The identification of biophysical parameters which reflect skin status following mechanical and chemical insults

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Abstract

Background: Skin is constantly exposed to mechanical and chemical insults, in the form of prolonged loading, overhydration or exposure to irritants. An array of non-invasive biophysical tools has been adopted to monitor the changes in skin response. The present study aims to identify a set of robust parameters sensitive to mechanical and chemical challenges to skin integrity.

Materials and methods: Eleven healthy participants were recruited to evaluate the skin response following mechanical loading, tape stripping, overhydration and chemical irritation. Forearm skin responses were recorded at baseline and at three time points following the insult. Measurements included transepidermal water loss, sub-epidermal moisture, erythema and laser Doppler imaging. Thresholds were informed by basal values, and the sensitivity of parameters to detect skin changes was evaluated.

Results: High degree of variability in skin response was observed with selected biophysical parameters, such as sub-epidermal moisture, laser Doppler imaging and erythema, even in the absence of an applied insult. Temporal skin response revealed distinct response profiles during each evoked insult. Indeed, the sensitivity of the biophysical parameters was influenced by the threshold values and time point of measurement. Some statistically significant correlations were determined between the biophysical parameters.

Conclusion: The study revealed that thresholds derived from single biophysical parameters were limited in detecting skin changes following insults. A complementary evaluation using combined parameters has the potential to provide a more sensitive assessment. Further research is required to identify robust biophysical parameters, to aid the early detection of skin damage in clinical settings.

Keywords
biophysical parameters, chemical irritation, mechanical loading, overhydration, pressure ulcers, sensitivity analysis, skin response
1 | INTRODUCTION

Human skin acts as the first line of defence against a number of external insults ranging from mechanical, chemical, biological and thermal challenges. Prolonged exposure of skin to various types of insults, particularly in a clinical setting, such as pressure, friction, shear and moisture, could lead to the formation of wounds. Indeed, individuals with impaired mobility and incontinence are more likely to develop chronic wounds such as pressure ulcers (PUs) and incontinence-associated dermatitis (IAD). These wounds represent a major financial burden to healthcare providers, in addition to their detrimental effects on an individual’s quality of life. Indeed the annual cost of managing chronic wounds after adjusting for co-morbidities has been reported to be between £4.5 billion and £5.1 billion in the UK (Guest et al., 2015).

In order to mitigate the formation of chronic wounds, individuals are regularly examined and evaluated, and the necessary preventive measures are implemented in a range of acute and community care settings. Risk assessment scales (RAS) have been introduced into clinical practice to identify patients at risk of PUs. These RAS, including the Braden, Waterlow and Norton scales, are based on clinical factors known to be important in the development of PUs, such as redness and erythema, blanchability, mobility, nutritional status and the medical history of the individual (Papanikolaou et al., 2007). These subjective risk assessment methods often either under- or overestimate the risk of the individual developing a PU. For example, the sensitivity and specificity values of Norton Scale have been reported to be 0.76 and 0.75, respectively (Balzer et al., 2007). The relatively low sensitivity indicates that approximately 24% of patients at high risk might not receive adequate preventive measures (Balzer et al., 2007). The introduction of false positives will inevitably allocate resources to individuals with low risks of developing PUs (Defloor & Grypdonck, 2004; Schoonhoven et al., 2002). Therefore, there is a compelling need for a robust and objective diagnostic test that could reliably determine skin status and inform clinical decision-making.

A number of bioengineering tools have been developed to monitor skin response when it is subjected to pressure, shear and moisture. These include non-invasive methods to monitor the barrier function, pH, elasticity, blood flow, structural changes and colour of the skin (Worsley & Voegeli, 2013). For example, an increase in transepidermal water loss (TEWL), indicative of altered skin barrier function, has been observed in a number of skin conditions, such as atopic dermatitis and in experimental perturbation studies, wherein skin is subjected to repetitive mechanical loading or application of solvents (Bostan et al., 2019; de Jongh et al., 2006). Another biophysical measure that has gained recent attention is sub-epidermal moisture (SEM) that estimates electrical capacitance as a means to evaluate local oedema in the epidermal/sub-epidermal tissues (Gefen & Ross, 2020; Mayrovitz et al., 2009). Imaging techniques such as laser Doppler imaging (LDI) have also been employed in real time in vivo assessment of blood flow in dermal tissues (Leutenegger et al., 2011). Elevation in skin blood flow response identified using LDI was reported when skin was subjected to chemically induced irritation (Petersen, 2013). In a number of studies, erythema has been used as an independent prognostic factor of PU incidence (Shi et al., 2020; Vanderwee et al., 2007). In an alternative approach, inflammatory markers and metabolites such as IL-1alpha and lactate, respectively, have been used to detect early signs of skin damage (Kimura et al., 2019; Soetens et al., 2019b).

