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Title: Participatory co-design of patient-reported outcome indicators and an N-of 1 evaluation of a dressing glove for Epidermolysis Bullosa

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King's College London licenses the manufacturing of the Skinnies WEB™ garments to Skinwear Limited and receives royalties.

Abstract

Aims: In Recessive Dystrophic Epidermolysis Bullosa (RDEB) repeat blistering results in finger webbing and severe contractures of the hands. The aim was to codesign patient-reported outcome indicators for hand therapy with patients, carers and clinicians and use these to proof of concept test a novel dressing glove for RDEB with cost analysis.

Method: Qualitative interviews and focus groups with patients and carers generated content for the indicators. Validity and reliability were established through expert review, piloting and consensus between patients, carers and clinicians. The indicators were self-reported by patients before and whilst wearing the dressing glove in an N-of-1 study. Time for dressing changes and use of conventional products were also self-reported.

Results: A total of 11 indicators were initially generated from the thematic analysis. Expert review, piloting and consensus involved six patients, five carers and eight clinicians (total n=19). Participants agreed 14 indicators, covering hand skin condition (n=4), webbing between the digits (n=4), experiences of wearing and changing dressings (n=2), hand function (n=2), wrist function (n=1) and hand pain (n=1). In Phase 3, 12 patients scored indicators before wearing the gloves and four patients completed scoring while wearing the gloves. Statistically significant improvements between pre-glove and with-glove periods were found for most participants' experience scores. Skin appearance also improved for most participants.

Conclusion: The indicators generated useful data, differentiation between scores and participants demonstrating proof-of-concept for RDEB patients who could wear the dressing gloves. The indicators are being used in routine practice supporting clinical follow up, commercialisation and regulatory governance of the dressing glove.

Keywords

Hand therapy; Epidermolysis Bullosa; wound care; public and patient involvement; n-of-1 methodology; routine clinical follow up

Key points

- Rare diseases are challenging to study due to patient heterogeneity and small populations, but the need is great due to their debilitating and chronic nature.

- A novel approach to testing medical devices in these patient groups was adopted through participatory co-design of patient-recorded outcome indicators which were then used to proof-of-concept test a novel dressing glove for Epidermolysis Bullosa.

- The 14 indicators cover experiences of wearing and changing dressings (2), and hand skin condition (4), extent of webbing between the digits (4) wrist function (1) hand pain (1) and hand function (2).

- The indicators provide preliminary clinical evidence of device performance showing improved experiences and appearance of the skin for participants who could wear the dressing gloves.

- Longitudinal data collection using the same online patient-recorded outcome indicators is continuing in routine care providing ongoing evidence of safety and effectiveness for patients, clinicians, researchers and industry.

Introduction

Rare diseases are complex and absorb high proportions of health service resources. Almost invariably, they are chronic and degenerative with no effective cure although research into orphan drugs and genomics are paving the way to targeted therapeutic approaches to increase longevity. [1] Although considered uncommon, there are over 6000 identified rare diseases affecting 6-8% the population. [2 3] Over 75% of people with rare diseases are children and the impact on families and carers in immense. Management is based on delaying disease progression and maintaining and improving quality of life. Medical devices, which include wound care products, play an important role in these goals [4] and research to develop new devices is the priority.[5] Recent device regulations place increasing responsibility on industry for clinical follow-up with patient-recorded outcomes, to demonstrate the benefits, risks, safety and effectiveness of therapeutic devices. [6-8] In rare diseases, however, developing patient-recorded outcomes is particularly challenging because clinical representation is individual, multi-systemic and characterised by complex co-morbidity.[9 10] Previous research into patient experiences is lacking and small study populations make it difficult to generate enough data to measure differences. [11 12] In addition, due to the chronic nature of rare diseases, achieving a balancing between illness and research burden is often difficult to accomplish.[13] To overcome these methodological challenges, we adapted a participatory model to co-design patient-recorded outcome indicators and test a novel dressing glove [14] in an n-of-1 proof-of-concept study with people with Epidermolysis Bullosa (EB) and their carers (Figure 1). [15-17] The model includes continuing clinical follow up after the testing phase using the same patient-recorded outcome indicators. Outcomes data are thereby collected routinely enabling longitudinal data collection, off-setting small data sets obtained during the N-of-1 research phase. This provides health service providers and industry with ongoing evidence of safety and effectiveness for regulatory governance.[6-8]

EB is a rare, inherited, life-limiting condition which affects around 5,000 individuals in the UK. [18] People with severe types, including Recessive Dystrophic EB (RDEB), experience painful skin blistering and severe hand contractures (Figure 2, 3 and 4). [19-21] Hand therapy devices such as dressings and splints are conventionally prescribed to delay the progression of disease-related disability, but they cause maceration, restrict function and are not well tolerated.[14] Dressing changes are time-consuming, painful and can cause skin damage. [22-24] Existing quality of life and outcome measures in EB are not sensitive to patient experiences of hand function. [25-27] The ABILHANDS-Kids [28] measures hand function but lacks the ability to detect small, nuanced, changes which are clinically significant in severe types of EB. Similarly, the DASH measure (Disabilities of the Arm, Shoulder and Hand Score)[29], used frequently in hand therapy is not specific enough to capture clinically significant changes in EB hands. EB specialists advocate grading systems and photography to assess contractures of the hand but these are not used uniformly.[30-32] Health Organisations also generate their own paper-based, clinician-recorded assessments.[33]

The GLOVE project (Generation and evaLuation Of hand therapy deVices for Epidermolysis Bullosa) was undertaken with patients with RDEB, carers, clinicians, engineers, a knitwear manufacturer and materials specialists to co-design a disposable dressing glove (Figure 4), a reinforced web-spacer glove with improved breathability and fit, and a prototype Adjustable Splint Glove. Patient-recorded outcome indicators were co-designed with patients, carers and clinicians and incorporated into a digital software tool, Hand Therapy-Online (HTO). People with EB often live long distances from specialist centres making face-to-face consultation problematic. A telehealth system such as the HTO tool enables remote, real-time communication, and a prompt response to worsening hand condition. This paper reports on the development of the patient-recorded outcome indicators for hand therapy devices in EB and their use in a N-of-1 proof-of-concept study with cost analysis to investigate the performance of the disposable dressing glove, compared with conventional dressings

and bandages. The clinical follow up phase and testing of the adjustable splint glove is currently ongoing and will be published in due course.

