MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
02 April 2019

Agenda Item No	04.1
National Programme	Internal Medicine
Clinical Reference Group	Specialised Dermatology
URN	1805

Title
Allogenic Mesenchymal Stromal Cell Infusion Therapy for Children with Severe Generalised Recessive Dystrophic Epidermolysis Bullosa

Actions Requested	1. Support the adoption of the policy statement
	2. Recommend its approval as an in-year service development

Proposition
This is a policy statement proposition recommending not for routine commissioning of this treatment for this indication. This will be in place whilst a research proposal is developed to support collection of data on effectiveness which may inform a policy position in the future. The treatment is not currently available for this indication and therefore does not alter the current commissioning position.

Clinical Panel recommendation
The Clinical Panel recommended that policy statement development progressed to confirm that the treatment was not commissioned.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review and Clinical Panel Report.
2.	The Head of Acute Programme confirms the proposal is supported by a: Rapid Impact Assessment; Stakeholder Engagement Report; Equality Impact and Assessment Report; Clinical Policy Statement. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.

4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Statement Proposition
2.	Evidence Review comprising three supporting papers
3.	Clinical Panel Report
4.	Stakeholder Engagement Report
5.	Equality Impact and Assessment Report

No	*Metric*	*Summary from evidence review*
1.	Survival	Not assessed.
2.	Progression free survival	Not assessed.
3.	Mobility	A clinical trial was performed by Petrof *et al.* (2015) to examine the clinical efficacy of mesenchymal stromal cells (MSCs) in treating recessive dystrophic epidermolysis bullosa (RDEB). This was a single centre, non-randomised phase I/II clinical trial to assess the efficacy of MSCs in 10 children with RDEB. Mobility was not formally assessed; however, qualitative analysis conducted via semi-structured telephone interviews with the parents of all trial participants. One of the subjective disclosed perceived benefits included improved mobility. This uncontrolled unblinded prospective study had a small sample size (n=10), limited statistical analysis and lacks a comparator thereby limiting the strength of the conclusions that can be drawn.
4.	Self-care	Not assessed.
5.	Usual activities	Petrof et al. (2015) assessed fatigue during the course of the clinical trial. Results reported for fatigue did not show any statistically significant difference at either day 60 or day 180 compared with baseline.
6.	Pain	Petrof et al. (2015) examined the impact of MSCs on pain during the clinical trial. Results reported for pain did not show any statistically significant difference at either day 60 or day 180 compared with baseline.
7.	Anxiety /	Not assessed.

	Depression	
8.	Replacement of more toxic treatment	Not assessed.
9.	Dependency on care giver / supporting independence	Semi-structured telephone interviews with the parents of trial participants reported a range of subjective perceived benefits of the intervention on dependency on care giver / supporting independence. This uncontrolled unblinded prospective study had a small sample size (n=10), limited statistical analysis and lacks a comparator thereby limiting the strength of the conclusions that can be drawn.
10.	Safety	Adverse events were categorised according to their relationship to the MSC infusion ranging from definitely to not related (Petrof *et al.* 2015). A total of 163 adverse events were experienced by all of the children in the study (n=10). None of these were serious and the majority (65%, 107) did not require any action. Thirty-two adverse events were recorded as being directly attributable to the administration of MSCs and included: dimethyl sulfoxide (DMSO, a preservative used in MSCs) odour, abdominal pain, bradycardia and nausea. These adverse events did not require any alteration to the dose or discontinuation of the infusions. Laboratory assessments did not reveal any adverse impact of MSCs on renal, liver or bone marrow function (Petrof *et al.* 2015), although no further data is provided for this. This uncontrolled unblinded prospective study had a small sample size (n=10), limited statistical analysis and lacks a comparator thereby limiting the strength of the conclusions that can be drawn.
11.	Delivery of intervention	Not assessed.

Other health outcome measures determined by the evidence review		
No	Metric	Summary from evidence review
1.	Severity	The single centred, non-randomised clinical trial (n=10) conducted by Petrof et al. (2015) assessed severity using two specific scoring systems. The Birmingham Epidermolysis Bullosa Severity (BEBS) score demonstrated a reduction in severity at day 180 (mean difference -6.9, 95% CI: -12.7, -1.1) compared with baseline (defined as up to 120 days prior to starting the first infusion of MSCs). The Global Severity Score

		(GSS) demonstrated a reduction in severity at day 60 (mean difference -2.4, 95% CI: -3.4, -1.4) and reduced further at day 180 (mean difference -1.6, 95% CI: -2.96, -0.24) compared with baseline. This uncontrolled unblinded prospective study had a small sample size (n=10), limited statistical analysis and lacks a comparator thereby limiting the strength of the conclusions that can be drawn.
2.	Blister Counts and suction blister time	Petrof et al. (2015) conducted a clinical assessment of the skin by conducting a blister count, identifying the suction blister time and taking photographs of patients' skin at various time points during the trial. • Median blister count: at baseline the blister count was 5.5 (interquartile range (IQR) 2.0, 6.0). This was lower at day 60 (median 3.5, IQR 1.0, 7.0) and day 180 (median 3.5, IQR 3.0, 7.0). • The suction blister time is a measure of the time taken to form a blister by the application of suction (negative pressure) to an area of skin. This is approximately 60 minutes in a healthy person. There was an improvement in the suction blister time at day 100 (mean difference 1.7 minutes, 95% CI: -0.5, 3.9) compared to baseline but this was not statistically significant. • Photographs published in the paper demonstrated improved appearances of the skin in subjects following the administration of MSCs. This uncontrolled unblinded prospective study had a small sample size (n=10), limited statistical analysis and lacks a comparator thereby limiting the strength of the conclusions that can be drawn.
3.	Pruritus	Petrof *et al*. (2015) reported no statistically significant difference for pruritus at either day 60 or day 180 compared with baseline.
4.	Quality of Life	The Paediatric Quality of Life score (Parent version) demonstrated an improvement at day 60 (mean difference -4.4, 95% CI: -8.1, -0.7). This uncontrolled unblinded prospective study had a small sample size (n=10), limited statistical analysis and lacks a comparator thereby limiting the strength of the conclusions that can be drawn.

Considerations from review by Rare Disease Advisory Group
The Highly Specialised Commissioning Team did not specifically ask RDAG for advice on this product because it was agreed as not for routine commissioning but RDAG was made aware of the potential NIHR supported clinical trial and was satisfied that this could inform the evidence base to support a policy proposal in the future.

Pharmaceutical considerations
This policy proposition does not recommend intravenous infusions of mesenchymal stem cells for children with recessive dystrophic epidermolysis bullosa. This product does not currently have a Marketing Authorisation.

Considerations from review by National Programme of Care
The proposal received the full support of the Internal Medicine National Programme of Care on 31st January 2019. It was noted the policy statement is to provide clarity on the not for routine commissioning position to support clinicians and commissioners on an interim basis. An NIHR research proposal is being developed.