However, as highlighted in a recent review by the authors, there are limited data on well-established bioengineering tools to distinguish mechanical, chemical and environmental challenges (Bader & Worsley, 2018). Therefore, there is a pressing need to identify a set of robust parameters that clearly differentiates the variable nature of insults, which commonly occur in clinical settings. Accordingly, a study was designed to examine the tissue response using an array of biophysical techniques, following exposure to a range of insults mimicking clinical situations in a cohort of able-bodied volunteers.

2 | MATERIALS AND METHODS

2.1 | Participants

Eleven healthy participants (6 males and 5 females) were recruited from the local community. The participants were aged between 23 and 64 years (mean age 37 years) with a mean height and weight of 1.7 ± 0.1 m and 76 ± 14 kg, respectively, and a corresponding mean BMI of 25 ± 5 kg/m². The demographics of the participants are summarized in Table 1. Exclusion criteria included a history of skin-related conditions or neurological or vascular pathologies that could affect tissue health. Institutional ethics was granted for the study (ERGO-FOHS-26040), and informed consent was obtained from each participant prior to testing.

2.2 | Test equipment

An array of measurement techniques, including biophysical and imaging techniques, was employed to assess the skin response to...
a selection of insults. Skin barrier function was measured using an open-chamber TEWL probe (TEWL, MP9A, Courage & Khazaka, Germany). Skin blood flow was measured using Scanning Laser Doppler Imaging (SLDl, Moor Instruments Ltd, Axminster, UK), with a helium–neon red gas laser (wavelength, 635 nm). Sub-epidermal moisture was measured using a hand-held, portable, diagnostic device (SEMScanner, Bruin Biometrics LLC, USA), and erythema was evaluated using a mobile imaging application (ScarletRed Holding, GmbH, Austria).

### 2.3 Skin output parameters

TEWL was measured according to international guidelines (Pinnagoda et al., 1990) by placing the probe in gentle contact with skin for a period of one minute, sampling data at 1 Hz. A mean value of TEWL was estimated over a 5 second window during a period of equilibrium and recorded in defined units (g m\(^{-2}\) h\(^{-1}\)). SEM measurements were recorded at five points on and around each test site using a standard protocol (Gefen & Ross, 2020). This included one location directly over the test site and four other sites ∼10 mm from the test site at 90° intervals aligned with the body axis (cranial, right, caudal and left). Pressure was applied at an optimal level indicated by the SEM device, prior to taking a reading. This device converts the bio-capacitance of soft tissues into arbitrary units (AUs) to establish a delta between adjacent skin sites. In particular, an estimated SEM delta was calculated by subtracting the average of four circumferential measurements from the value at the test site. A SEM delta value of 0.6 has been recommended by the manufacturer as a threshold indicative of tissue damage (Gefen & Ross, 2020). LDI was implemented over the local test sites, corresponding to 100 x 150 mm (252 x 368 pixels) scans, sampled at 4 ms/pixel. Both greyscale and flux images were stored to identify the test sites, and the LDI data were analysed offline using the manufacturer’s software package. Key parameters from the images included mean and standard deviation of the flux values recorded in arbitrary units (AUs). Erythema parameters were obtained using the ScarletRed digital skin imaging mobile application by imaging a region of interest (ROI) over the test site along with a coloured reference patch provided by the manufacturer (Partl et al., 2017). The images were calibrated for illumination and colour using the reference patch. The image characteristics from the ROI were estimated, including the mean and standard deviation of erythema values derived in arbitrary units.

