INTERNATIONAL **CONSENSUS DOCUMENT**

SKIN SUBSTITUTES FOR THE MANAGEMENT OF HARD-TO-HEAL WOUNDS

WOUNDS | INTERNATIONAL

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Foreword

Skin substitutes—which may also be referred to under the umbrella terms 'tissue scaffolds' or 'tissue-engineered products', 'cellular tissue products (CTPs)', and 'cellular, acellular and matrix-like products (CAMPs)'—have seen exponential development in recent years and become a commonplace tool within wound care. As products have been developed and the evidence base has grown, these products offer an increasingly important resource for managing complex wounds.

There is a plethora of products on the market, including those that are animal/human-derived, synthetic, or composite. These products provide useful management tools, particularly in wounds that are unresponsive to traditional wound management modalities (chronic or hard-to-heal wounds).

However, there is still confusion and a lack of awareness and guidance over best practice for product use, and how patient outcomes can be optimised through use of these advanced therapies. A lack of unbiased guidance to clarify different product categories and their use in practice was identified.

As such, a group of international experts met online on 21st June 2024 to discuss this novel product category. Their discussion forms the basis of this consensus document on the use of biological cellular and acellular matrices and tissue replacements.

This international consensus document aims to:

- Provide clarity on biological matrices and dressings, and definitions of products within this category
- Enable clinicians to differentiate between skin substitutes, their ability to expedite wound closure, and the rationale for their use
- Provide guidance for product selection, rationale and when to use in practice
- Provide practical tips on application and use in practice
- Link guidance to evidence in common wound aetiologies (e.g. diabetic foot ulcers, venous leg ulcers).

While the use of different products will be influenced by a number of external factors—including availability, staff knowledge and training, cost, and the local healthcare system/setting—this consensus document aims to increase clinicians' knowledge and awareness, helping to promote confidence in using these advanced therapies wherever available and appropriate, with the ultimate aim of improving patient outcomes.

Gerit Mulder, Chair

Role of extracellular matrix in wound healing

The extracellular matrix (ECM) of the dermis is a three-dimensional scaffold for cell attachment formed of rigid structural fibres and elastic non-fibre-forming molecules (Tracy et al, 2016). The most common structural fibres include collagen, fibrin, fibronectin, vitronectin and elastin (Tracy et al, 2016; Sullivan and Myers, 2022). These fibres impart rigidity to the framework, therefore providing resistance to compressive forces. Non-fibre-forming molecules such as glycoproteins, proteoglycans, and glycosaminoglycans (GAGs) form an elastic, amorphous and osmotically active region, which has roles in hydration, buffering, and force dispersion of the skin (Tracy et al, 2016; Sullivan and Myers, 2022).

Glycoproteins within this region facilitate cell adhesion, while proteoglycans and GAGs bind cytokines and growth factors, acting as reservoirs of these bioactive molecules to regulate cell proliferation and migration.

The mechanical properties of the ECM significantly influence fibroblast behaviour through a process known as mechanotransduction. This process involves ongoing bidirectional cell-ECM interactions (known as dynamic reciprocity; Schultz et al, 2011), where forces generated within the cells are transmitted to the ECM, and physical signals generated by the ECM's mechanical properties are transmitted to the cytoskeleton of the attached cells and converted into biochemical signals. This reciprocal interaction causes the fibroblasts to secrete additional ECM components to repair the damaged tissue and drives normal fibroblast cell behaviour (i.e. cell adhesion, spreading, and proliferation), as well as fibrogenic behaviour such as the differentiation of fibroblasts into myofibroblasts (Tracy et al, 2016; Hui et al, 2021).

ECM in chronic and hard-to-heal wounds

Chronic wounds are characterised by their inability to progress through the wound healing process within a normal time frame, remaining in a state of chronic inflammation (Falanga et al, 2022). Due to this prolonged inflammation phase, there is an excess of matrix metalloproteinases (MMPs), which degrade the native ECM and secreted growth factors, impairing wound healing (Przekora, 2020). A growing understanding of the importance of the ECM in wound healing **[see Box 1]** has led to the development of tissue engineering products many of which contain a 'dermal' component that stimulates, supports and regenerates the function of the native ECM. These products act as a three-dimensional scaffold or a temporary support into which cells can migrate and proliferate in an organised manner, leading to tissue regeneration and, ultimately, wound closure (Wounds International, 2011; Vecin and Kirsner, 2023).

