in this way justify the increased expense. An economic study identified was limited by the quality of its inputs, and was not generalizable to the UK NHS (Kowal *et al.*, 2019). All the other clinical studies were published in abstract form only and could not be interpreted with confidence. This was because, as well as lacking peer review, it was not possible to convey the nuances of these populations and interventions in abstract format.

Skin burns represent a complex condition, and there is a wide range of patient heterogeneity. The expert advisors emphasised that burn patients represent a diverse group and management costs are sometimes very high; occasionally exceeding £1 million per patient. Alternative or adjunctive treatments such as cadaveric or allografts are very expensive, as is autologous cell culture. Each burns patient is unique, and sample sizes available for research are likely to be small with many confounding variables, complicating analysis and interpretation.

Research into treatment of burns is thus subject to significant challenges, and it may not be possible to extrapolate results from a specific burns population to a more generalised case mix. Routine sources of data, such as iBID, are not suitable for assessing the effectiveness of specific technologies like ReCell, and UK-based experimental research appears to have been curtailed. The EAC therefore concludes that the evidence base for the use of ReCell in the treatment of burns has not advanced substantially since the publication of MTG21, and a full update of the guidance is not warranted at this stage.

Appendix A – Relevant guidance

NICE guidance – published

None identified.

NICE guidance – in development

None identified.

Guidance from other professional bodies

None identified.

Appendix B – Details of studies and ongoing trials

Table B1. *Summary of fully published studies in peer reviewed journals.*

Study reference and location	Title	Study design	Population	Intervention	Comparator	Principal outcomes	Comment
(Holmes *et al.*, 2019) United States	"Demonstration of the safety and effectiveness of the RECELL® System combined with split-thickness meshed autografts for the reduction of donor skin to treat mixed-depth burn injuries"	RCT Within-subject allocation Double-blind (participant, outcomes assessor)	30 patients with mixed-depth burn injuries (inclusive of full-thickness) Age 39.1 (±15.8) years Burn area: 21.0% (±13.0%) TBSA ITT: 30 PP: 26	ReCell system using skin sample (1cm^2 per 80cm^2 of intended treatment area). Tefla clear wound dressing. Used in conjunction with STSG.	Standard of care using STSG	Primary Confirmed treatment area closure (at 8 weeks) Comparison of actual expansion ratios Secondary POSAS	Published as protocol at NCT02380612. This study was identified as a fully published study following identification of an abstract.
(Holmes *et al.*, 2018b) United States	"A Comparative Study of the ReCell® Device and Autologous Split-Thickness Meshed Skin Graft in the Treatment of Acute Burn	RCT Within-subject allocation Unmasked	101 patients with acute burns. Age 39.5 (±13.1) years Burn area: 10.0% (±4.5%) TBSA	ReCell system, using donor site 4.7 cm^{2}on average. 320cm^2 using 1:80 expansion ratio. Tefla clear	Standard of care using autograft from donor site (2:1 mesh) Tefla clear wound dressing.	Primary Incidence of wound closure (≥95% re-epithelialization) of the treated at week 4. Incidence of complete donor	Published protocol at NCT01138917.

Study reference and location	Title	Study design	Population	Intervention	Comparator	Principal outcomes	Comment
	Injuries"		ITT: 101 PP: 87 MPP: 83	wound dressing.		site healing at 1 week (100% re-epithelialization) <u>Secondary</u> Pain and visual appearance using VAS. Scarring using VSS.	
(Kowal *et al.*, 2019) United States	"Cost-Effectiveness of the Use of Autologous Cell Harvesting Device Compared to Standard of Care for Treatment of Severe Burns in the United States"	Cost-effectiveness study utilising cohort decision analytic model. Monte Carlo simulation.	Simulated cohort with severe burns eligible for ASCS (ReCell). Target population for the model is adults(average 42 years of age), with severe burns of TBSA ≥ 10% receiving inpatient care.	ReCell system.	Standard of care (autograft).	Cost-effectiveness. Budgetary impact.	Perspective was from perspective of burns centre. Costs in US$. Cost ReCell system $7500.00. Clinical inputs from burns registry and clinical studies.
Abbreviations: ASCS, autologous skin cell suspension; ITT, intention to treat; MPP, modified per protocol; PP, per protocol; POSAS, Patient and Observer Scar Assessment Scale; RCT, randomised controlled trial; STSG, split thickness skin graft; TBSA, total body surface area; VAS,							

Study reference and location	Title	Study design	Population	Intervention	Comparator	Principal outcomes	Comment
visual analogue scale; VSS, Vancouver Scar Scale.							