### 2.4 Test protocol

All the measurements were carried out in the Biomechanics Testing Laboratory in the Clinical Academic Facility in Southampton General Hospital, with the environment controlled at a temperature of 23 ± 2°C and a relative humidity of 42 ± 6%. Participants were requested to wear comfortable loose-fitting clothing and attend data collection sessions on two consecutive days. Each of the measurements was taken with the participant in a sitting position, with their arms resting at chest height on a table surface. Forearm was chosen as site of investigation owing to its ease of accessibility. The volar aspect of each forearm was marked with three assessment zones of 20 mm diameter separated by at least 20 mm. Four separate insults were imposed on the test sites to simulate real-life conditions, while two sites were used as negative controls (Figure 1). Tape stripping (n = 40), which represents a minimally invasive method that removes the skin layers, was used as a positive control as in previous studies (Bostan et al., 2019; Koppes et al., 2016; Koudounas, 2019). Chemically induced irritation was simulated by applying a surfactant, sodium lauryl sulphate (SLS) at 0.5% concentration, to the skin surface. SLS has been used to simulate chemical irritation of the skin, for example, in the case of contact dermatitis (Koudounas, 2019; di Nardo et al., 1996; Schnetz et al., 2000; Tupker et al., 1997). Mechanical loading and moisture in the form of a water-saturated pad, simulating sitting/lying and overhydration conditions, respectively, represented the other two insults. In the first session, the six sites were measured at baseline (24 h) using the four separate measurement techniques. Following the baseline recordings, insults were applied to two skin sites, namely:

- **Site 1 – Saturated water pad (ø 20 mm) worn for 24 h**
- **Site 4 – Saturated pad (ø 20 mm) containing sodium lauryl sulphate (SLS) solution, worn for 24 h**

In the second session, insults were applied to the two other sites, namely:

- **Site 3 – Mechanical loading equivalent to a pressure of 11.0 kPa (80 mmHg) was applied using a circular indenter of diameter 42.4 mm with an integrated load cell which constantly monitored the loading over a period of 30 min**
- **Site 6 – Tape stripping 40 times using medical tape**

Immediately following the removal of each skin insult, a second reading was taken for each of the measurement tools (0 h), and subsequent measurements repeated at 1 hour (1 h) and 3 hours (3 h) to monitor recovery characteristics. A schematic of the test protocol is illustrated in Figure 1.

### 2.5 Data analysis

Data were assessed for normality using probability plots and the Shapiro–Wilk test. Individual responses were presented to assess response patterns to different insults. To assess sensitivity, appropriate thresholds (mean ± 2 SD) were selected for each of the parameters based on the response at control sites. The choice of threshold encompassing the mean ± 2 SD is commonly employed threshold in medical diagnostics to distinguish between findings from healthy and non-healthy cohorts (Indrayan, 2017). To examine the bivariate associations between the skin output parameters, Pearson’s correlation analysis was performed. MATLAB (MathWorks, USA) was used to create bubble plots of the data.
For the purpose of three-parameter representation, skin outputs were normalized to their baseline values to account for inter-individual variations, with the exception of the SEM ‘delta’ parameter, which by its use of a delta accounts for inter-individual variations.

3 | RESULTS

The individual skin responses at each of the six test sites are presented for the four separate biophysical parameters in Figure 2. Changes for each parameter are most conveniently described separately.

3.1 | TEWL

The TEWL values at both control sites revealed minimal variability throughout the test period (Figure 2a), with a mean of $4.12 \pm 1.80$ g m$^{-2}$ h$^{-1}$. On application of the saturated water pad, an increase was observed in all participants immediately after the insult (0 h) with values ranging between 10.80 and 35.60 g m$^{-2}$ h$^{-1}$, followed by a restoration to basal values at 1-hour post-insult. With respect to mechanical loading, a minimal change was recorded post-loading, with one exception (#1) who exhibited a transient increase, which was restored to baseline at 1-hour post-insult. Both tape stripping and chemical irritation resulted in elevated TEWL responses, which were sustained throughout the test period. However, close examination revealed distinct differences in individual responses to these two insults. For example, on exposure to chemical irritation, one sub-group exhibited a very high increase in TEWL values (# 1,5,8,9,11), while another exhibited a moderate response (# 2,3,4,6,7,10).