Figure 1: A model of medical device co-design and evaluation for rare diseases (adapted for dressing glove for EB from Grocott et al 2007 [15])

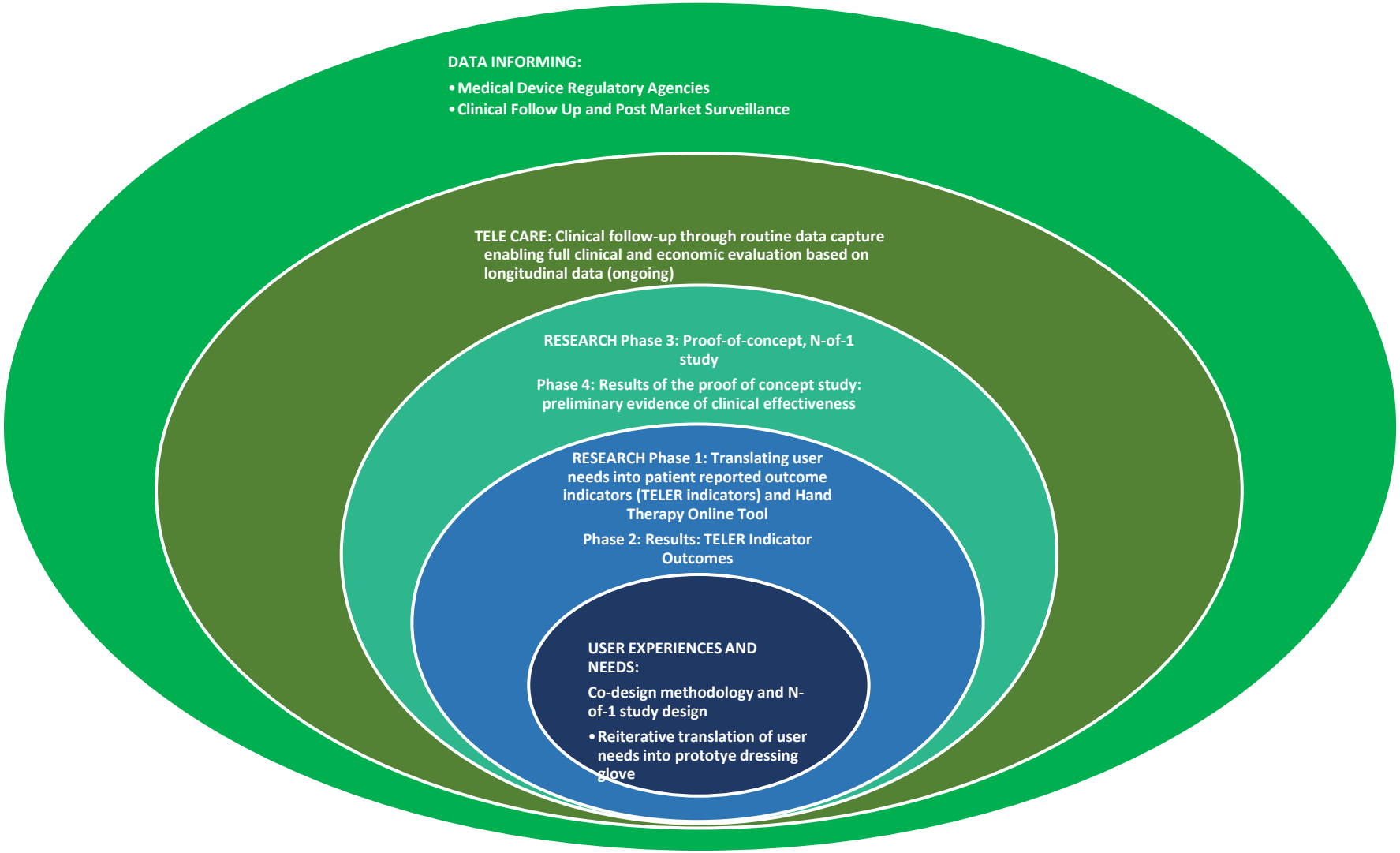


Figure 2: Recessive Dystrophic Epidermolysis Bullosa Clinical Profile

- Epithelia, mucosae, including digestive, respiratory and ocular systems are affected by blistering. [20]
- Hands may be normal at birth but are subjected to a destructive cycle with repeat blistering and healing by scar tissue.[73]
- Repeat blistering results in skin breakdown and healing with scar tissue. [20] Scar tissue results in finger webbing and contractures of the hands, which require surgery to regain hand function. [21,74]
- Following surgery, hand therapy interventions, including medical devices, are essential to maintain and regain hand function [21,74-76]
- EB hands are small due to contractures and bone resorption. [73,77]
- Wound healing is compromised by malnutrition, anaemia, infection and pruritus. [78-81]
- Hand dominance does not influence disease progression deformity; clinical experience indicates that contractures differ in each hand. [81-82]

Figure 3: Adult male with Recessive Dystrophic Epidermolysis Bullosa with no dressings

