NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Centre for Health Technology Evaluation

Review Decision

Review of MTG21: The RECELL Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury

This guidance was issued in November 2014.

1. Review decision

Transfer the guidance to the 'static guidance list.' The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the medical technologies guidance on the static list should be flagged for review.

2. Original objective of guidance

To assess the case for adoption of RECELL Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury.

3. Current guidance

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.

4. Rationale

Updated literature searches identified 10 new studies that were within scope (please see section 5). NuTH EAC concluded that the new clinical and economic evidence did not substantively add to the evidence base; the uncertainties leading to research

recommendations had not been answered. Changes in costs of the technology did not have a significant impact on the cost case and did not affect the scenarios in which the technology would be cost saving or incurring. Additionally, changes in cost of the technology are not relevant to the NHS as the technology is not currently available to new NHS customers. The technology is still available to existing users in the NHS and the guidance remains relevant for these users. The decision is therefore to place the guidance on the static list.

5. New evidence

The search strategy from the original assessment report was re-run. References from November 2013 onwards were reviewed. Additional searches of clinical trials registries were also carried out and relevant guidance from NICE and other professional bodies was reviewed to determine whether there have been any changes to the care pathways. The company was asked to submit all new literature references relevant to their technology along with updated costs and details of any changes to the technology itself or the CE marked indication for use for their technology. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix 2 for further details of ongoing and unpublished studies.

5.1 Technology availability and changes

The technology is still available in the UK for existing users. The technology has been updated to a newer version called RECELL 1,920. RECELL 1,920 is intended to treat a larger surface area of up to 1,920cm^2 which differs from the original device which is intended to cover an area of up to 320cm^2. To facilitate this modification the newest version of the technology includes additional buffer solution (40ml), increased number of 10ml syringes (7), double the number of 18-ga needles, scalpels and nozzles. RECELL 1,920 also comes with a cell strainer but no longer includes 5ml syringes. The updated device received a CE mark in March 2015. The updated device uses the same CE mark as the previous version. The cost of the technology has increased from £950 to £2700 (excluding VAT) per unit.

5.2 Clinical practice

There is currently no NICE pathway for the treatment of acute burn injuries.

Burns injuries are first assessed for depth. The depth of the wound informs the treatment decision. Partial thickness and full thickness wounds are surgically excised within a day or two of admission. For mixed depth partial thickness scalds or burns, skin grafts are recommended if the wound remains

unhealed 14-21 days following excision. For full thickness wounds of over 1cm diameter a skin graft will be required. For deep partial thickness or full thickness burns, autologous split thickness skin grafts taken from an area of unburnt skin are considered the gold standard. Where large grafts are required donated skin can be perforated (or meshed) to increase the surface area. The donor site is also a wound and will require treatment to ensure healing. Allografting (skin from another person), or xenografting (skin from an animal) can also be used for temporary skin closure but do not provide a long-term solution as they'll be rejected by the body. Other alternatives include artificial skin products.

There have been no changes to the care pathway since the publication of the original guidance for RECELL Spray on Skin. The technology is currently being used in 25 NHS trusts. The technology is only available to existing users of RECELL; the company are not selling the technology to new NHS users within the UK. Three expert advisors contributed to the development of this document, all have used the technology and 1 no longer uses it as they believed the technology did not result in improved patient outcomes**.** One acknowledges that a competing treatment of burns, autologous keratinocyte culture service, has ceased in the UK, however, this service was not standard care. Another expert recognised a competitor called Cellutome has been developed and overlaps with RECELL in design and population.

5.3 NICE facilitated research

An RCT commissioned by NICE from Cedar EAC was cancelled in October 2018 due to withdrawal of company financial and material support before the trial commenced. This withdrawal occurred at the same time as the limiting of RECELL sales to existing customers of the product. Following October 2018 RECELL has not been actively marketed to new NHS users, the sale of RECELL in the UK is currently still limited to existing users.