Product classification and terminology

These products are commonly referred to as **skin substitutes**, **cellular and/or tissue-based products (CTPs)** or **cellular, acellular and matrix-like products (CAMPs)**, umbrella terms for the wide range of products that provide temporary or permanent wound coverage and support or promote wound healing through various mechanisms (Vecin and Kirsner, 2023). These products address different deficiencies in the chronic wound bed, including but not limited to granulation in the wound bed, cellular deficiencies and absence of growth factors.

The literature regarding skin substitutes uses a wide variety of terminology and definitions. To avoid confusion, the panel agreed on key terminology, definitions and product classifications used throughout this consensus.

The term **'skin substitutes'** is an umbrella term for the wide range of biological dressings and biological matrices, which facilitate the repair and/or regeneration of the skin through various mechanisms. While this term is widely used, the use of the word 'substitute' can be misleading; it is important to note that these products are not a true replacement of the skin, but rather facilitate tissue regeneration.

Box 1. Functions of the ECM in wound healing

- Structural scaffold for cell attachment
- Regulates cell behaviour by:
  1. Mechanotransduction
  2. Acting as a reservoir of bioactive molecules (cytokines and growth factors).

The term **'biological'** describes products/materials that behave as biological modulators. **A biological modulator** is a material or substance derived from natural and/or synthetic sources that influence biological processes, such as the wound healing cascade (Wounds International, 2011).

Skin substitutes can be divided into two broad categories:

1. Biological dressings
2. Biological matrices.

Depending on the layer(s) of the skin that the skin substitute aims to mimic in order to facilitate the regeneration process, **biological matrices** can be further classified as either (Ferreira, 2011; Vecin and Kirsner, 2023):

- Dermal matrices
- Epidermal-dermal matrices.

Biological dressings are temporary wound coverings that perform some of the functions of the epidermis (i.e. protect from mechanical trauma, infection and fluid loss), thereby maintaining a moist environment to facilitate wound healing (Tran et al, 2023; Vecin and Kirsner, 2023).

The panel suggested the term 'biological dressings' to differentiate these products from other wound dressings, as they act as biomodulators by augmenting the wound environment through the release of active growth factors and other biomolecules that can regulate endogenous cells in a wound environment (Lei et al, 2017).

Dermal and epidermal-dermal matrices may sometimes, but not necessarily always, become integrated within the wound bed and provide permanent wound coverage. These matrices act as a stable, often biodegradable, three-dimensional matrix, stimulating and replacing the function of the damaged ECM to promote the formation of granulation tissue (and eventual re-epithelialisation) by allowing host and/or seeded cells to attach, migrate and proliferate as the wound progresses towards closure. These products also behave as biological modulators by delivering or augmenting the production of cytokines and growth factors to facilitate wound healing (Vecin and Kirsner, 2023). Skin substitutes may also be differentiated based on their cellularity, as either:

- **Cellular** – containing living cells harvested from the host tissue (e.g. autologous) or donor tissue (e.g. allogenic)
- **Acellular** – containing non-living cells.

They can also be differentiated on their source of origin (Wounds International, 2011):

- **Natural tissue** (synthesised by nature):
  - Animal (e.g. bovine, porcine, equine, ovine)
  - Human (e.g. cadaveric skin, placental and umbilical)
  - Plant (e.g. containing oxidised regenerated cellulose/collagen)
- **Synthetic materials** (derived from man-made materials)
- **Composite materials** (containing two or more components, which may be biological and/or synthetic).

Key points

- The extracellular matrix (ECM) of the dermis plays a crucial role in tissue formation, as it has a range of effects on fibroblast behaviour, including cell adhesion, proliferation, migration, differentiation and collagen production
- A growing understanding of the importance of the ECM in wound healing has led to the development of tissue engineering products, many of which contain a 'dermal' component that stimulates and replaces the function of the affected ECM, particularly in hard-to-heal wounds that are 'stuck' in an extended inflammatory phase
- These tissue engineering products are commonly referred to as skin substitutes or cellular and/or tissue-based products (CTPs), which can be further classified as biological dressings or matrices
- The panel have suggested the term 'biological dressings' to differentiate these products from other wound dressings, as they act as biomodulators by augmenting the wound environment through the release of active growth factors and other biomolecules that can regulate endogenous cells in a wound environment.