Table B2. *Summary of abstracts.*

Study reference and location	Title	Study design	Population	Intervention	Comparator	Principal outcomes	Comment
(Carter *et al.*, 2019) United States	"Evaluation of Pediatric Population Treated for Burn Injuries Using an Autologous Skin Cell Suspension"	Retrospective observational study	Children (≥ 5 years) with severe burns. n=33	ASCS (presumed ReCell).	None	Healing Surgical intervention Survival rate.	Conference abstract
(Craig *et al.*, 2019) United States	"Post-Operative Wound Management Following the Use of RECELL® Autologous Cell Harvesting Device in the Treatment of Patients with Life-Threatening Injuries: A Single Center's Experience"	Prospective observational study	243 distinct wounds treated in 27 patients who presented with a life-threatening burn injury and lacked adequate STSG donor sites. 20% to 91% TBSA Mean age 24.6 (±19.3) years	ASCS (ReCell).	None	Wound closure Regrafting.	Conference abstract
(Foster *et al.*, 2018) United States	"Cost-effectiveness (CE) of an Autologous Regenerative Epithelial	Cost-effectiveness study. Decision tree.	Simulated patients with severe burns.	ASCS	Standard care (STSG)	Incremental costs. Quantitative data not	Conference presentation. This study may have some cross-

Study reference and location	Title	Study design	Population	Intervention	Comparator	Principal outcomes	Comment
	Suspension (RES) versus Standard of Care (SOC) for Treatment of Severe Burns in the United States"					reported.	over with that of Kowal *et al.* (2018).
(Hickerson *et al.*, 2019) United States	"Evaluation of autologous skin cell suspension for definitive closure of extensive burn injuries in adult population"	Prospective uncontrolled observational study	22 patients (≥ 18 years) with extensive burns injuries. TBSA: 61.2% (range 52% to 91%)	ASCS (presumed ReCell) STSG	None	Re-epithelialisation. Surgical graft intervention. Wound appearance. Adverse events.	Conference abstract. Included a mixture of interventions, so difficult to interpret.
(Walker *et al.*, 2018) United States	"Initial Experience with Autologous Cell Suspension for Treatment of Partial Thickness Facial Burns"	Observational case series	6 patients with large burns. Mean age 20.4 (± 17.3) years	ASCS (presumed ReCell) with STSG	None	Cosmetic parameters Reoperations	Conference abstract.
(Sood *et al.*, 2015) United States	"A comparative study of spray keratinocytes and autologous meshed split-thickness skin graft in the treatment of acute burn	Prospective within patient comparison.	10 patients with acute burn injuries.	ASCS (presumed ReCell)	STSG	Graft take Pigmentation Scarring Pain	Conference abstract.

Study reference and location	Title	Study design	Population	Intervention	Comparator	Principal outcomes	Comment
	injuries"						
(Othman *et al.*, 2016) United Kingdom	"Comparative Retrospective Analysis of Long Term Scarring, Dyspigmentation and Itching Outcomes of Partial Thickness Paediatric Scalds Treated with Conventional Dressings Biobrane®, ReCell® and Split Skin Grafting at a Regional Burn Centre"	Retrospective observational study.	100 partial thickness paediatric scalds	ReCell ReCell combined with Biobrane	Standard dressings Biobrane alone STSG	Scarring Itching Pigmentation.	Conference presentation.
Abstracts supplied from the company							
Holmes *et al.* United States Date and place of publication unknown.	"Compassionate use of ReCell in large burns: A single-center U.S. experience"		13 adults and children with large burns. Adults (n=8) mean age: 34 years Mean TBSA: 63% Children (n=5) mean age 1.3 years	ReCell combined with STSG	Comparison with historical controls or patients from burns registry	Mortality Length of hospital stay.	Conference abstract.

Study reference and location	Title	Study design	Population	Intervention	Comparator	Principal outcomes	Comment
			Mean TBSA : 36%				
Foster *et al.* United States Date and place of publication unknown.	"Budget Impact of Autologous Cell Harvesting Device (ACHD) Use versus Standard of Care (SOC) for Treatment of Severe Burns: A Case Study"	Budget impact study	Patients eligible for ASCS for treatment of severe burns	ASCS (presumed ReCell)	Standard of care	Budgetary impact	Conference abstract Likely to be derived from same data as Kowal *et al.* (2018)
Molnar *et al.* United States Date and place of publication unknown	"Evaluation of Autologous Skin Cell Suspension for Healing of Burn Injuries of the Hand"	Observational study	30 patients with hand burns (n = 50 hands). Mean age: 36.7 (± 21.0) years TBSA: 47.8% (±23.7%)	ASCS (presumed ReCell) combined with STSG	None	Re-epithelialisation Cosmetic improvement Adverse events Surgical reoperation	Conference abstract Patients must also have had widespread burns aside from the hands.
Platt *et al.* United States Date and place of publication unknown	"Autologous Skin Cell Suspension Reduces Length of Stay for Burn Injuries"	Retrospective observational study	18 patients with severe burns Mean age 41 Mean TBSA: 22%	ASCS (presumed ReCell)	Historical comparison with burns registry.	Length of hospital stay.	Conference abstract
Sood. United Kingdom	"A Prospective Evaluation of Spray Keratinocytes to	Ongoing prospective uncontrolled	7 patients with life threatening burns.	"Spray keratinocytes": presumed to be	None	Healing rate. Donor re-epithelialisation	Conference abstract.