5.4 New studies

NuTH EAC reviewed the evidence. The updated literature searches identified 10 studies relevant to the scope. The literature included 6 comparative (Holmes et al, 2018;; Holmes et al, 2019; Holmes et al, 2020; Othman et al, 2016; Platt et al, 2019; Sood et al, 2015;) 6 non comparative (Carter et al., 2019, Craig et al., 2019, Hickerson et al., 2019, Molnar et al, 2019,); Sood et al, date unknown; Walker et al., 2018) and 3 economic studies Foster et al, 2018; Foster et al, 2019; Kowal, 2019). Four studies are ongoing, see Appendix 2.

The comparative evidence consisted of 2 full text peer review randomised control trials and 4 abstracts. The two RCTs; compared RECELL (Holmes et

al 2018) or RECELL combined with split thickness skin grafts (STSG) (Holmes et al 2019) with STSG alone in adults and children with acute deep partial thickness burns. Both RCTs reported that wounds showed non-inferior rates of healing when treated with RECELL (97% achieved ≥95% re-epithelialisation at 4 weeks [Holmes et al, 2018) or RECELL plus STSG (92% of wounds healed at 8 weeks [Holmes et al, 2019]) compared with STSG graft alone (100% wounds ≥95% re-epithelialisation at 4 weeks [Holmes et al 2018]; 85% of wounds healed at 8 weeks [Holmes et al, 2019]). A 32% reduction in utilized donor skin (Holmes et al, 2019) was reported in the RECELL group compared with STSG ($p<0.001$). The use of less donor site skin results in significantly improved donor site healing, evidenced by a statistically significant difference in 1 and 2 week healing rate (Holmes et al 2018) when comparing RECELL with STSG alone (week 1 healing, 21.8% and 10.0% [$p=0.04$], respectively; week 2, 90.0% and 67.3% [$p<0.001$], respectively). The use of RECELL was associated with reduced donor site pain (Holmes et al., 2018).Outcomes related to donor site size or healing rate were not included in NICE's research recommendations. One RCT reported no significant difference in scarring between RECELL and STSG. Abstracts and single arm observational studies also reported comparative data, however, the EAC believed these data were unreliable due to limited detail and poor reporting.

The non-comparative data consisted of 6 single-arm observational studies reported only as abstracts. Four of the studies reported over 90% healing rate (wound closure or re-epithelialisation) at week 8 using RECELL (Carter *et al.*, 2019, Craig *et al.*, 2019, Hickerson *et al.*, 2019, Sood *et al.*, 2015). Two observational studies reported patient length of stay to be reduced compared with historical norms (Holmes et al, 2020; Platt, 2019). The EAC noted that the lack of methodological detail and poor-quality reporting of results made it difficult to interpret the findings.

The economic evidence consisted of 1 full text and 2 abstracts. The full text study (Kowal, 2019) used a decision tree model to estimate the cost of using RECELL in a specialist burns hospital. The study reported using RECELL for treatment of burns in specialist hospital would be cost saving or cost neutral compared with standard care. The EAC noted the inputs used to inform the model were sourced from low quality studies and the model did not include clinical effectiveness or quality of life data. The EAC anticipates that it is likely that the two additional abstracts included in the review (Foster et al, 2018; Foster et al, 2019) reported the same data as were described in the full text. None of the economic studies modelled the cost using RECELL in the UK and lack generalisability to the NHS.

Four ongoing studies are relevant to the scope (see Appendix 2). One study is described as a parallel RCT and 3 are observational studies. The RCT is intended to compare RECELL plus a specialised dressing with Mepilex (a polyurethane foam dressing), the study is active and currently recruiting. The other 3 studies are observational studies, it is unclear whether these studies contributed to data published in abstracts.

5.5 Cost update

NuTH EAC reviewed and updated the RECELL cost case (please see EAC cost update). The changes to the area of coverage and cost of the technology mean the original cost case is no longer valid. The EAC incorporated the increased cost of RECELL and updated any relevant associated costs. Table 1 presents the original and updated costs of the technology. Despite these changes, the updated analysis reports savings and increased costs within the same scenarios as were reported in the base case, only the magnitude of the cost difference has changed. The EAC concluded the impact of changes in the cost changes do not support the case for guidance update.