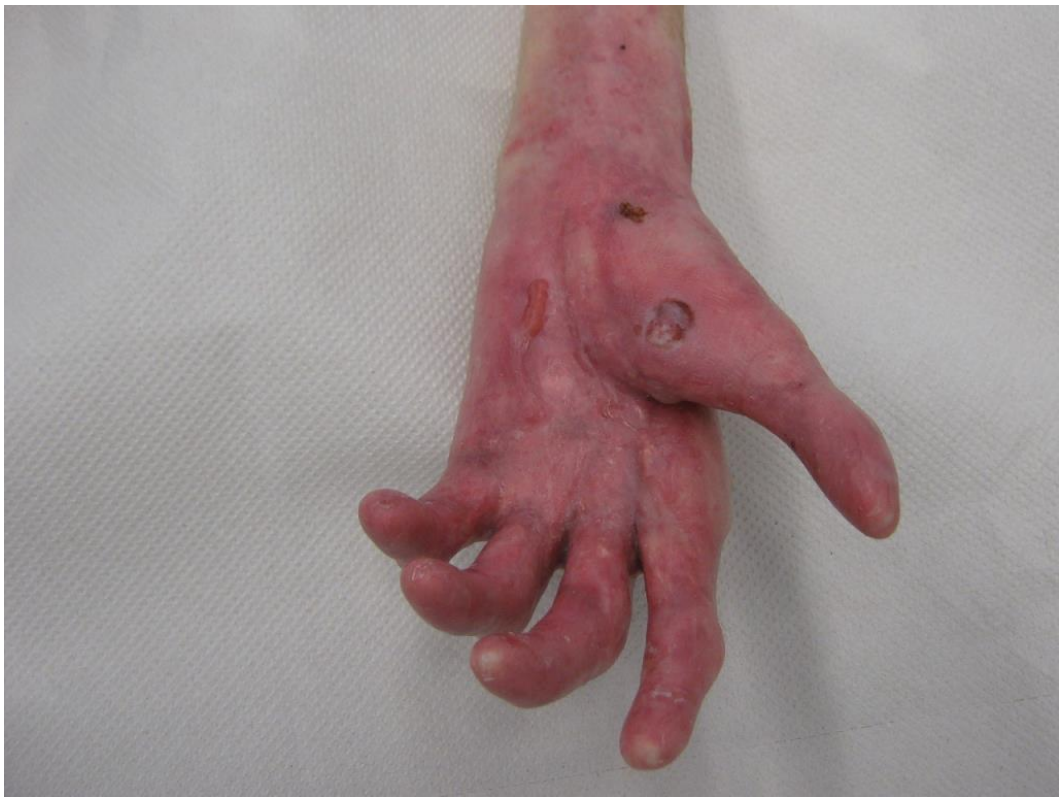
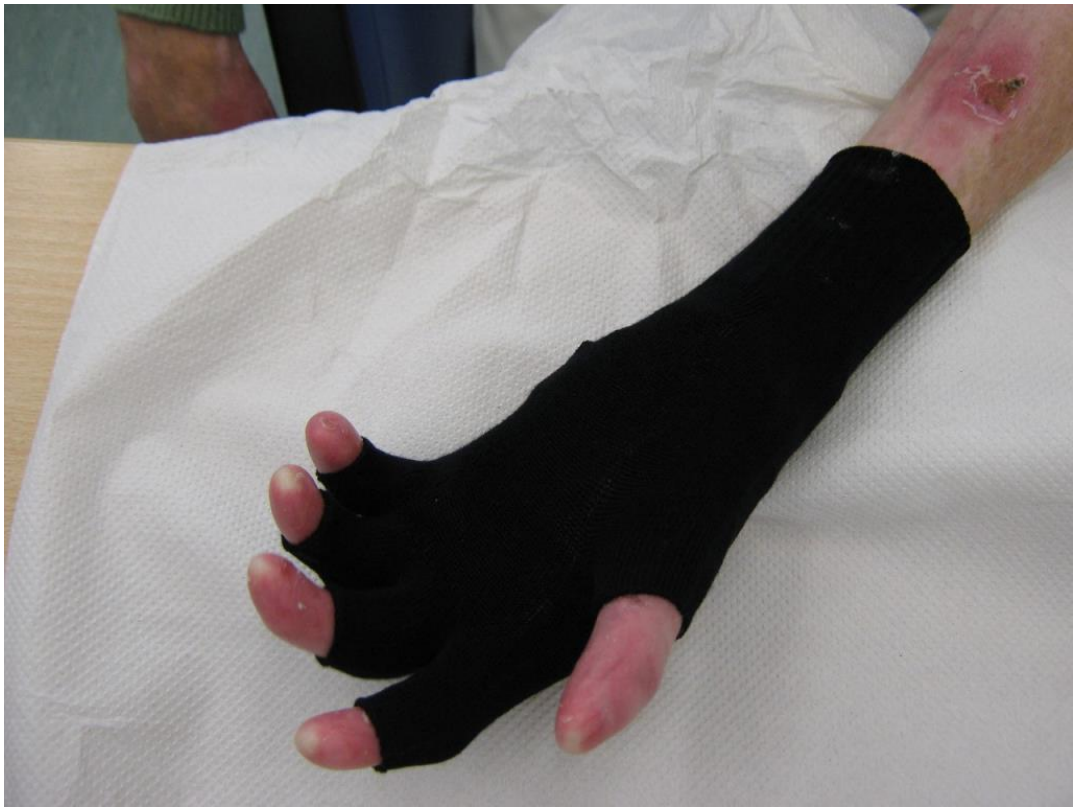


Figure 4: Same adult male as in Figure 3 above in a dressing glove



Methodology and Methods

Research design: Co-design and N-of-1 methodology

Evaluating medical devices with a rare disease group necessitates an alternative to traditional group-level statistical approaches because of small sample sizes and complex comorbidity. [11 34] Disease rarity and complexity also makes it challenging to conduct psychometric testing for developing outcomes. [35] Our aim was to develop outcome indicators for a sub-type of EB (in which hand deformities develop) so the number of potential participants was even further reduced. We adopted a participatory co-design approach whereby patients, clinicians and carers were defined as users of therapeutic devices. This recognises the role of clinicians (who are viewed by industry as pivotal in advising patients on which products work best), and patients and carers (who are the expert 'end-users' in managing the condition) for providing important knowledge.[36 37] In medical device development, user involvement is central to ensure safety, improved outcomes and satisfaction.[38 39] By adopting a co-design methodology to develop the indicators, we extended the co-design process from the development of the device itself to the device evaluation.[40] Focus groups, interviews, expert review and consensus validation were undertaken to integrate user experiences into the development of the indicators (Phases 1 and 2, Figure 1). These methods model patient-centred care where shared decision-making and treatment goals are negotiated within user partnerships. The indicators were then subsequently used in evaluating the performance of the dressing glove (Phases 3 and 4, Figure 1).

