National Institute for Health and Care Excellence

Medical Technologies Evaluation Programme

MT205 - The ReCell Spray-On Skin system for treating skin loss, scarring and depigmentation after burn injury

Consultation comments table

MTAC meeting date: 11 September 2014

There were 22 consultation comments from 3 consultees (1 NHS professional, 1 sponsor and 1 External Assessment Centre representative.) The comments are reproduced in full, in guidance section order.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
1	1 (NHS professional)	**1**	Agree with recommendations	Thank you for your comment.
2	1 (NHS professional)	**2**	Management of burn wounds depends on site, size and depth of the wound and can only be generalised as a guide.	Thank you for your comment. Current clinical practice, including available treatments and management strategies, is described in section 2 of the guidance.
3	2 (Sponsor)	**2.3**	This paragraph states that: "The claimed benefits of ReCell are shorter wound healing time, leading to: Reduced frequency of dressing changes… Reduced need for dressing changes under anaesthetic.. Etc etc" We believe that the primary interpretation in the first line that ReCell leads to shorter healing times is less relevant than the individual items listed, which encapsulate its true benefits. The patients in whom ReCell is most likely to be used are those who are also being treated with meshed	Thank you for your comment. The claims are based on those stated in the sponsor's notification and revised in developing the draft scope, on which stakeholders, including the sponsor, has the opportunity to comment. Unless otherwise stated, each claim is considered to have equal weight.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
			autografting, so that the clinical and economic benefit of ReCell is stated more clearly in terms of the reduction of patient burden (or risk) associated with that autografting. In acute care (burns, trauma), ReCell contributes to definitive closure of acute wounds with reduced harvesting of skin for autografting. Burn surgery is fundamentally about managing the balance and interplay of risks and costs associated with delayed healing (e.g., infection, poor scar outcomes) and the risks and costs associated with autografting (donor site pain/infection/scar). Data around these risks and benefits and their applicability to individual patient characteristics drive the decision of whether and when to pursue surgical autografting. Once a decision for surgical intervention has been made, risks and benefits are balanced in the determination of whether and how much to expand the skin harvested for autografting. Better take rates (i.e. graft success) and cosmetic outcomes are achieved with less tissue expansion (lower meshing ratios), however in cases where donor skin is limited, wider expansion (higher meshing ratios) may be required. Surgical intervention for treatment of an acute cutaneous injury proceeds when the clinical benefit of timely closure outweighs the risks associated with the harvesting of donor skin.	