Study reference and location	Title	Study design	Population	Intervention	Comparator	Principal outcomes	Comment
Date and place of publication unknown	Treat Large TBSA Injuries"	observational study.	Age 3.9 to 61.8 years. Mean TBSA 60% (range 43% to 95%) Mean treatment area 2425.0 cm^2 Mean donor area 325.0 cm^2.	ASCS (ReCell). Combined with STSG.		rate.	
Abbreviations: ASCS, autologous skin cell suspension; POSAS, Patient and Observer Scar Assessment Scale; RCT, randomised controlled trial; STSG, split thickness skin graft; TBSA, total body surface area.							

Table B3 *Key results of comparative studies.*

Study Reference	Population description	Healing of treatment site	Healing of donor site	Length of hospital stay	Scarring and pigmentation	Safety	Others
(Holmes *et al.*, 2019) United States	30 patients with mixed-depth burn injuries	Wound closure Week 4: I 50%, C 48% Week 6: I 78%, C 74% Week 8, I 92%, C 92% 7.7% with the upper bound of the 97.5% CI (6.40%), establishing non-inferiority. No subjective difference in healing.	Relative reduction in donor skin "The between-treatment difference (32% reduction in utilized donor skin for RECELL treatment) was statistically significant (p<0.001)"	Not reported	Not reported	Not differences in AEs reported (57% both treatments)	No difference in subject satisfaction. No difference in POSAS.
(Holmes *et al.*, 2018b) United States	101 patients with acute burns.	Definitive closure at 4 weeks (≥95% re-epithelialisation) I 97.6%, C 100% −2.4% (95% CI: −8.4% to 2.3%), no statistical	Healing at donor site 1 week: I: 21.8% C: 10.0% (p=0.04) 2 weeks: I: 90.0% C: 67.3% (p<0.001)	Not reported	Weeks 16, 24, and 52: subjects expressed greater satisfaction with the visual appearance of the ReCell donor sites	Mild AEs I: 83.3% C: 91.3% "Five device-related AEs were reported as follows: two mild skin graft	Reduction in pain at donor site at 8 weeks (p≤0.005)

Study Reference	Population description	Healing of treatment site	Healing of donor site	Length of hospital stay	Scarring and pigmentation	Safety	Others
		difference.			compared with the Control donor sites (p≤0.005). "Reduced scarring" (p≤0.005).	failures and three hypertrophic scarring (two mild and one moderate)".	
(Foster *et al.*, 2019) United States	73 patients with burn injuries.	Not reported	Not reported	Not reported	<u>Pigmentation</u> "Pigmentation and color match ratings were identical at week 52 and the Modified Vancouver Scar Scale scores were comparable" <u>Scarring</u> "One subject rated the autologous cell harvesting site [ReCell] as having a better appearance, while the		<u>Pain</u> "In early follow-up visits, pain ratings were slightly elevated in the [ReCell] group due to graft healing; however, in visits following week 2, pain ratings at the [ReCell] and STSG sites were rated similarly by all patients".

Study Reference	Population description	Healing of treatment site	Healing of donor site	Length of hospital stay	Scarring and pigmentation	Safety	Others
					remaining subjects rated their ReCell and STSG sites appearances as being comparable".		
(Othman *et al.*, 2016) United Kingdom	100 partial thickness paediatric scalds	Not reported	Not reported	Not reported	<u>Scarring</u> Biobrane: 47% Biobrane with ReCell: 25% Dressings: 26% ReCell: 25% STSG: 78% <u>Depigmentation</u> Biobrane: 33% Biobrane with ReCell: 37% Dressings: 15% ReCell: 25% STSG: 18%	Not reported	<u>Itching</u> Biobrane: 19% Biobrane with ReCell: 12% Dressings: 11% ReCell: 0% STSG: 12%
Holmes *et al.* United States	13 adults and children with large burns.	Not reported	Not reported	"Mean hospital length of stay was significantly reduced in adults, as compared to	Not reported	Not reported	<u>Mortality</u> "There were no deaths in either the adult or the pediatric cohorts"

Study Reference	Population description	Healing of treatment site	Healing of donor site	Length of hospital stay	Scarring and pigmentation	Safety	Others
				historic institutional controls (1.0 day vs. 1.9 days, p<0.0001)"			
Platt *et al.* United States	18 patients with severe burns			"Patients treated with ASCS had a mean LOS of 24 days compared to those in the NBR [National Burns Registry] which had a mean LOS of 55 days".			<u>Mortality</u> 0% (both groups)
Abbreviations: ACS, autologous cell spray; AE, adverse events; C, comparator; I, intervention; POSAS, Patient and Observer Scar Assessment Scale; STGS, split thickness skin graft.							