Patient heterogeneity within rare disease groups, such as EB, requires capturing within-individual changes to obtain a meaningful understanding of treatment effects. [11] This was achieved with an N-of-1 design and repeated observations over time enabling statistical analysis of a small sample, typical of rare disease groups.[41 42] N-of-1 studies consider clinically relevant treatment outcomes rated at several points during the control and intervention periods with each participant acting as

their own control. [43] Each developed indicator was independent, and mean scores for each indicator in the pre and with-glove phase were calculated and compared (Phases 3 and 4, Figure 1).

Phase 1: Co-design of the TELER indicators and Hand Therapy Online Tool

TELER (Treatment Evaluation by A. Le Roux's method) comprises a generic online system for making clinical notes and recording patient-centred outcomes of treatment and care.[44] The approach has been applied in hard to heal wound management,[45 46] physiotherapy,[47] health visiting,[48] and medical education.[49] Measurement is based on a numerical six-point ordinal scale of observable patient outcomes called TELER indicators. Code 5 is the treatment goal; code 0 is the clinical deficit; codes 4, 3, 2 and 1 are clinically meaningful steps towards (improvement) or away from (deterioration) the treatment goal over time. The TELER method is based upon these assumptions:

- Effective treatment is patient-centred
- Effective treatment is grounded in theory
- The essential purpose of treatment is to induce or prevent change
- Change (or lack of change) occurs in clinically significant periods of time
- The effects of clinically significant change are not necessarily measurable on an interval or ratio scale, but they are observable

Unquantifiable terms such as 'somewhat, 'moderate' or 'mild' are not used. Instead mutually exclusive outcomes based on clinical, patient and carer knowledge define observable functions and experiences. The definitions of the indicators are presented in lay, accessible language. Following the TELER approach, the indicators were incorporated into a software system, Hand Therapy Online (HTO). The tool comprises a clinical profile, patient and clinician note making capabilities,

photographs and treatments used which additionally enables data collection on use of dressings and emollients for cost calculation.

User needs and experiences: generating content for the indicators

Focus groups and interviews were conducted at two UK EB National Centres with patients and carers, facilitated by researchers and co-facilitated by clinicians. EB patients are experts in their condition and have respectful relationships with their clinicians.[50] Encouraging collaborative discussions was integral to the co-design process ensuring shared understanding of hand therapy experiences and treatment goals.[51] Discussions were framed by a topic guide, developed with patients and clinicians. Each was audio-recorded, transcribed verbatim and supplemented with field notes.

The data were subjected to an inductive thematic analysis [52] framed by an interpretivist approach.[53] We conducted a team analysis, adding rigor by challenging each team member's interpretations of the data.[54] Similar codes were grouped to form themes categorising patient and carer needs and experiences of hand therapy. Each theme was scrutinised to ensure the data were mutually exclusive and consistent within each theme. The themes were then translated into indicator titles, outlining important aspects for assessing hand therapy devices in RDEB. Data collection and analysis continued until no new themes emerged.[53] Data were used to devise six mutually exclusive clinically significant steps and components for codes 0 to 5 for each indicator.

Expert review, piloting and consensus

Draft indicators were reviewed by patients, carers and clinicians in face-to-face meetings and by email.[40] Changes made were supported by a rationale and reflected in the next iteration of indicators shown to patients, carers and clinicians for validation.[35 40] This process was followed for

each revised indicator. An independent review for lay terminology was undertaken by TELER consultants in the UK. The TELER indicators and online HTO tool were piloted by patients, carers and a clinician. Participants were asked to self-report their scores online twice a week from home for six weeks. Parents completed the indicators on behalf of their children. Participants provided iterative feedback on the process of self-reporting scores, the content and wording of the indicators via telephone, emails and home visits.

In EB, treatment outcomes are dependent on close collaboration between patients and clinicians. Shared decision-making is achieved through information exchange leading to a better understanding of the factors involved.[55 56] Acknowledging these interactions, validity and reliability was established through consensus between the patients and clinicians as defined in Figure 5. Patients engaged in face-to-face discussions with clinicians to agree which codes accurately reflected their hand condition, function and experiences. Where there was disagreement, patients and clinicians provided a rationale for their coding and negotiated a mutual agreement.

Figure 5: Validity and reliability through expert review and shared agreement

- Content validity is based on generating definitions for each code (0–5), drawing on clinical and patient knowledge, which are acceptable and relevant to patients and clinicians in terms of tracing clinically significant change over time. Content validity is predicated on the shared ownership of the language of the indicators.

- Construct validity: the steps between the definitions of the codes indicate mutually exclusive changes which represent clinically significant problems determined by (i) current evidence and practice in hand therapy e.g. clinical guidelines and (ii) knowledge and experiences of patients, carers and clinicians. The steps between each code are also clinically meaningful in their relationship to other indicators meeting the requirements of measurement theory.

- Reliability: the indicators are reliable if they are coded in the same way by the assessors; patients, parents, carers, clinicians. Reliability is also predicated on the meaning of that code being the same for all participants. It is not appropriate to blind clinician from patients scores to test for reliability rather a process of consensus is facilitated through shared decision-making within the ongoing therapeutic relationship. Both the patient and clinician train each other in their understanding of each outcome code leading to agreement. Reliability is a continual process. It is facilitated over time as patients and clinicians re-train each-other during face to face clinic visits to reach a shared understanding of the meaning of each code.

- Concurrent validity, the degree to which the scores on a measure are related to the scores on an established measure or other valid criterion administered at the same time, was not addressed. As mentioned in the Introduction, we established a lack of existing patient-recorded outcomes that are sensitive enough to capture clinically significant changes in hand condition and function for RDEB patients.