3.2 | SEM

For the majority of participants (n = 10/11), the control sites revealed SEM delta values from −0.25 to 0.25, with the exception of one participant (# 5), who had a higher delta response throughout the test period (Figure 2b). Immediately after exposure to moisture (0 h), there was a high degree of variability in the delta values ranging from −0.5 to 0.5. Following the mechanical insult, SEM delta values exceeded the recommended threshold of 0.6 in a small number of participants (n = 4/11), which was not sustained over the test period. The responses to chemical irritation and tape stripping were also highly variable, with a small proportion of individuals exceeding the 0.6 delta threshold immediately after the insults (0 h). Across each test site, no consistent temporal trend was observed.

3.3 | LDI

Skin blood flow response assessed with LDI revealed a mean intensity value of $102 \pm 37$ AUs at the control sites (Figure 2c). In a similar manner to the other measures, there were clusters of individuals demonstrating distinct responses. For example, following exposure to the saturated water pad, a subset of participants (# 5,8,10) exhibited an elevated response that was maintained
throughout the 3-hour test period. Two participants (# 4,6) displayed an elevated response that was restored to basal values with time. However, the majority of participants (# 1,2,3,7,9,11) displayed no change from basal values. Mechanical loading also resulted in minimal changes in LDI values. By contrast, elevated responses were observed in distinct groups following both chemical irritation and tape stripping. The corresponding individual responses were maintained throughout the test period.

**FIGURE 2** (a) TEWL, (b) SEM, (c) LDI and (d) erythema response to different skin insults. The black arrows indicate when the insults were applied. The red dotted lines in b indicate threshold value recommended by the manufacturer.

**TABLE 2** Descriptive summary of skin output parameters for a range of insults

| Parameter (Units) | Range | Insult | Threshold | Immediate response after insult (0 h) | 1-hour post-insult (1 h) | 3 hours post-insult (3 h) |
|-------------------|-------|--------|-----------|-------------------------------------|------------------------|--------------------------|
|                   |       |        |           | No. of participants exceeding the threshold | No. of participants exceeding the threshold | No. of participants exceeding the threshold |
| TEWL (g m⁻² h⁻¹) | 0.8–8.9 | 1.6–79.7 | ≥8 | 10 | 2 | 1 | 11 | 11 | 10 | 1 | 10 | 8 |
| SEM - delta (AU) | -0.28 to 0.55 | -0.5 to 1.0 | ≥0.6 | 4 | 4 | 2 | 0 | 2 | 1 | 1 | 0 | 2 | 0 | 1 | 0 |
| LDI flux (AU)    | 52–216 | 48–453 | ≥177 | 4 | 1 | 7 | 5 | 3 | 1 | 5 | 3 | 2 | 1 | 5 | 3 |
| Erythema (AU)    | 0.004–0.054 | 0.001–0.093 | ≥0.06 | 1 | 6 | 4 | 1 | 3 | 1 | 5 | 3 | 2 | 4 | 5 | 2 |

CI, Chemical irritation; ML, Mechanical loading; SW, Saturated water pad; TS, Tape stripping.
3.4 | Erythema

The control sites revealed a mean erythema value of 0.03 ± 0.01 AUs (Figure 2d). The response following insults revealed a high degree of variability and few clear temporal trends. As with the other biophysical measures, some dichotomy of response was observed between those with elevated erythema post-insult and those with minimal change from basal values. For example, following mechanical loading, erythema values were found to be elevated for a sub-group of participants (# 4, 8, 10, 11) immediately after the insult (0 h), whereas the other 7 participants exhibited either no change or a decrease in the value.

3.5 | Identification of biophysical parameters reflecting skin status

Arbitrary thresholds for each parameter associated with TEWL, LDI and erythema were estimated based on a value of 2 standard deviations above the mean value measured at control sites. In the case of SEM ‘delta’ parameter, a threshold of 0.6 was used based on manufacturer recommendations. Table 2 details the number of participants whose response exceeded these thresholds. It is clear that no single parameter was sensitive across each of the insults. Many of the parameters revealed a temporal trend following an insult, with the number of participants exceeding the threshold diminishing with time, indicating skin recovery. The main exception to this trend is revealed in the TEWL response to chemical irritation (CI) and tape stripping (TS), where the majority of participants (8-11/11) exceeded the threshold over the 3 h test period. It is of note that the thresholds for SEM delta, LDI and erythema were exceeded in less than 50% of the cases, in the majority of evaluations.