Table B4 *Key results of single-armed studies.*

Study Reference	Population description	Healing of treatment site	Healing of donor site	Length of hospital stay	Scarring and pigmentation	Safety	Others
(Carter *et al.*, 2019) United States	33 children (≥ 5 years) with severe burns.	4 weeks: 88.1% 8 weeks: 92.4%	Not reported	Not reported	Not reported	Not reported	"Surgical intervention was required for graft failure in 8% of the wounds and for contracture release in 3% of wounds". "Survival rate was 100%".
(Craig *et al.*, 2019) United States	27 patients with life threatening burns wounds.	"At 8 weeks, 96% of the evaluable wounds had ≥95% wound closure."	Not reported	Not reported	Not reported	Not reported	"Minimal regrafting was required on 10% of wounds evaluated. Twenty-nine of the treated wounds (12%) required scar contracture release".
(Hickerson *et al.*, 2019) United States	22 adult patients with extensive burns injuries (150 wounds).	"At 8 weeks, 96% of wounds achieved healing (≥95% re-epithelialization)"	Not reported	Not reported	"Subjective assessment of wound appearance by the physician at 1 year ……	"No AEs were reported as related to the ASCS treatment"	Surgical intervention was required for graft failure in 8% (12/150) of wounds and for

Study Reference	Population description	Healing of treatment site	Healing of donor site	Length of hospital stay	Scarring and pigmentation	Safety	Others
					texture was reported as matched or mildly mismatched to uninjured skin for the majority of wounds, 83%, 78%, and 70%, respectively"		contracture release in 3.3%"
(Walker *et al.*, 2018) United States	6 patients with large burns.	Not reported	Not reported	Not reported	Not reported	"There were no major complications and minor complication rate was 16.7% [1 patient] consisting of a superficial facial hematoma".	"Re-operations in the first 3 months after treatment occurred in 33.3% (N=2) of the patients". "All outcomes were judged to be equivalent or superior to current techniques of split thickness skin grafting".
Molnar *et al.* United States	30 patients with hand	Healing (≥95% re-	Not reported	Not reported	"At one year, the majority of	Not reported	"Surgical intervention was

Study Reference	Population description	Healing of treatment site	Healing of donor site	Length of hospital stay	Scarring and pigmentation	Safety	Others
Date and place of publication unknown	burns (n = 50 hands).	epithelialisation) 1 week: 51% 4 weeks: 86%			all evaluable hands were matched or mildly matched in color (23/29), pigment (21/29) and texture (15/29) when compared to uninjured surrounding skin".		required for regrafting (14%) and contracture release (16%) of hands treated".
Sood. United Kingdom Date and place of publication unknown	7 patients with life threatening burns.	4 weeks: 93.5% of the wounds treated had ≥95% re-epithelialization.	1 week: 86.7% achieved ≥95% re-epithelialization	Not reported	Not reported	Not reported	"Two sites required additional Treatment"
Abbreviations: ACS, autologous cell spray; AE, adverse events; STGS, split thickness skin graft.							

Table B5. *Summary of on-going research (study protocols).*

Study ID **Type** **Sponsor**	**Population**	**Sample size**	**Intervention**	**Comparator**	**Principal outcomes**	**Status**
NCT02992249 Observational case series. Avita Medical.	People with burns who have a life-threatening wound requiring grafting.	100 participants	ReCell Autologous Cell Harvesting Device (ReCell) as an adjunct for closure.	None	Wound Healing (>95% epithelialization with a contiguous layer of viable epithelium).	Active, not recruiting. Last updated: June 25th, 2019.
NCT03626701 Parallel RCT 52 weeks Avita Medical.	Children (aged 1 to 16 years) with a partial-thickness thermal burn injury.	210 participants	RECELL combined with Telfa™ Clear and Xeroform™ dressings Conventional autografting (only when indicated)	Mepilex® Wound Dressing Conventional autografting (only when indicated)	Index burn area healing time Pain recovery following treatment Reported need for conventional autografting POSAS QoL (BCQ) Investigator treatment preference Health economics / medical resource utilisation	Not yet recruiting Last updated: August 13th 2018
NCT03333941 Continued access observational study Avita Medical.	Patients requiring skin grafting as a result of an acute thermal burn injury (>5 years)	76 participants	ReCell® Autologous Cell Harvesting Device applied over skin grafts meshed more widely than	None	Wound Healing (confirmed at two consecutive study visits at least 2 weeks apart up to 24 Weeks) Treatment area will be evaluated via direct	Completed Last updated: June 25th 2019