Table 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 (a biosynthetic dressing) unit cost, £	Note that prices vary according to dressing 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 [redacted] 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 (which 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 model remains cost saving where RECELL, used both alone and alongside the biosynthetic dressing Biobrane, is compared with conventional dressings. The model also remains cost-incurring where RECELL, used both alone and with Biobrane, is compared with Biobrane alone. The updated cost of the technology, however, has impacted the magnitude of the difference in costs resulting in reduced savings across both cost-saving arms and additional increases in costs in both cost-incurring arms. Table 2 summarises

the difference in cost between the interventional and comparator arms of the model, discrepancies in the original model were also identified and corrected for.

Table 2 Difference between intervention and comparator costs in the original submission, the corrected original submission and the updated costs.

Comparison	Difference in cost (original submission), £	Difference in cost (original submission with correct technology costs applied), £	Difference in cost (updated), £
RECELL vs. Conventional dressing	-1650.83	-1244.35	-965.66
RECELL+Biobrane vs. Conventional dressing	-1755.71	-1575.54	-1060.10
RECELL vs. Biobrane	1494.11	1613.46	2237.59
RECELL+Biobrane vs. Biobrane	1389.23	1282.27	2143.15

6. Summary of new information and implications for review

New literature has become available, some of which address outcome measures described in the research recommendations for MTG21 RECELL. Despite the updated evidence base, the majority of the evidence is of low quality and does not add substantively to the evidence base. Two RCTs (Holmes et al 2018a; Holmes et al 2018b) address the decision problem, both report that using RECELL results in non-inferior healing rates compared to standard care. One new economic study reports that RECELL may be cost-saving or cost-neutral (≤ 2% difference), the data used to inform the parameters were sourced from poor quality evidence and addressed only the perspective of a specialist burns hospital in the United States.

Changes to the area of coverage and cost of the technology limit the validity of the original cost-case. Updates to the model reported the technology remained cost-saving used alone or in combination with Biobrane when compared to standard care alone, however, the magnitude of the cost-savings were reduced. An update to the guidance is not supported as the new evidence does not report patient or systematic benefit compared to standard care.

7. Implementation

The technology is only available to existing users. The technology is not available to new NHS users.

8. Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

The MTG21 RECELL scope recognised the use of trypsin enzyme to disaggregate the skin cells from the biopsy during RECELL treatment 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. No additional equality issues have been identified.

Contributors to this paper:

Technical analyst:	Rebecca Owens
Technical adviser:	Chris Pomfrett
Project Manager:	Sharon Wright
Project Coordinator:	Joanne Heaney

Appendix 1 – explanation of options

If the published Medical Technologies Guidance needs updating NICE must select one of the options in the table below:

Options	Consequences	Selected – 'Yes/No'
Amend the guidance and consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	No
Amend the guidance and do not consult on the review proposal	The guidance is amended but the factual changes proposed have no material effect on the recommendations.	No
Standard update of the guidance	A standard update of the Medical Technologies Guidance will be planned into NICE's work programme.	No
Update of the guidance within another piece of NICE guidance	The guidance is updated according to the processes and timetable of that programme.	No

If the published Medical Technologies Guidance does not need updating NICE must select one of the options in the table below:

Options	Consequences	Selected – 'Yes/No'
Transfer the guidance to the 'static guidance list'	The guidance remains valid and is designated as static guidance. Literature searches are carried out every 5 years to check whether any of the Medical Technologies Guidance on the static list should be flagged for review.	Yes
Defer the decision to review the guidance	NICE will reconsider whether a review is necessary at the specified date.	No
Withdraw the guidance	The Medical Technologies Guidance is no longer valid and is withdrawn.	No

Appendix 2 – supporting information

Relevant Institute work

Published

MTG2 moorLDI2-BI: a laser doppler blood flow imager for burn wound assessment is due to be updated in August 2020. The case for adopting this technology is currently supported for assessing burns that are of uncertain depth or healing potential.

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.