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
4	2 (Sponsor)	**2.6-2.7**	The treatment pathway for those with superficial or deep burns is relatively clear-cut. Patients with indeterminate burn depth present special problems, owing to the uncertainty regarding the ultimate outcome. Early skin grafting minimises the risk of impaired healing, but carries with it the risk of an aesthetic poor result in a patient who may not have required grafting anyway. Conservative treatment maximises the chance of avoiding surgery but if grafting does become necessary, results following a delayed procedure may not be as good as following earlier operation. In a recently published case series (Dunne JA, Rawlins JM. Early paediatric scald surgery – a cost effective dermal preserving surgical protocol for all childhood scalds. Burns 2014;40:772-83), 40 children with scalds were treated with an early intervention algorithm. 7/40 were deemed to have deep burns and received early SSTG. 20/40 had superficial burns and were treated with Biobrane. 13/40 had indeterminate depth wounds and were treated with ReCell + biobrane. Based on this approach, 27/40 patients were discharged without further grafting. There was an overall reduction in the number of skin grafts undertaken, compared to a non-algorithmic approach and analgesic and dressing costs were reduced by 29%.	Thank you for your comment. Please refer to the response to comment 2. The paper cited by the consultee is a letter to the editor of the journal and refers to the same study described in Dunne and Rawlins (2012a). This study formed part of the evidence assessed by the External Assessment Centre and is discussed in section 3.8 of the guidance. The External Assessment Centre reviewed the letter and concluded that it did not represent a significant addition to the relevant evidence. The authors describe an early-treatment regime for all paediatric scalds, of which ReCell formed part of the treatment only for mid-dermal depth scalds. Although the authors reported a 29% reduction in analgesic and dressing costs, the External Assessment Centre judged that the outcomes were attributable to the complete treatment regime used and that the contribution of ReCell could not therefore be determined.
5	3 (External Assessment Centre)	2.7	Treatment of mixed depth or indeterminate burns is not standardised. Some centres may adopt a conservative approach, as described here, others may be more aggressive, with a greater likelihood of early grafting.	Thank you for your comment. Please refer to the response to comment 2.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
6	3 (External Assessment Centre)	**2.9**	Cells are not used as a direct alternative to autografts in the UK. They would not be applied directly to full thickness burns and probably not to deep partial thickness burns as cells require a dermal substrate on which to attach. In the UK they are used in conjunction with meshed autografts or may be applied to the donor site. I don't think that cells are attached to fibrin glue in clinical practice.	Thank you for your comment. Information on the use of cultured cells was taken from published literature on burns treatment that describes many modes of delivery for cultured cells, including attachment to a fibrin matrix or fixation with fibrin glue. The Committee heard clinical expert advice that cultured cells can be applied directly to debrided burns and can be attached to fibrin glue in clinical practice. The Committee decided not to change section 2.9 of the guidance.
7	1 (NHS professional)	**3**	Agree the evidence is lacking for the benefit-claims made by sponsors. Most of the studies claiming either equal efficacy or benefits over other treatments have not compared like with like	Thank you for your comment.
8	2 (Sponsor)	**3.2**	The reduction in requirement for donor sites and the reduced associated morbidity should be included in this paragraph. The first is inherent in the method – a 1cm2 donor site can cover 80cm2 of burn area, while the second has been evidenced in the data already reviewed by the committee	Thank you for your comment. The Committee decided to change section 3.2 of the guidance to add the outcome 'Number and size of donor sites' which was listed as an outcome in the scope decision problem. Reduced morbidity associated with the reduction in requirement for donor sites was not listed.
9	2 (Sponsor)	**3.5**	In addition to the studies identified for the MTEP assessment, further interim data are now available from an ongoing clinical trial that was identified in the original submission. These document the impact of the use of ReCell on important patient related outcomes such as donor site healing, pain and appearance.	Thank you for your comment. The Committee reviewed the interim data in full which was submitted as commercial in confidence and is included in appendix 1 of this document. The study is an ongoing multi-centre randomised within-patient controlled trial, based in the USA. The use of ReCell is compared to the use of meshed skin autografts. The External Assessment Centre reviewed this data and produced a supplementary report, which was presented to the Committee and is included in