			conventional autografting.		visualization..	
NCT02994654 Continued access within patient study Avita Medical.	Patients requiring skin grafting as a result of an acute thermal burn injury (>5 years)	12 participants	ReCell and skin graft. Each patient serves as their own control.	None	Confirmed Treatment Area Closure Ratio of Actual Expansion Ratios	Completed Last updated: December 24th 2018
Abbreviations: BOQ, burns outcome questionnaire; POSAS, Patient and Observer Scar Assessment Scale; quality of life, QoL						

Appendix C – Literature search strategy

Adverse events sources	Date searched	Results and search terms
FDA medical devices: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm from this page search: MAUDE database, *- search on device and manufacturer, but the information needs to relate to the device. We might also be able to restrict searching to the most recent version of the device e.g. Sherlock 4 (rather than just 'Sherlock')* *Do not include results that are pre the date limit*	28/10/2019	MAUDE = 0 results found MHRA = 0 results found
MHRA: http://www.mhra.gov.uk/index.htm *Search for the indication. if getting no results for the device name*		
Ongoing trials sources Clinical trials.gov http://clinicaltrials.gov/ct2/home WHO International Clinical Trial Registry Platform (ICTRP): (covering a number of registries) http://apps.who.int/trialsearch/ ISRCTN http://www.isrctn.com/	07/10/2019 - 28/10/2019	***Ongoing studies*** NCT02992249: Prospective Evaluation of the ReCell® Autologous Cell Harvesting Device For Specific Compassionate Use Cases Status: Active, not recruiting Primary comparator: none given Expected enrolment: 100 Estimated primary completion date: May 2019 Location: none given NCT03626701: RES Prepared With RECELL® Compared to Standard of Care Dressings

Include completed trials that are within the date parameter specified by the analyst		of Partial-thickness Burns in Ages 1-16 Years Status: not yet recruiting Primary comparator: Mepilex® Wound Dressing, conventional autografting (only when indicated) Expected enrolment: 210 Estimated primary completion date: October 31, 2020 Location: none given NCT04091672: RECELL® System Combined With Meshed Autograft for Reduction of Donor Skin Harvesting in Soft Tissue Reconstruction Status: Not yet recruiting Primary comparator: None given Expected enrolment: 65 Estimated primary completion date: August 2021 Location: None given NCT03624192: RES Prepared With RECELL® Compared to Conventional Care for Healing of Donor Sites in Ages 1-16 Years Status: Recruiting Primary comparator: Telfa™ Clear and Xeroform™ dressings Expected enrolment: 60 Estimated primary completion date: December 31, 2019 Location: Arizona, US NCT01640678: Autologous Cell Suspension Grafting Using ReCell in Vitiligo and Piebaldism Patients Status: Unknown Primary comparator: CO2 laser abrasion alone and no treatment Expected enrolment: 10

		Estimated primary completion date: September 2013 Location: Amsterdam, Netherlands NCT02070835: Study of ReCell® Treating for Diabetic Foot Ulcers Status: Unknown Primary comparator: none given Expected enrolment: 80 Estimated primary completion date: June 2016 Location: Guangdong, China ACTRN12618000511235: Spray on skin for diabetic foot ulcer healing: an open label randomised controlled trial Status: Recruiting Primary comparator: Expected enrolment: 150 Estimated completion date: Location: Wester Australia ACTRN12618000245291: Autologous skin cell suspension in partial thickness paediatric burns: The BRACS Randomised Trial. Status: Recruiting Primary comparator: standard silver dressings Expected enrolment: 84 Estimated completion date: Location: Queensland, Australia ***Completed studies*** NCT00615355: Epidermal Cell Transplantation in Vitiligo Skin With and Without Narrow-band Ultraviolet B (UVB) Treatment

		Primary comparator: none given Enrolment: 11 Completion date: December 2015 Location: Graz, Austria Publications: none given NCT01743053: A Pilot Trial of the Use of ReCell® Autologous Cell Harvesting Device for Venous Leg Ulcers Primary comparator: Standard care Enrolment:52 Completion date: October 2015 Location: Montpellier, France; Bradford, UK; Cambridge, UK; Cardiff, UK; Doncaster, UK; Leeds, UK; Manchester, UK Publications: None given NCT03333941: Continued Access to the Recell® Device for Treatment of Acute Burn Injuries Primary comparator: none given Enrolment: 76 Completion date: May 8, 2019 Location: Arizon, US; District of Columbia, US; Florida, US; Louisiana, US; North Carolina, US; Tennessee, US Publications: None given NCT02994654: CONTINUED ACCESS PROTOCOL: Demonstration of the Safety and Effectiveness of ReCell® Combined With Meshed Skin Graft for Reduction of Donor Area in the Treatment of Acute Burn Injuries Primary comparator: none given Enrolment: 12 Completion date: September 2018