Phase 2: Results-TELER Indicators

User needs and experiences: generating content for the indicators

Two focus groups were conducted with children and their parents; individual interviews were held with seven adults (Table 1). Five user experience themes were generated: Skin trauma associated with wearing and changing dressings, Skin breakdown associated with EB; Dressing limitations and failure; Importance of hand function and Hand pain. Eleven indicators and their corresponding codes were initially generated from the thematic analysis (see example in Table 2).

Table 1: Patient characteristics, recruitment and qualitative data collection method

Data collection method/Sample characteristics	**Focus group 1**	**Focus group 2**	**Individual interviews**
Number of individuals with RDEB	2	4	7
Number of Parents/carers	5	6	3 (three of the interviewees were accompanied by a parent or carer)
Total number of participants	7	10	10
Age range of individuals with RDEB	4-7 years	under 4 years	25-75 years
Gender of individuals with RDEB	1 male and 1 female	3 male and 1 female	3 males and 4 females
RDEB – recessive dystrophic Epidermolysis bullosa			

Table 2: Example of qualitative data analysis and application of patient and clinician knowledge to co-design the TELER indicators

Quote	**Codes**	**Theme (concept elicitation)**	**Patient experiences, Clinical knowledge and Evidence to devise clinically significant steps from 5 to 0 (Construct validity)**	**Final Outcome with codes**
Adult patient: *'Erm, I was hoping perhaps towards the end of next year to have my right hand redone again (surgery)…because it definitely was much, much better… I'm very disappointed that it has gone back really…yes it has been gradual, over a year, yeah, possibly more than that. And I don't know whether it's stopped regressing. My only measure is that I can't pick up a pint of beer.'*	Losing ability to squeeze Losing ability to pick up things Loss of thumb function Hands Change Shape	Importance of Hand function	Adult patient: '*Yes. See, I can't, now this is what makes me think I've regressed because I use to be able to pick up a pint of beer with my right hand and now I can't…I can force it in.'* Clinical evidence: Progressive finger flexion and thumb adduction makes gripping and grasping objects difficult. [30 57-59] Senior Clinicians' observation of hand function: '*Grasp involves opening and closing of the hand. Hold involves a static position, so I think 0-4 should be 'hold'. Then the difference is if you use one hand, one hand and support, 2 hands or a combination of hands/arms / body'*	Domestic activity: ability to hold can of drink (330ml for adult, 150 ml for child) 0 Unable to hold a can of drink or balance it on two hands 1 Unable to hold a can of drink but able to balance it on two hands 2 Able to hold a can of drink if someone places the can between both hands 3 Able to hold a can of drink using both hands without help 4 Able to hold a can of drink by pushing it into this hand using the other hand 5 Able hold a can of drink independently with one hand

Expert review, piloting and consensus

A total of 19 participants (six patients, five carers and eight clinicians) took part in the expert review, piloting and consensus validation process (Table 3). The expert review process comprised two meetings with each patient, carer and clinician, and two email exchanges with three patients, carers and clinicians. From the initial 11 indicators, two were deleted, one was amended and five were added, resulting in 14 indicators. For example, carers and patients noted hand appearance was an important indicator of disease progression. This resulted in amending the indicator entitled 'skin condition: wounds' into two new indicators 'appearance of the skin' and 'appearance of wounds'. Consensus validation took approximately 18 months. When coding the indicators together, patients, carers and clinicians agreed upon most outcomes. Where there was disagreement, a discussion took place to reach consensus (Box 1). During the pilot phase, technical issues with the online software were addressed by TELER Limited, namely participants being timed out, how best to collect treatment data and the software design. Patients and clinicians agreed on the indicator content and were able to complete the indicators online, easily indicating acceptability and feasibility. The 14 agreed indicators covered hand skin condition (n=4), extent of webbing between the digits (n=4), experiences of wearing and changing dressings (n=2), hand function (n=2), wrist function (n=1) and hand pain (n=1).

Box 1: Consensus validation example: scoring finger webbing indicator

Patient felt the scar tissue was higher than the hand therapist suggested. The hand therapist referred to the indicator and then to the patient's hand showing where she thought the scar tissue was situated in relation to the finger joint. The patient showed the hand therapist where he could feel his joint was. Clinical and patient knowledge that the scar tissue will creep upwards towards to next joint led both to agree that they should mark the level of scar tissue at the higher code.

Table 3: Development of the indicators by role and activity

Role	Development and validation activity undertaken				
	Qualitative interview participant/co-facilitator	Qualitative focus group participant/co-facilitator	Expert review	Piloting	Consensus validation
RDEB patient (adult)	*		*	*	*
RDEB patient (adult)	*		*	*	*
RDEB patient (adult)	*		*	*	*
RDEB patient (adult)	*				*
RDEB patient (adult)	*				*
RDEB patient (adult)	*				*
RDEB parent carer (of child with RDEB)		*	*	*	*
RDEB parent carer (of child with RDEB)		*	*	*	*
RDEB parent carer (of child with RDEB)		*	*		*
RDEB parent carer (of child with RDEB)					*
RDEB parent carer (of child with RDEB)					*
Specialist Clinical Occupational Therapist for EB (adults)	*		*	*	*
Consultant Plastic Surgeon (adults)			*		
Consultant Dermatologist (adults)			*		
Consultant in Paediatric Dermatology (paediatrics)			*		
Occupational Therapist with special interest in EB (paediatrics)		*	*		*
Occupational Therapist with a special interest in EB (paediatrics)			*		
Clinical Nurse Specialist in EB (paediatrics)		*	*		
Consultant and Plastic Hand Surgeon (paediatrics)			*		

Phase 3: N-of-1 proof-of-concept study

Study design, participants and intervention

In an earlier phase of the study, patients and carers co-designed a Class 1 medical device comprising a simple, non-sterile, disposable dressing glove.[14] Dressing glove performance, compared to conventional dressings, was observed and evaluated using the 14 indicators developed with patients in Phases 1 and 2. As some of the participants had co-designed the dressing gloves, randomisation was not appropriate. They acted as their own controls, providing self-reported indicators for conventional dressings (pre-glove) and with the dressing glove (with-glove).[11 43] Participants were diagnosed with RDEB, or with EB that presented as RDEB, and wore dressings on their hands or were advised to. Participants were invited to replace conventional dressings with the disposable dressing glove. Hand measurements were taken by therapists for adults and from hand photographs sent by parents of children in the study, so that bespoke dressing gloves could be manufactured. A perfect fit is required as tightness or looseness can rub the skin and cause blisters. A small sample (six adults; six children) was planned to accommodate reiterative glove fitting. The aim was to establish proof-of concept of the devices in the first instance and follow this with post study surveillance using the same indicators, to evaluate device performance in routine care.