Current use in practice and rationale for use

Biological matrices, with the exception of tissue engineered products, undergo a Food and Drug Administration [FDA] 510(k) clearance process [see page 8 for the US approval recommendations].

Clinical guidelines deem advanced therapies, such as skin substitutes, to be a suitable adjunct to standard of care (SOC) for hard-to-heal lower extremity wounds and chronic wounds – i.e. wounds that fail to respond to SOC alone and close or reduce in size by approximately 40–50% (depending on wound type) within 4 weeks (International Working Group on the Diabetic Foot [IWGDF], 2023; Vecin and Kirsner, 2023; Tettelbach and Forsyth, 2024).

By this definition, skin substitutes are indicated for the treatment or management of chronic and hard-to-heal wounds, such as:

- Diabetic foot ulcers (DFUs)
- Pressure ulcers (PUs)
- Venous leg ulcers (VLUs)
- Arterial ulcers
- Mixed aetiology ulcers
- Wounds secondary to trauma
- Post-surgical wounds
- Other wound aetiologies.

Natural placental tissue

Natural placental tissue is one of the examples of biological scaffolding (Ingraldi et al, 2023). It is a rich source of ECM proteins (e.g. collagens I, III, IV, VI, proteoglycans, glycoproteins), growth factors, cytokines, and viable endogenous cells, and mesenchymal stem cells that support the wound-healing process. These components influence cell differentiation, hormone/protein production, and basement membrane remodelling, making them beneficial for managing complex, chronic, non-healing wounds.

Dermal matrices

Dermal matrices can be formed of varying layers to act as durable skin substitutes and are designed to provide a stable three-dimensional matrix to promote the formation of granulation tissue. Their duration may be influenced by many factors related to the wound bed, including but not limited to: bacterial load, nonviable tissue, debris, levels of exudate and the presence of inflammatory cells.

Dermal substitutes provide several advantages over epidermal substitutes, such as their ease of use and durability. They may also improve scarring and minimise the risk of contracture (Vecin and Kirsner, 2023).

Dermal matrices can be further divided into the following categories:

- Acellular dermal matrices (ADM)
- Dermal skin substitutes (DSS)
- Small intestinal submucosa (SIS).

ADM can be composed of synthetic polymers, or natural materials such as porcine-derived dermis, fish skin, porcine urinary bladder matrix and de-epithelialised cadaveric skin, as well as naturally derived polymers including collagen, elastin and hyaluronic acid. A benefit of ADMs is their acellular nature, which provides the advantage of being non-immunogenic (Vecin and Kirsner, 2023).

DSS is a cryopreserved human fibroblast-derived dermal skin substitute composed of fibroblasts harvested from donated newborn foreskin tissue and a synthetic bioabsorbable polyglactin scaffold. During the manufacturing process, the human fibroblasts are seeded onto the polyglactin mesh scaffold. These fibroblasts proliferate to fill the interstices of this scaffold and secrete native ECM components such as collagen, ECM proteins, growth factors and cytokines, to form a three-dimensional human dermal substitute containing metabolically active, living cells. DSS promotes wound healing by secreting various growth factors, cytokines, proteins, and collagen (Tran et al, 2023; Vecin and Kirsner, 2023).

SIS matrices are acellular, usually animal-derived extracellular matrix scaffolds or collagen sheets that may contain several factors that support wound healing, such as collagen, elastin, glycosaminoglycans, proteoglycans, growth factors or an antimicrobial coat. Growth factors mitigate destruction by MMPs and induce angiogenesis. SIS products that incorporate an antimicrobial coating (e.g. Polyhexamethylene biguanide hydrochloride) are intended to support wound healing by acting as a barrier to microbial colonisation, while managing bioburden.