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
				appendix 4 of this document. The External Assessment Centre stated that, based on the information it obtained from clinical experts (published alongside the Committee's provisional recommendations during public consultation), the use of ReCell as an alternative to skin grafting in this study did not reflect current NHS practice. This potential use for ReCell has been incorporated into the considerations for research in section 3.33 of the guidance. The Committee decided to add a new section to the guidance (3.26) to include reference to the study findings and a further new section (3.38) to describe its considerations on the evidence presented in this study.
10	2 (Sponsor)	**3.20-3.25**	Further data from comparative trials relating to repigmentation are now available, although as they are, as yet, unpublished they should be regarded as academic in confidence. *Please see appendix 2 for study details* These two studies offer further confirmation of results already seen in vitiligo, and also demonstrate that the results are equally applicable to burns-related hypopigmentation.	Thank you for your comment. The Committee reviewed the data from the 2 comparative studies included in this comment which were submitted as academic in confidence. Details are included in appendix 2 of this document. This information was presented to the Committee in full. The studies describe the use of ReCell for vitiligo and hypopigmented burn scars. The External Assessment Centre's critical appraisal of the study data is included in appendix 4 of this document. The Committee decided to add a new section to the guidance (3.26) to include reference to the study findings and a further new section (3.38) to describe its considerations on the evidence presented in these studies.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
11	2 (Sponsor)	**3.31**	Treatment for patients with very large burns is not amenable to conventional evaluation using an RCT methodology. Individual circumstances, co-morbid conditions, multiple therapies and personalised care pathways effectively render the concept of a control treatment meaningless. In consequence, understanding and optimising the management of this type of patient will hinge on individual case reports or case series. The following is one such case report from the USA that illustrates the potential role of ReCell in these patients. It has been submitted for publication and therefore must be considered as academic in confidence. *Please see appendix 3 for study details* Cases of this type allow a narrative understanding of the role of ReCell in the management of large burns patients where there are limited options available for treatment. By allowing meshed grafting to be undertaken to large skin areas from a limited pool of healthy skin, with rapid healing of donor sites to allow re-donation, ReCell allows these complex patients to achieve re-epithelialisation in the most time-efficient manner, thereby reducing the risk of infection, poor healing and the need for later re-grafting. Clearly, matching patients like this in the context of a randomised controlled trial is rarely possible, as the individual patient circumstances and treatment requirements vary substantially.	Thank you for your comment. The Committee reviewed the case study included in this comment which was submitted as academic in confidence. Details are included in appendix 3 of this document. This information was presented to the Committee in full. This case report describes treatment for a patient with 75% total body surface area burns in the USA. The External Assessment Centre's critical appraisal of the study data is included in appendix 4 of this document. The Committee decided to add a new section to the guidance (3.26) to include reference to the study findings and a further new section (3.38) to describe its considerations on the evidence presented in this study.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
12	2 (Sponsor)	**3.32**	We believe that pigment matching in healed burn sites is of critical importance in the ultimate cosmetic result of burns treatment, especially for patients with darker skins. Although the evidence was relatively sparse at the time the EAG reviewed it, this is a fast evolving area and the new evidence outlined in our earlier comments offers further confirmation of the potential benefit of ReCell in this context.	Thank you for your comment. Please refer to the response to comment 10.
13	2 (Sponsor)	**3.33**	We agree that observational data collected by the International Burn Injury Database (IBID) could prove useful to document some of the missing information on burns management but would like to bring to the committees attention that: A) Information on mode of treatment is not currently collected in IBID and therefore it would not allow assessment of the impact of ReCell B) Unfortunately data from IBID is not currently publically accessible, other than a summary report issued in 2008 covering the years 1987-2007 – neither the sponsor nor the EAG was able to gain access to the current database and therefore it is probably does not represent a viable data source	Thank you for your comment. Section 1.2 of the guidance notes that relevant databases and registers are available. Any future collaborative research facilitated by NICE will fully explore the potential contribution of available data sources.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
14	3 (External Assessment Centre)	**3.33**	ReCell is inappropriate for use with sheet autografts. We suggest that reference to sheet grafts is removed unless the intention is to include the possibility of using ReCell as an alternative to grafting, in which case this should be made explicit. The Committee was advised that ReCell is not used in this way in the UK (3.29).	Thank you for your comment. The considerations for research were aimed at covering a variety of different uses for ReCell including its potential as an alternative to grafting for burns other than full thickness (see section 3.29 of the guidance), rather than for its use with sheet autografts. The reference to sheet grafting in this section was also included to cover the potential treatment of donor sites with ReCell for recipients of skin grafts. The aim of a research recommendation is to address gaps in the current evidence base and if necessary, to recommend changes to current NHS practice once those gaps have been addressed. The Committee decided to change the text (now in section 3.34 of the guidance) to read 'burns that need skin grafting'.
15	2 (Sponsor)	**3.35**	For the reasons highlighted in our response to 3.31 above – the prospect of achieving meaningful comparative controlled trial data in large burns is very small. Even if it were possible to match such complex patients with controls in a statistically valid fashion, the incidence of these severe burns is thankfully very low and it could take many years to accumulate a sufficiently large number of patients. We will, however, continue to document individual cases from the US compassionate use programme and from centres in other countries that currently have access to ReCell.	Thank you for your comment.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
16	1 (NHS professional)	**4**	Agree with the conslusions; burn wound care practise varies vastly across the nation and often even among practitioners in the same set up!	Thank you for your comment.
17	2 (Sponsor)	**4.1**	An additional benefit that has potential resource consequences for the NHS is the reduction in size, number and morbidity of SSG donor sites.	Thank you for your comment.
18	3 (External Assessment Centre)	**4.3**	The EAC report may have overstated the variability in the frequency of dressing changes in an attempt to be as inclusive as possible. In general dressings are changed every 2-3 days in the more minor burns, however the use of cells or biosynthetic dressings alters what dressings are changed (e.g. outer dressings are changed but not interface dressings). In the large area burns the frequency of dressing changes in the early stages is confounded by the ongoing nature of surgical treatment. However, both daily and weekly dressing changes (as stated in the sponsor's claims) are unlikely. Variability in dressing regimes also included the type of dressing, and use of anaesthesia. We suggest this is replaced with: "The Committee accepted the findings from the External Assessment Centre's report that there was variation in practice in the frequency and nature of dressing changes, types of dressing used and use of anaesthesia. The Committee considered that evidence about the possible effect of using ReCell on the resources used in dressings changes could be gathered in further research."	Thank you for your comment. The Committee decided to change section 4.3 of the guidance to provide further clarification on the variation in practice regarding dressing changes.
19	1 (NHS professional)	**5**	Agree	Thank you for your comment.