Data collection procedures

Researchers trained participants and (for child participants) their parents to score the 14 outcome indicators. During the training session, understanding was confirmed on each score through discussion between the participants and the researchers. Participants were asked to record their scores using the online reporting platform (HTO tool) twice a week for (a) the period before wearing the dressing gloves; (b) the familiarisation phase when glove fit was adjusted and (c) after glove fit was achieved. The periods before and after introducing the dressing glove were planned to be 6 weeks. Participants were also asked to record the time-taken for hand dressing changes and

quantities of conventional dressings and emollients used so that costs could be calculated and compared (pre glove vs with glove).[60] They were also invited to write contemporaneous notes on the HTO tool. Researchers sent a monthly reminder email. Data collection took place between May 2017 and January 2018.

Methods of data analysis

Visual inspection of plotted scores across the repeated observations were used to evaluate changes in outcomes. This evaluation method is acceptable for n-of-1 studies, however, is open to bias.[61] Self-reported data were validated through telephone interviews with participants on how and why the dressing glove performed for them. The number of self-reported outcomes varied between weeks, so a weekly mean score value was calculated to ensure frequent recordings over short periods were not overly influential. In weeks where there were no observations, the previous mean was carried forward. An unpaired t-test was used for each indicator, hand and participant to compare the mean of the weekly score values for the pre-glove period with the with-glove period. Several iterations were required to achieve a perfect fit for most participants, so outcomes recorded whilst familiarisation was ongoing were not included in the analysis. Primary outcome indicators were experiences of wearing and changing dressings, and hand skin condition. Secondary outcome indicators were extent of webbing between the digits, wrist function, hand pain and hand function.

Cost analysis

Costs for consumables were applied based on the amounts reported, and prices (pounds sterling 2016), mostly obtained from NHS Drug Tariffs. The cost of the dressing glove was based on likely steady state production costs provided by the manufacturer (taking account of technician time, number of iterations to get a perfect fit, number of gloves likely in a production run). Some patients used a web spacer glove in combination with dressings and the cost of this was included in the analysis, based on manufacturer information and an assumed life of 30 washes. The therapist time

(to measure and fit) at each iteration was calculated and costed using nationally validated unit costs in British pounds (at 2016 values).[62] Family members' time helping at dressing changes was not costed. Since duration of the pre and with- dressing glove periods varied between participants, costs were standardised and presented as weekly, based on self-reported frequencies of dressing changes.

Phase 4: Proof-of-concept study results: preliminary evidence of clinical effectiveness

A total of 12 participants, most of whom had also taken part in Phase 1, were recruited, trained on HTO and completed baseline assessments. Of these, nine were measured for a dressing glove and four completed the study (Table 4). Most participants who tested the gloves but did not complete the study had extensive webbing between their fingers indicating advanced disease progression. For these participants, glove fitting was not achieved. For participants who completed the study, achieving dressing fit took between zero and six iterations over 0–6 weeks. Most of these participants reported an improvement in their experience of wearing and changing dressings (n=3) and improved appearance of their skin (n=3). Few changes occurred in web spaces and wrist function (n=4) (Table 4). All participants who completed the study wanted to remain in the dressing gloves. Participants reported a thicker viscose material could improve absorption and provide more protection

Results of the cost analysis

The use of consumables and associated costs in the pre-glove and with-glove periods per participant who completed the study are summarised in Table 5. The developmental cost to achieve glove fit during the familiarisation phase varied between participants. Excluding this, the dressing glove was cost neutral for Participant 1. For the other participants, costs increased with use of the glove, compared with conventional dressings. For Participants 2 and 3, this was because use of the glove facilitated more frequent dressing changes. For Participant 4, the dressing glove, at £5.00 per pair,

was more expensive than the conventional dressings in the pre-glove period. The cost of the dressing glove was estimated to be £5.00, at the lower end of the estimate range based on likely steady state production costs provided by the manufacturer (taking account of technician time, number of iterations to get a perfect fit, number of gloves likely in a production run). Some patients used a web spacer glove in combination with dressings and the cost of this was included in the analysis, based on manufacturer information and an assumed life of 30 washes. The cost of a pair of web spacer gloves was assumed to be £9.00, also at the lower end of the manufacture estimate range. After wearing the dressing glove for three weeks, this participant then used only the web spacer glove at a similar cost to the initial phase.