In progress

None identified

Registered and unpublished trials

Trial name and registration number	Details
NCT02992249 Observational case series. Avita Medical.	100 people with burns who have a life-threatening wound requiring grafting. Active – not recruiting
NCT03626701 Parallel RCT 52 weeks Avita Medical.	210 children (aged 1-16yrs) with a partial thickness thermal injury. Intervention: RECELL combined with Telfa™ Clear and Xeroform™ dressings Comparator: Mepilex Active – recruiting

Trial name and registration number	Details
NCT03333941 Continued access observational study Avita Medical.	76 patients requiring skin grafting as a result of an acute thermal burn injury (>5yrs) Complete – last updated 25th July 2019
NCT02994654 Continued access within patient study Avita Medical.	12 patients requiring skin grafting s a result of an acute thermal burn injury (>5 years) Complete – last updated 24th December 2018

Appendix 3 – changes to guidance

No amendments suggested.

References

Carter, J. et al. 2019. Evaluation of pediatric population treated for burn injuries using an autologous skin cell suspension. Journal of Burn Care and Research, 40, 3.

Craig, C.K 2019. Post-operative wound management following the use of an autologous cell harvesting device in the treatment of patients with life-threatening injuries: A single center's experience. *Journal of Burn Care and Research*, 40, 69.

Foster, K.N. et al. 2018. Cost-effectiveness (CE) of an autologous regenerative epithelial suspension (RES) versus standard of care (SOC) for treatment of severe burns in the United States. *Journal of Burn Care and Research*, 39, 113.

Foster, K.N. et al. 2019. Healing of donor sites with an autologous skin cell suspension for large tbsa burn injuries: A prospective evaluation. *Journal of Burn Care and Research*, 40(S1):S225-226.

Hickerson, W. et al. 2019. Evaluation of autologous skin cell suspension for definitive closure of extensive burn injuries in adult population. *Journal of Burn Care and Research*, 40, 230-s231.

Holmes J.H. et al. 2018. A comparative study of the RECELL device and autologous split-thickness meshed skin graft in the treatment of acute burn injuries. *Journal of Burn Care and Research*, 39, 694-702.

Holmes, J.H. et al.. 2019. Demonstration of the safety and effectiveness of the RECELL((R)) System combined with split-thickness meshed autografts for the reduction of donor skin to treat mixed-depth burn injuries. *Burns*, 45, 772-782.

Holmes, J.H. et al. 2020. Real world treatment trends for patients TBSA ≤20%: Evaluating important shifts in care and budget impact of ASCS adoption. *Journal of Burn Care & research, 41 S115.*

Kowal, S. et al. 2019. Cost-Effectiveness of the Use of Autologous Cell Harvesting Device Compared to Standard of Care for Treatment of Severe Burns in the United States. *Advances in Therapy*, 36, 1715-1729.

Molnar, J. 2019. Evaluation of autologous skin cell suspension for healing of burn injuries on the hand. Presented at American Burn Association (ABA); April 2-5; Las Vegas, NV, USA

NBBC. 2012. National Burn Care Referral Guidance [Online]. Available: https://www.britishburnassociation.org/wp-content/uploads/2018/02/National-Burn-Care-Referral-Guidance-2012.pdf [Accessed 7th February 2020].

NICE. 2014. The RECELL Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury [Online]. Available: https://www.nice.org.uk/guidance/mtg21 [Accessed 6th February 2020].

Othman et al. 2016. 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. *Journal of Burn Care and Research*, 37, 150.

Platt, B. 2019. Autologous skin cell suspension reduces length of stay from burn injuries. Presented at Louisiana State Chapter, ACS; January 19-20; New Orleans, La, USA.

Sood, R. et al. 2015. A comparative study of spray keratinocytes and autologous meshed split-thickness skin graft in the treatment of acute burn injuries. *Wounds : a compendium of clinical research and practice,* 27, 31-40.

Walker, N, J. et al.. 2018. Initial experience with autologous cell suspension for treatment of partial thickness facial burns. *Journal of Burn Care and Research*, 39, 44.