Com. no.	Consultee number and organisation	Sec. no.	Comments	Response
20	1 (NHS professional)	**6**	Agree with the conclusions	Thank you for your comment.
21	1 (NHS professional)	**7**	no comments	Thank you for your comment.
22	1 (NHS professional)	**8**	adequate	Thank you for your comment.

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or Advisory committees."

Appendix 1

Study details submitted as part of comment 9:

[redacted]

[redacted]					

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

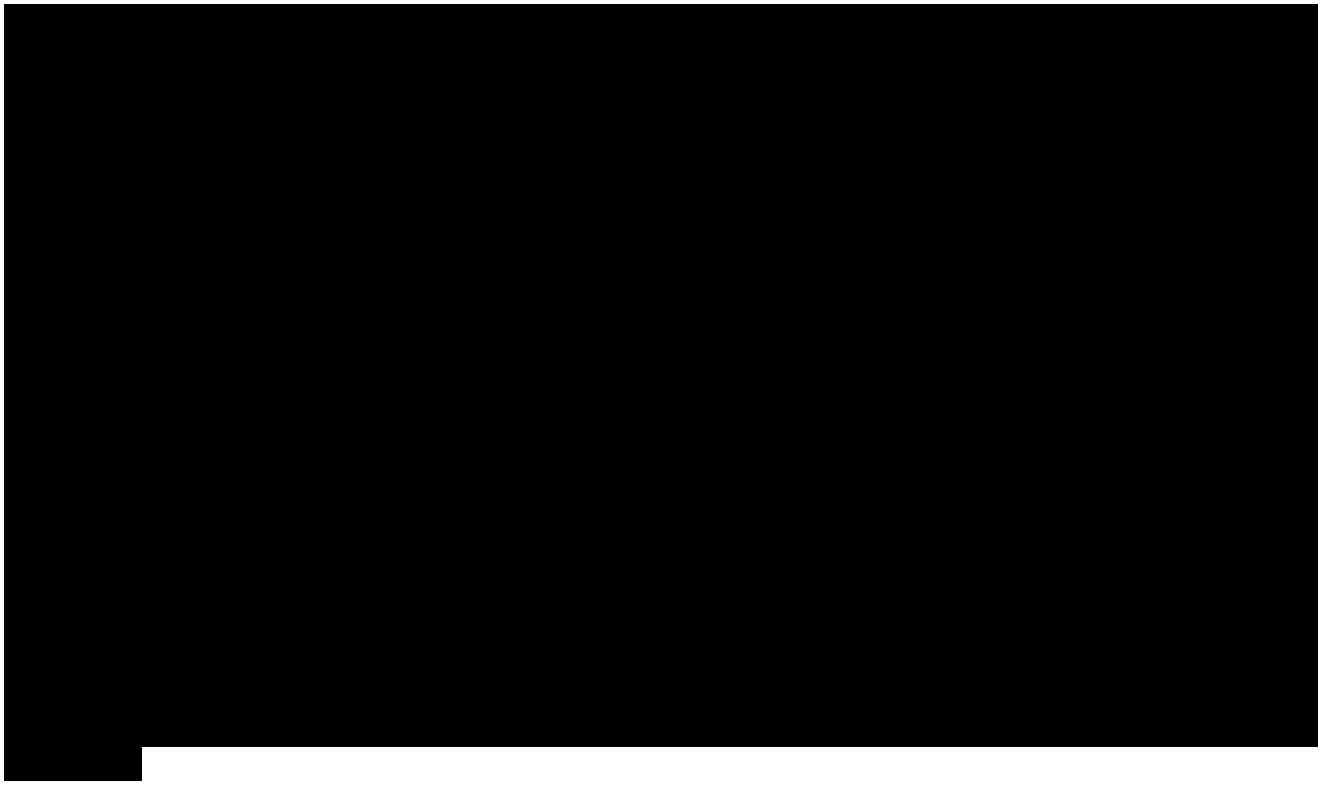
[redacted]