		Location: Arizona, US; District of Columbia, US; North Carolina, US; Tennessee, US; Texas, US Publications: None given NCT01138917: A Multicenter Comparative Study of the ReCell Device and Autologous Split-thickness Meshed Skin Graft in the Treatment of Acute Burn Injuries Primary comparator: none given Enrolment: 101 Completion date: August 2015 Location: Arizona, US; California, US; District of Columbia, US; Florida, US; Indiana, US North Carolina, US; Tennessee, US; Texas, US; Virginia, US Publications: None given NCT02380612: ReCell® Combined With Meshed Skin Graft in the Treatment of Acute Burn Injuries Primary comparator: none given Enrolment: 30 Completion date: April 2016 Location: Arizona, US; District of Columbia, US; Florida, US; North Carolina, US; Tennessee, US; Texas, US Publications: none given NCT02458417: Autologous Cell Suspension Grafting Using ReCell in Vitiligo and Piebaldism Patients Primary comparator: None given Enrolment: 10 Completion date: January 2016 Location: Amsterdam, Netherlands Publications: van Geel N, Ongenae K, Naeyaert JM. Surgical techniques for vitiligo: a review. Dermatology. 2001;202(2):162-6. Review.

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		ISRCTN63305738: Cultured keratinocytes in burn wound care Primary comparator: standard care Enrolment: 10 Completion date: Location: London, UK Publications: none given NCT02469168: Epidermal Coverage of Traumatic Wound Injuries Via Use of Autologous Spray Skin Applied Over Bilayered Wound Matrix Status: Terminated (lack of funding) Primary comparator: Standard meshed split thickness skin graft over wound pretreated with INTEGRA™ MBWM Wound Matrix Enrolment: 1 Completion date: December 2017 Location: Maryland, US Publications: Moiemen NS, Vlachou E, Staiano JJ, Thawy Y, Frame JD. Reconstructive surgery with Integra dermal regeneration template: histologic study, clinical evaluation, and current practice. Plast Reconstr Surg. 2006 Jun;117(7 Suppl):160S-174S. Wood FM, Giles N, Stevenson A, Rea S, Fear M. Characterisation of the cell suspension harvested from the dermal epidermal junction using a ReCell® kit. Burns. 2012 Feb;38(1):44-51. doi: 10.1016/j.burns.2011.03.001. Epub 2011 Nov 12. Waaijman T, Breetveld M, Ulrich M, Middelkoop E, Scheper RJ, Gibbs S. Use of a collagen-elastin matrix as transport carrier system to transfer proliferating epidermal cells to human dermis in vitro. Cell Transplant. 2010;19(10):1339-48. doi: 10.3727/096368910X507196. Epub 2010 Jun 3. Wood FM, Stoner ML, Fowler BV, Fear MW. The use of a non-cultured autologous cell

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EPPI-R 5

Download search results in RIS format → create EPPI review (with a codeset) → import RIS files → de-dupe results → add analyst and SIM lead → send email to analyst

- Create a review using the following naming convention:
  - MIB485_Amniosense for amniotic fluid testing during pregnancy_2019
- Select the 'Intervention' review type for your topic
- Add codeset from template – 'gIS Screening on title and abstract with second opinion codeset'
- Add the analyst and SIM lead (currently Nicola Walsh) as 'Admin'

Add files to ER5 and dedupe. See notes on how to ensure conferences are identifiable. See ER5 Guide for help including how to convert .txt files (for CRD databases) into RIS for EPPI.

When emailing the analyst, let them know the name of the EPPI review and include the instructions on how to identify/isolate conference abstracts. (see 'message to analyst' section).

There is no need to sift search results (though they should be de-duped).

Databases*	Date searched	No retrieved	Version/files
MEDLINE (Ovid)	29/10/2019	227	1946 to October 28, 2019
MEDLINE In-Process (Ovid)	29/10/2019	99	1946 to October 28, 2019
EMBASE (Ovid)	29/10/2019	310 (+240 conference abstracts)	1974 to 2019 October 28
Ovid ePubs	29/10/2019	13	1946 to October 28, 2019
CDSR (Wiley)	29/10/2019	3	Issue 10 of 12, October 2019
**Database of Abstracts of Reviews of Effects – DARE (CRD)	29/10/2019	0	-
HTA database (CRD)	29/10/2019	3	-
CENTRAL (Wiley)	29/10/2019	170	Issue 10 of 12, October 2019
**NHS EED (CRD	29/10/2019	0	-
Econlit (for economic searches)	29/10/2019	1	1886 to October 17, 2019
Total		1066	
Total after de-duplication		779	

**Add/Delete as appropriate*
******From January 2015 no new records/commentaries will be added to DARE or NHS EED.*

Use “entry date” not “publication year” to limit the searches and put a note in the cover email to the analyst to explain that this will include all records added to databases since the last search and may include older material.