One consideration and potential drawback in using porcine SIS substitutes is their cultural acceptability;

recent research suggests that use of animal-derived wound care products is increasingly at odds with some moral, cultural and religious views and may be problematic for some patients, requiring considered communication and informed consent (Brocklehurst, 2022).

Epidermal-dermal matrices

Epidermal-dermal matrices are bi-layered products comprised of a stable three-dimensional dermal matrix layer to promote the formation of granulation tissue and an epidermal layer that stimulates re-epithelialisation. These products can be classified as:

- Dermal regenerative template (DRT)
- Bilayer cellular construct (BLCC).

DRTs are a bilayer regeneration matrix comprised of an acellular dermal layer composed of cross-linked bovine collagen and chondroitin-6-sulfate, a type of glycosaminoglycan, and a semipermeable polysiloxane (silicone) layer that overlays the dermal layer and acts as the epidermis (Vecin and Kirsner, 2023).

BLCC is comprised of a bovine-derived collagen lattice, which acts as a scaffold for allogenic fibroblasts derived from human neonatal foreskin to generate granulation tissue. Allogenic keratinocytes are cultured over the fibroblast layer to form a stratified epidermis. These cellular components of BLCC secrete growth factors such as fibroblast growth factor, vascular endothelial growth factor, platelet-derived growth factor, transforming growth factor, and multiple interleukins, paralleling those secreted by healthy human skin. The product is easy to apply in a clinic after appropriate wound bed preparation (Marston, 2019).

Cellularity is considered an important discriminator between skin substitute products unless the tissue is immunologically privileged, as the presence of allogenic cells increases the rejection risk and manufacturing complexity. A summary of each of the subcategories within biological dressings and biological matrices, along with their cellularity is presented in **Box 2**.

Box 2. Placental-derived allografts in current use

- Epidermal tissue transplants (amniotic/placental-derived)
  - Dehydrated human amniotic membrane (dHAM) – Acellular
  - Cryopreserved placental membrane with viable cells (vCPM) – Cellular
  - Dehydrated human amnion-chorion membrane (dHACM or dACM) – Acellular
  - Hypothermically stored amniotic membrane (HSAM) – Cellular
  - Hypothermically stored chorion membrane (HSCM) - Cellular
- Dermal Matrices
  - Acellular Dermal Matrices (ADM) – Acellular
  - Dermal skin substitutes (DSS) – Cellular
  - Small intestinal submucosa (SIS) – Acellular
- Epidermal-Dermal Matrices
  - Bi-layered cellular construct (BLCC) – Cellular
  - Dermal regeneration template (DRT) – Acellular

Key points

- Skin substitutes are intended for use as a barrier in the treatment or management of chronic and hard-to-heal wounds, as well as acute wounds of various aetiologies, including DFUs, PUs, VLUs and leg ulcers with other underlying causes
- Clinical guidelines deem advanced skin substitutes to be a suitable adjunct to SOC for hard-to-heal lower extremity wounds and chronic wounds – i.e. wounds that fail to respond to SOC alone and fail to close or reduce in size by approximately 40–50% (depending on wound type) within 4 weeks
- A range of products are available for use in practice, as highlighted in **Box 2**.

Current use in practice and rationale for use *(Continued)*

US approval recommendations

Unlike placental tissue and dermal and epidermal matrices, all biological xenograft matrices undergo a rigorous and expensive FDA 510(k) clearance process before the product is introduced into the market.

The FDA's 510(k) submission process is, in short, a quality and compliance barrier designed to only let safe, effective medical devices onto the US market, and into contact with American patients. Listed are some of the key components that are required to obtain a FDA 510(k) clearance that would allow a medical device product to be distributed in the US.

1. Pre-market requirements:

a. Design history file for the proposed device, which would include a detailed risk analysis of the proposed device, the proposed processing method, proposed sterilisation and packaging methods. This will need to be updated on a regular basis (often yearly) post FDA-clearance of the proposed device.
b. Validation of all equipment and consumables that are utilised in the manufacture of the device.
c. Qualification of the proposed manufacturing facility and capital equipment that will be utilised in generating the finished device.
d. Often times, a pre-submission meeting with the FDA detailing the proposed device and its intended use for their opinion on the suitability of the device.