Appendix 2

Study details submitted as part of comment 10:

Appendix 3

Study details submitted as part of comment 11:



Appendix 4

External Assessment Centre Report on Sponsor's Comments

1 Ongoing Clinical Trial in Burns (section 3.5 of the guidance; comment 9)

1.1 Methodology

Information regarding this study is taken from the sponsor's comments on the consultation document and the Clinical Trials Gov register (as submitted by the manufacturer, http://clinicaltrials.gov/ct2/show/NCT01138917). This ongoing multi-centre trial, based in the US (trial identifier NCT01138917) is a randomised within-patient controlled study being conducted for submission to the FDA. The population is adults with second-degree (partial thickness) burns of at least 2 x 100 cm^2 for which meshed autologous split thickness skin grafts (SSG) have been deemed necessary. The use of ReCell alone on one area of burn wound is compared to the use of [redacted] meshed SSG alone on the other. The size of burn wound being compared is between 100-320 cm^2 in patients with 1-20% TBSA. The donor sites for the SSG and ReCell are harvested separately.

Primary outcome measures are (1) the incidence of donor site healing at 1 week and (2) the incidence of burn site healing at 4 weeks. Secondary outcomes are percent epithelialisation of the burn wound (over 16 weeks follow up), burn wound closure (2 weeks) and patient assessment of pain and appearance of the burn and donor site wounds (up to 52 weeks follow-up). Assessment of healing is intended to be conducted by independent clinicians, [redacted]

The study is intended to demonstrate non-inferiority of ReCell to SSG regarding healing of the burn wound and superiority of ReCell regarding healing of the donor site.

1.2 Results

[redacted]

[redacted]

1.3 Critical Appraisal

[redacted]

1.4 EAC Comments

The overall study design is similar to that in Gravante et al. (2007); an intra-patient comparison between ReCell alone and SSG alone.

[redacted]

[redacted] It is a consequence of the method of use that ReCell donor sites are smaller than would be required for an SSG for the same treatment area. It also appears reasonable to assume that smaller skin wounds are less painful and heal faster than larger ones.

[redacted] However, the most important comment on this study is that it does not reflect current UK practice or opinion on the use of ReCell in acute burn wounds. During the EAC's survey it was clear that UK burns surgeons did not consider ReCell to be a suitable *alternative* to SSGs and would not use it as a sole treatment for burns that were thought to require grafting.

2 Comparative Studies in Non-burns Indications (sections 3.20-3.25 of the guidance; comment 10)

2.1 Study 1

[redacted].

2.2 Study 2

[redacted]

[redacted]

2.3 Overall

[redacted] Previous studies have suggested that treatment outcomes in vitiligo are highly variable and liable to change over time – results at 6 months may not reflect longer term outcomes (EAC additional report, section 3.1.2, p11 of 48).

[redacted]

3 Case Report (section 3.31; comment 11)

The EAC recognises the difficulties of conducting controlled trials in patients with very large burns. As the sponsor indicates, an RCT using patients as the unit of randomisation is neither practical nor appropriate in this population. The sponsor provides a comparison between a single patient report and an institutional aggregate to support their claims. However, the EAC disagrees that a controlled trial in such patients would not be possible as other study designs, such as intra-patient comparisons (as in Gravante et al. 2007 and the ongoing US trial) or multi-centre registries, could be utilised. The recommendation in the MTEP consultation document for ReCell is for further research. Case studies and case series will not provide the comparative data required for Medical Technologies Guidance to be reviewed in future.

[redacted] The sponsor appears to claim that the use of ReCell allowed more rapid recropping of the donor sites.

[redacted] An alternative interpretation of the sponsor's comments is that

the use of ReCell enabled wider than usual meshing of the SSGs, so that a larger area could be treated from a small reserve of spared skin. The FDA has recently granted an exemption for compassionate use of ReCell in patients with life-threatening injuries and insufficient healthy skin for conventional grafting “to allow greater coverage by the grafts while using less donor skin area” (http://www.avitamedical.com/index.php?ob=2&id=272). However, such practice was ruled out by UK burns surgeons in the EAC’s survey.