Table 4: Mean scores on 14 outcome indicators for participants who completed the study (pre and with glove)

Mean scores, range 0 (worst) to 5 (best)		Participant 1 Pre glove: 37 days, 4 observations Fitting, familiarisation: 6 weeks Post glove: 40 days, 8 observations				Participant 2 Pre glove: 53 days, 17 observations Fitting, familiarisation: 6 weeks Post glove: 60 days, 12 observations				Participant 3 Pre glove: 40 days, 9 observations Fitting, familiarisation: 6 weeks Post glove: 150 days, 41 observations				Participant 4 Pre glove: 31 days, 13 observations Fitting, familiarisation: 0 weeks Post glove: 152 days, 7DG, 6WSG obs.			
Outcome Measure	Number and Description	Left		Right		Left		Right		Left		Right		Left, with DG		Right, with DG	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Hand skin condition	1 Location blisters	5.00	4.90	5.00	5.00	4.70	4.71	4.75	4.438	4.33	4.34	4.28	4.00	3.50	4.44	3.28	4.60
	2 Skin appearance	3.75	3.40	3.83	3.40	**2.37**	**3.86**	**2.21**	**3.75**	**0.58**	**1.74**	**0.78**	**1.79**	4.45	4.83	4.46	4.90
	3 Wound	5.00	4.90	5.00	5.00	4.00	3.86	3.79	3.75	**1.13**	**2.69**	**1.06**	**2.83**	4.70	5.00	4.65	5.00
	4 Degloving	5.00	5.00	5.00	5.00	5.00	5.00	4.96	4.94	**3.88**	**4.94**	**4.39**	**4.96**	5.00	5.00	5.00	5.00
Experience	13 Dressing change	**4.00**	**5.00**	4.00	5.00	**4.08**	**4.71**	4.08	4.43	**0.33**	**2.73**	**0.33**	**2.68**	2.45	2.56	2.47	2.73
	14 Hand dressing	**4.25**	**5.00**	**4.33**	**5.00**	4.00	5.00	**4.00**	**4.81**	**0.88**	**2.47**	**0.89**	**2.48**	2.00	2.00	2.10	2.00
Web space	5 2nd finger	4.00	4.00	5.00	5.00	4.06	4.00	4.13	4.00	4.00	4.00	4.00	4.00	5.00	5.00	5.00	5.00
	6 3rd finger	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	3.83	4.00	4.00	4.00	5.00	5.00	5.00	5.00
	7 4th finger	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	4.00	4.00	4.00	4.00	5.00	5.00	5.00	5.00
	8 Thumb	5.00	5.00	5.00	5.00	4.96	5.00	5.00	5.00	4.04	4.00	3.94	3.98	5.00	5.00	5.00	5.00
Pain and Function	9 Wrist	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	3.25	3.06	3.22	3.00	5.00	5.00	5.00	5.00
	10 Hand Pain	N/A	N/A	5.00	5.00	4.91	4.00	3.54	3.06	**2.38**	**3.00**	2.56	2.98	4.21	4.22	3.90	4.00
	11 Hold pen	N/A	N/A	N/A	N/A	3.50	3.00	3.04	3.00	**2.96**	**5.00**	**3.28**	**5.00**	5.00	5.00	5.00	5.00
	12 Hold can of drink	4.00	4.00	4.00	4.00	2.92	3.00	2.73	3.00	**2.38**	**3.86**	**2.28**	**3.00**	5.00	5.00	5.00	5.00
	Values in bold p<0.05 N/A = Missing data																

Table 5: Summary of pre dressing glove and with dressing glove costs and outcomes

DG: Dressing Glove; WSG: Web Spacer Glove

Participant	Participant 1 Child		Participant 2 Child		Participant 3 Adult		Participant 4 Adult	
Study phase	Pre glove	With glove	Pre glove	With glove	Pre glove	With glove	Pre glove	With glove
Participant assistance for dressing changes	Family	Family	Family	Family	Family	Family	Self	Self
Observation period (days)	37	40	53	60	40	150	31	152
Number of dressing changes reported	3	10	16	6	14	51	3	0
Number of dressing changes per week	2	3	7	14	2	3 or 4	3	3(assumed)
Mean minutes to change dressing, each hand	10	2	10	8.2	18.1	11.6	4	Not available
Consumables cost (£,2016 values) per week each hand	18.12	18.00	82.04	235.76	135.32	187.53	7.92	19.44
Comment	More dressing changes per week with glove. But gloves substitute for most expensive dressing item so no significant change in costs of consumables/ week		Cost of consumables tripled because number of dressing changes doubled, and DG was added without reduction in other consumables.		Consumables gradually reduced over post glove period but were still higher than the pre glove period due to the increase in number of dressing changes, and the cost of the gloves. [1 weighted average of costs; 2 changed 2 – 3 times per day		Participant only wore one glove at a time. Costs approximately neutral with WSG; Costs rise with DG	

Discussion

We applied a participatory model to co-design patient-recorded outcome indicators for treatment evaluation of hand therapy devices in EB. The indicators were used to proof-of-concept test an innovative dressing glove providing preliminary clinical evidence of device performance compared to conventional dressings. For participants who completed the study, clinical outcomes and experiences when wearing the dressing glove mostly improved or were maintained. This is an encouraging finding in a condition where deterioration is the norm and dressing changes are painful and time-consuming.

Generating an evidence based for Recessive Dystrophic Epidermolysis Bullosa

Existing Epidermolysis bullosa hand therapy outcomes are either not sufficiently responsive to measuring change in subtypes, such as recessive dystropic Epidermolysis bullosa, or are in clinical terminology, (i.e., not easy to understand lay terminology). In our study, patients explained how they were able to see if their hands were deteriorating or improving.[35] These experiences were translated into observable definitions with clinically meaningful differences towards or away from an achievable goal. The indicators differentiated scores within and between participants in both the piloting phase and proof-of-concept study, demonstrating responsiveness in detecting changes important to patients. [35 63] Patient-recorded outcomes of dressings in managing EB have previously been developed with patients but these are for the whole body.[46] The patient-reported indicators reported in this study are the first to measure the experience and outcomes of wearing hand dressings in EB specifically. These indicators also meet the recommendation for outcomes in wound healing that are meaningful to EB patients, including reduction in pain.[64]

Co-creating indicators with patients and carers enables shared ownership over monitoring their condition. Regular recording of hand condition using the Hand Therapy Online tool enables

responsive treatment and individualised care through shared decision making between clinician, patient and family carer. The HTO tool can be used for research purposes to evaluate specific treatments, and in routine clinical practice. Currently there are no epidemiological data on the frequency of finger webbing or its development. Data quality varies and is limited with preoperative information not always available. The HTO tool and indicators can be used to assess the trajectory of the condition over time supporting surveillance and timing of hand therapy interventions including surgery to determine when interventions are indicated. This method of co-designing patient-recorded outcome indicators is applicable to other chronic conditions where treatment outcomes are dependent on a close therapeutic relationship and patients are hard to reach.