As indicated in Table 2, the arbitrary thresholds were limited in detecting the changes in the skin following the prescribed insults. A secondary sensitivity analysis was performed to extend the recommended threshold of SEM ‘delta’ parameter, to include a range of values from 0.1 to 0.7. The relative sensitivity of each threshold at the three insults, there was a decrease in the percentage of participants exceeding each threshold from immediately post-insult (0 h) to three hours post-insult (3 h). It was interesting to note that even at the lowest threshold value of 0.1, the number of participants did not exceed 65% in detecting skin changes following tape stripping and chemical irritation. By contrast, the thresholds were more sensitive to mechanical loading, particularly at delta value ≤0.3, a value which represented 50% of that recommended by the manufacturers.

Associations between the different output parameters revealed some statistically significant trends, as summarized in Table 3. In particular, following tape stripping and chemical irritation, the parameters for TEWL and SEM delta were found to be significantly correlated (p < 0.05) at each of the three time points. Skin barrier integrity (TEWL) and skin blood flow response (LDI) were significantly correlated immediately following tape stripping, whereas these parameters were statistically correlated at 1 h and 3 h following chemical irritation. It is of note that no other combination of parameters was found to be statistically significant (p > 0.05).

3.6 | Bubble plot representation of biophysical parameters

Parameters revealing some significant correlation (Table 3), namely TEWL, SEM and LDI, were integrated to form bubble plots, in order to compare characteristics of individuals to a composite biophysical response. This presentation approach was used to examine the influence of intrinsic factors, such as body mass index (BMI) and age. As an example, a bubble plot investigating the influence of BMI following tape stripping at the three time points has been illustrated in Figure 4. The size and the colour intensity of each bubble is proportional to the normalized LDI and SEM responses, respectively, with the y-axis corresponding to the normalized TEWL response. It can be clearly seen that the same
sub-group of individuals (# 1, 4, 5, 6) exhibited an elevated response for all three parameters throughout the test period. Although they all presented with a BMI of less than 25 kg/m², others with similar BMI, that is # 2, 3, 7, 8, did not present with an elevated response. A similar approach with respect to age of individuals revealed no consistent trends (data not shown).

### DISCUSSION

The primary aim of this study was to examine the skin response to a range of insults in a healthy cohort using established biophysical techniques. Four established insult models of skin were used, namely mechanical loading, chemical irritation, overhydration and

| Insult                  | Parameter | Parameter | Immediately after insult (0 h) | 1 h post-insult (1 h) | 3 h post-insult (3 h) |
|-------------------------|-----------|-----------|-------------------------------|----------------------|----------------------|
| Tape stripping          | TEWL      | SEM       | 0.72*                         | 0.65*                | 0.70*                |
|                         | TEWL      | LDI       | 0.64*                         | ns                   | ns                   |
| Chemical irritation     | TEWL      | SEM       | 0.62*                         | 0.87***              | 0.78**               |
|                         | TEWL      | LDI       | ns                            | 0.62*                | 0.78**               |
| Saturated water pad     | TEWL      | LDI       | ns                            | ns                   | 0.61*                |

ns, not significant, *p < 0.05, **p < 0.01, ***p < 0.001.
tape stripping, each representing common clinical scenarios. The findings highlighted that there were sub-groups of individuals within the cohort who responded distinctly to specific insults. Accordingly, the overall sensitivity of the thresholds derived from the biophysical techniques was limited in detecting temporal changes evoked by the skin insults (Table 2). The variability of the parametric values associated with erythema and SEM, apparent at both control sites (Figure 2b and d) and following insults, limited the potential to identify changes in skin integrity. Nonetheless, there were some significant correlations between the biophysical parameters derived from TEWL, SEM and LDI, which provide some confidence that individual responses to insults could be robustly identified (Table 3).

Other studies have reported the skin response when exposed to a range of mechanical and chemical insults including moisture and irritants. For example, the skin response to moisture exposure revealed a transient increase in TEWL value, reflecting a compromise to skin integrity (Fader et al., 2011). Continuous monitoring following this increase revealed a slow return to basal values with the associated area under the drying curve, that is TEWL vs time representing an estimate of the total water loss from the skin surface. In the present study, with TEWL measured at discrete time points, a similar transient response was evident when skin was exposed to a pad saturated with water (Figure 2a). Sustained mechanical loading, a widely recognized risk factor for PUs, has been reported to result in both a temporary loss of skin barrier function and erythema (Han et al., 2017). Results from the present study indicated a marked increase in the biophysical parameters following chemical irritation (Section 3.5), which revealed that for a given threshold, there were clear differences in sensitivity with respect to both time and nature of the insult. The present findings reveal that it is important to monitor the temporal changes in SEM delta values to diagnose early signs of skin damage, supporting a recent proposition (Gefen & Ross, 2020).