See the OneNote searching document for tips on using a date limits: S:\Information Resources\Guidance IS\SERVICES\Methodology\Guides\Database guides hints & tips\Database Tips.one

Search strategies

Database: MEDLINE
Strategy used:

Database: Ovid MEDLINE(R) <1946 to October 28, 2019>
Search Strategy:
---
1 exp Burns/ (56514)
2 (burn* or scald* or cicatrix or "skin loss" or depigmentation).tw. (85500)
3 Wound healing/ (91102)
4 (wound* adj4 heal*).tw. (57809)
5 Skin Transplantation/ (35023)
6 dermatoplast*.tw. (160)
7 (skin adj4 (graft* or transplant*)).tw. (20055)
8 Transplantation, autologous/ (49004)
9 (autologous adj4 transplant*).tw. (17640)
10 (autografting* or autotransplantation*).tw. (6180)
11 or/1-10 (296230)
12 Suspensions/ (7601)
13 suspension.tw. (61153)
14 (spray adj4 (skin or epiderm* or epithel* or fibrin or cell or cells)).tw. (336)
15 or/12-14 (65707)
16 11 and 15 (1115)
17 (recell or "avita medical").tw. (32)
18 16 or 17 (1130)
19 animals/ not humans/ (4604703)
20 18 not 19 (824)
21 limit 20 to english language (707)
22 limit 21 to ed=20131101-20191029 (227)

Database: MEDLINE in PROCESS

Strategy used:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to October 28, 2019>
Search Strategy:
---

1 exp Burns/ (0)
2 (burn* or scald* or cicatrix or "skin loss" or depigmentation).tw. (12078)
3 Wound healing/ (0)
4 (wound* adj4 heal*).tw. (8778)
5 Skin Transplantation/ (0)
6 dermatoplast*.tw. (2)
7 (skin adj4 (graft* or transplant*)).tw. (1856)
8 Transplantation, autologous/ (0)
9 (autologous adj4 transplant*).tw. (1578)
10 (autografting* or autotransplantation*).tw. (411)
11 or/1-10 (23493)
12 Suspensions/ (0)
13 suspension.tw. (12129)
14 (spray adj4 (skin or epiderm* or epithel* or fibrin or cell or cells)).tw. (58)
15 or/12-14 (12183)
16 11 and 15 (126)
17 (recell or "avita medical").tw. (7)
18 16 or 17 (129)
19 animals/ not humans/ (0)
20 18 not 19 (129)
21 limit 20 to english language (126)
22 limit 21 to dt=20131101-20191029 (99)

Database: MEDLINE EPUBS

Strategy used:

Database: Ovid MEDLINE(R) Epub Ahead of Print <October 28, 2019>

Search Strategy:

---

1 exp Burns/ (0)
2 (burn* or scald* or cicatrix or "skin loss" or depigmentation).tw. (1531)
3 Wound healing/ (0)
4 (wound* adj4 heal*).tw. (1359)
5 Skin Transplantation/ (0)
6 dermatoplast*.tw. (2)
7 (skin adj4 (graft* or transplant*)).tw. (209)
8 Transplantation, autologous/ (0)
9 (autologous adj4 transplant*).tw. (268)
10 (autografting* or autotransplantation*).tw. (63)
11 or/1-10 (3272)
12 Suspensions/ (0)
13 suspension.tw. (894)
14 (spray adj4 (skin or epiderm* or epithel* or fibrin or cell or cells)).tw. (12)
15 or/12-14 (905)
16 11 and 15 (12)
17 (recell or "avita medical").tw. (3)
18 16 or 17 (13)
19 animals/ not humans/ (0)
20 18 not 19 (13)
21 limit 20 to english language (13)

Database: EMBASE

Strategy used:

Search Strategy:

---

1 exp Burn/ (66078)
2 (burn* or scald* or cicatrix or "skin loss" or depigmentation).tw. (123531)
3 Wound healing/ (110693)
4 (wound* adj4 heal*).tw. (90811)
5 Skin Transplantation/ (13214)
6 dermatoplast*.tw. (140)
7 (skin adj4 (graft* or transplant*)).tw. (26063)
8 autotransplantation/ (22427)
9 (autologous adj4 transplant*).tw. (33250)
10 (autografting* or autotransplantation*).tw. (8000)
11 or/1-10 (351622)
12 Suspension/ or Autologous skin cell suspension/ (19041)
13 suspension.tw. (89452)
14 (spray adj4 (skin or epiderm* or epithel* or fibrin or cell or cells)).tw. (516)
15 or/12-14 (97944)
16 11 and 15 (1677)
17 (recell or "avita medical").tw. (61)
18 avita.dm. (22)
19 recell.dv. (41)
20 or/16-19 (1736)
21 Nonhuman/ not human/ (4515524)
22 20 not 21 (1412)
23 limit 22 to english language (1207)
24 limit 23 to dc=20131101-20191029 (550)
25 limit 24 to (conference abstract or conference paper or "conference review" or conference proceeding) (240)
26 24 not 25 (310)

Database: ECONLIT

Strategy used:

Database: Econlit <1886 to October 17, 2019>
Search Strategy:
---

1 [exp Burns/] (0)
2 (burn* or scald* or cicatrix or "skin loss" or depigmentation).tw. (1325)
3 [Wound healing/] (0)
4 (wound* adj4 heal*).tw. (12)
5 [Skin Transplantation/] (0)
6 dermatoplast*.tw. (0)
7 (skin adj4 (graft* or transplant*)).tw. (1)
8 [Transplantation, autologous/] (0)
9 (autologous adj4 transplant*).tw. (7)
10 (autografting* or autotransplantation*).tw. (0)
11 or/1-10 (1344)
12 [Suspensions/] (0)
13 suspension.tw. (437)
14 (spray adj4 (skin or epiderm* or epithel* or fibrin or cell or cells)).tw. (1)
15 or/12-14 (437)
16 11 and 15 (1)
17 (recell or "avita medical").tw. (1)
18 16 or 17 (1)
19 [animals/ not humans/] (0)
20 18 not 19 (1)
21 limit 20 to english language [Limit not valid; records were retained] (1)
22 limit 21 to dt=20131101-20191029 [Limit not valid; records were retained] (1)

Database: Cochrane

Strategy used:

Search Name:

Date Run: 29/10/2019 10:39:33
Comment:

ID	Search	Hits
#1	MeSH descriptor: [Burns] explode all trees	1602
#2	((burn* or scald* or cicatrix or "skin loss" or depigmentation)):ti,ab,kw	10330
#3	MeSH descriptor: [Wound Healing] this term only	4476
#4	((wound* near/4 heal*)):ti,ab,kw	10185
#5	MeSH descriptor: [Skin Transplantation] this term only	465
#6	(dermatoplast*):ti,ab,kw	2
#7	((skin near/4 (graft* or transplant*))):ti,ab,kw	1431
#8	MeSH descriptor: [Transplantation, Autologous] this term only	1545
#9	((autologous near/4 transplant*)):ti,ab,kw	4896
#10	((autografting* or autotransplantation*)):ti,ab,kw	644
#11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10	25064
#12	MeSH descriptor: [Suspensions] this term only	370
#13	(suspension):ti,ab,kw	6313
#14	((spray near/4 (skin or epiderm* or epithel* or fibrin or cell or cells))):ti,ab,kw	105
#15	#12 or #13 or #14	6480
#16	#11 and #15	256
#17	((recell or "avita medical")):ti,ab,kw	29
#18	#16 or #17 with Cochrane Library publication date Between Nov 2013 and Oct 2019	1732

Database: CRD

Strategy used:

	Line	Search	Hits	

	1	MeSH DESCRIPTOR burns EXPLODE ALL TREES	102	Delete
	2	((burn* or scald* or cicatrix or "skin loss" or depigmentation))	597	Delete
	3	MeSH DESCRIPTOR Wound healing	515	Delete
	4	((wound* and heal*))	1471	Delete
	5	MeSH DESCRIPTOR Skin Transplantation	56	Delete
	6	(dermatoplast*)	0	Delete
	7	(skin) AND ((graft* or transplant*))	150	Delete
	8	MeSH DESCRIPTOR Transplantation, autologous	239	Delete
	9	((autologous and transplant*))	394	Delete
	10	((autografting* or autotransplantation*))	8	Delete
	11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	2391	Delete
	12	MeSH DESCRIPTOR Suspensions	3	Delete
	13	(suspension)	97	Delete
	14	(spray) AND ((skin or epiderm* or epithel* or fibrin or cell or cells))	23	Delete

☐	15	#12 OR #13 OR #14	122	Delete
☐	16	#11 AND #15	14	Delete
☐	17	((recell or "avita medical"))	0	Delete
☐	18	#16 OR #17	14	Delete

Notes:

Record any important decisions on how the strategy was developed

[May include notes from analysts or IS colleagues, links to correspondence, etc. For example, why particular search terms included/excluded. Consider annotating the search strategy if this is easier.]

Appendix D – References

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