Preliminary evidence of clinical effectiveness

Using indicators developed with patients, carers and clinicians, the proof-of-concept study provides evidence of how and why the dressing gloves performed, compared to using conventional dressings. Of the participants who completed the study, the indicators show improved experiences and appearance of the skin. These participants were able to wear the dressing glove. Most participants who tested the gloves, but did not complete the study, had advanced hand deformities. This made it difficult to manufacture a glove that fitted the hand well. Wound care in EB is complex and changing dressing practice takes, time, patience, and the support of the clinical team.[65] Despite finding conventional dressings and bandages onerous to apply and wear, they are familiar. The children were used to wearing strips of dressing material between their web spaces. The dressing glove was an unknown and for these participants putting the glove on their hands was difficult.

Improvements in hand skin condition with the dressing glove may be attributable to increased dressing change frequency and the use of an innovative, breathable fabric, which wicks heat and moisture associated with skin maceration and blistering in EB.[65 66] Participants reported reduced restriction of movement with the dressing gloves. A reduction in dressing materials also created an

environment for the skin that is less prone to maceration. Improvements in the experience of wearing and changing dressings may also explain the increase in the frequency and reduced time for hand dressing changes. The latter is noted as a desirable patient-focussed outcome in a recent expert review of clinical research on wound healing in EB.[64]

The increased frequency of dressing changes increased costs for two participants. However, the associated improvements in skin condition may result in delayed disease progression and reduced interventions (e.g. surgery) over a longer period. Previous studies have focussed on the cost of wound care for the entire body noting high costs in a small population.[67] This is the first study investigating the costs of EB hand wound care. These results provide early proof-of-concept for the disposable dressing glove for RDEB patients who could wear gloves. The participating NHS Trusts are maintaining bespoke supplies of the dressing glove. Further refinements addressing absorption and protection will be made by the manufacturer. These findings will be followed up in routine clinical care as part of the model of device co-design guiding this work.

Clinical follow-up through routine data capture

Large scale randomised controlled trials of medical devices present challenges due to the iterative nature of the development process and effect of context, even in commonly occurring conditions [68] [69] and are almost impossible with rare diseases.[9] [11] Proof-of-concept studies involving novel medical devices with heterogeneous sampling provide valuable information regarding device and technology refinements in rare disease groups, before products are finalised and commercialised. When coupled with clinical follow-up, using the same patient-reported outcome indicators, they generate robust clinical evidence to support prescribing, purchasing and de-commissioning by health services supply chains.[70] [71] Clinical follow up can also provide further data offsetting small sample sizes typical of rare disease groups.[10] This type of routine data accrual can overcome the limits to gold standard

evidence for medical devices generated through RCTs, which tend to recruit participants with less complex conditions and co-morbidities. This is especially relevant for rare disease groups. [10]

Longer periods of clinical follow up are required to assess the effectiveness of the dressing glove in delaying disease progression over time, including finger webbing, contractures and surgical interventions. To this end, DEBRA UK (the charity supporting the EB community in the UK) has funded an evaluation of the HTO tool, encompassing the outcome indicators developed in this study, in one NHS Trust. This ongoing study is enabling longitudinal data capture and further comparisons of patient outcomes and costs against conventional dressings. The results will provide further evidence to support dressing glove commercialisation. Through the international network of DEBRA charities, EB patients and clinicians from three countries are trialling the dressing glove, and applications to other conditions affecting the hand including burns are being pursued. The adjustable splint glove prototype is being progressed to proof-of-concept studies and commercialisation. [72] This will complete the three compatible hand therapy devices for EB, which will continue to be evaluated using the patient-reported outcome indicators developed in this study.

Limitations

During the study, the well-known pattern of fluctuating comorbidities associated with recessive dystrophic Epidermolysis bullosa was observed for our participants, including repeat hand surgery. Living with this chronic and complex condition adversely affected self-reported data collection and eight participants were lost to follow-up. Conducting research with a rare disease group means that sample sizes are small and retention is challenging.[41] Collecting data intensively with a small number of patients can ensure the impact of participants leaving the study is minimised. as power in an N-of-1 study is derived from repeated observations, not numbers of patients.[11]

Conclusion

Outcome indicators for hand therapy in Epidermolysis bullosa described in this study, were codesigned with patients, carers and clinicians through qualitative interviews, expert review, piloting, and consensus validation. The indicators provided preliminary clinical evidence of mostly improved or maintained hand skin appearance and experience for patients who could wear a novel dressing glove. Routine monitoring of hand therapy is ongoing using the same outcome indicators, remotely in patients' homes and in clinic thereby accruing an evidence base for treatment evaluation and supporting device regulation.

Reflective questions

- What clinical and patient-recorded indicators are used to evaluate treatments in your practice?

- Do digital data capture systems, with clinicians and patients recording data to the electronic patient record, facilitate therapeutic relationships for long term conditions?

- Can proof-of-concept data and routine clinical follow-up collected with valid clinical and patient-recorded indicators, provide enough evidence to support clinical decision-making, purchasing and regulatory requirements for wound care?

Ethics

The project was granted ethical approval by the London Bridge Research Ethics Committee (codesign of the TELER indicators ref: 14/LO/0802; piloting the indicators ref: 16/LO/1046; proof of concept study ref: 17/LO/0420). All participants over the age of six years provided informed consent. Children aged 4–6 years provided informed assent and their parents provided consent. For piloting the indicators, parents provided consent on behalf of themselves and their children (aged 6–16 years) as they were being asked to complete the indicator scores online together.

Supplementary data

Supplementary data on patient outcomes and costs are available upon request from the authors. The Hand Therapy Online tool is a bespoke software package for hand therapy in Epidermolysis Bullosa, full details of indicators are available from Health Outcomes Solution Technology www.TELER.com

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