The study is clearly limited by the small sample size and the use of forearm site, thereby precluding the generalizability of its findings to all tissue sites. Moreover, the study is conducted on a healthy cohort and further testing on vulnerable individuals is critical in order to translate the findings to a clinical setting. Measurements such as erythema are highly influenced by variations in skin tone associated with individuals of different ethnicity. In this study, however, the effect of ethnicity was not investigated due to the preponderance of Caucasian participants (10/11). In this study, skin response was investigated using a number of established measurement techniques, although further work could involve the use of biomarkers which have been shown to reflect the status of skin integrity (Minematsu et al., 2014; Soetens et al., 2019b). In some cases, such as with SLS and tape stripping, recovery was not achieved after 3 h. This time period was considered relevant for participant studies and representative of clinical schedules for skin assessment. However, the examination of temporal response over days and weeks would clearly be of benefit to assess whether skin changes would be reversible in nature, particularly in individuals with co-morbidities.

Sustained mechanical loading, a high number of tape strips (n = 40) when compared to some previous research. It is well-acknowledged that the magnitude of the skin response is dependent on the nature of tape used, peel force and the number of tape strippings (Bashir et al., 2001; Breternitz et al., 2007).

Clear delineation of responses for some parameters was limited because of the basal variability in the data. This was particularly evident for SEM (Figure 2b), LDI (Figure 2c) and erythema (Figure 2d), for both the experimental and control sites. By contrast with respect to TEWL, the skin responses to insults were clearly distinct compared to control values (Figure 2a). Accordingly, the selection of a threshold for these biophysical tools is challenging and requires further research to optimize both the sensitivity and specificity of each parameter. Indeed, recent clinical investigations using the SEM scanner revealed that the current threshold had a low specificity of 33% indicating a high number of false positives (Okonkwo et al., 2020). In addition, the associated positive predictive value (PPV) for SEM was reported to be 14% suggesting further research is required to identify a more robust delta threshold for clinical utility (Okonkwo et al., 2020). This motivated the sensitivity analysis of the SEM delta (Section 3.5), which revealed that for a given threshold, there were clear differences in sensitivity with respect to both time and nature of the insult. The present findings reveal that it is important to monitor the temporal changes in SEM delta values to diagnose early signs of skin damage, supporting a recent proposition (Gefen & Ross, 2020).
the importance of cluster analysis when examining the response of able-bodied cohorts to skin challenges (Bostan et al., 2019; Soetens et al., 2019a). A major element of the clinical challenge to introduce appropriate preventive strategies and to reduce the unacceptably high incidence of PUs and IAD is to identify the individuals at particularly high risk. This might be achieved by screening individual responses to specific insults in a manner adopted in the present study. Additionally, the use of a three-parameter representation, as suggested in this study (Figure 4), could provide a more comprehensive means of identifying individuals at increased risk.

5 | CONCLUSION

In this study, the sensitivity of parameters derived from biophysical techniques to monitor skin response following mechanical and chemical challenges was evaluated. A difference in temporal response of the biophysical parameters was observed depending on the type and degree of the insult. With the exception of TEWL, the other parameters, namely SEM, LDI and erythema, revealed considerable variability limiting clear delineation of responses. Thresholds indicative of skin changes lacked sensitivity in a number of the parameters, with for example, the SEM ‘delta’ being affected by both time and threshold magnitude. It was evident that a single biophysical parameter could not effectively capture the tissue response to a range of insults. An integration of robust biophysical techniques could provide means to achieve complementary evaluation of skin health.

ACKNOWLEDGEMENTS

The work was supported by the EPSRC-NIHR ‘Medical Device and Vulnerable Skin’ Network and NetworkPLUS (Refs. EP/M000303/1 and EP/N02723X/1) and European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 811965 ‘STINTS – Skin Tissue Integrity under Shear’.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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