2. FDA-submission requirements:

a. Device classification: Determining the device classification. Most wound care products are classified as Class II devices, which typically require a 510(k) submission. Some products may be categorised as 'Unclassified' by the FDA.
b. Predicate device identification: Identifying a legally marketed predicate device that is similar to the products for which a company is seeking 510(k) clearance. This is crucial for demonstrating substantial equivalence.
c. Technical documentation:
   - Device Description: Provides detailed descriptions of the critical raw materials, as well as information regarding sourcing of the key components of the medical device (e.g. ISO 22442 Compliance)
   - Indications for use: Clearly states what the device is intended to do. Any claims made for the medical device must match those of the predicate device. An example indication is provided below:
     'Product XYZ is indicated for use in the management of the following wounds: partial and full-thickness wounds; pressure ulcers; venous ulcers; diabetic ulcers; chronic vascular ulcers; tunneled/undermined wounds; surgical wounds (donor sites/grafts, post-Mohs surgery, post-laser surgery, podiatric, wound dehiscence); trauma wounds (abrasions, lacerations, partial-thickness burns, and skin tears); draining wounds'
   - Chemical characterisation and toxicological risk analysis: Provide a detailed analysis (after extractables testing) of any component present within the device and, if so, in the amounts they are present. Once identified, a toxicological risk analysis of all the components identified to any potential human health risk. This will include the proposed maximum amount of the device/its components that will come into contact with the intended patient.
d. Performance testing:
   - Biocompatibility testing: Conduct tests in accordance with ISO 10993 standards to ensure the device is safe for use in humans. These tests include cytotoxicity, acute systemic toxicity, sub-acute, sub-chronic and chronic toxicity, skin irritation and sensitisation testing, genotoxicity, carcinogenicity, and pyrogenicity testing. These tests are done either in prescribed animal models, or in validated *in vitro* models. Both the protocol and test reports are reviewed by the FDA for their relevance and interpretation of the results.
   - Mechanical and biochemical testing: If applicable, include data on tensile strength, flexibility, and other relevant mechanical properties as well as simulated bench top testing to support device function.
   - Sterility assurance: If the device is sterile, provide validation for your sterilisation process (ISO 11137 Compliance).
   - Packaging validation: This is a check to ensure that products are packaged in a way that maintains their quality, safety, and efficacy

throughout their intended shelf life (ISO 11607 Compliance).

e. Pre-clinical studies: Depending on the intended use and claims, you may need to submit data from product testing in animals to support safety and effectiveness. These study protocols normally require approval from an Institutional Animal Care and Use Committee (IACUC) and be relevant to the intended clinical use of the device.
f. Labeling requirements: Includes proposed labeling, instructions for use (IFU), and any claims made about the device's performance.
g. Quality system regulations (QSR): Demonstrates compliance with FDA's QSR (21 CFR Part 820). Most medical device companies adhere to ISO 13485 Quality Management System (QMS) requirements.
h. Risk analysis: The medical device company will need to conduct a risk analysis as per ISO 14971 to identify and mitigate potential risks associated with the device.
i. Submission preparation: Prepare the 510(k) submission, ensuring that all required sections are complete and follow FDA guidelines.
j. FDA review process: After submission, the FDA will review the 510(k), generally a 90-day turn around period. You will then need to be prepared to respond to any questions or requests for additional information.

3. Post-clearance activities:

If cleared, maintain compliance with regulatory requirements and consider post-market surveillance.

- Each batch of products will undergo a set of quality control tests (e.g. endotoxin testing, biochemical testing) established during the product and process validation period to ensure that each batch meets predetermined quality standards. This ensures no product variability between batches
- Quarterly dose audits are conducted on a regular basis for terminally sterilised products to ensure accuracy and compliance to the established sterility levels for each product
- The facility and all records be available for inspection by the FDA on a site audit (usually once every other year).

Evidence for use

Due to the rising incidence and cost of chronic wounds (Guest et al, 2020), it is vital that advanced therapies such as skin substitutes are supported by high-quality evidence of efficacy and cost-effectiveness, to reduce practice variation and increase their facility for use in practice.

While some randomised clinical trials (RCTs) compare skin substitutes, demonstrating the superiority of one product for a particular wound aetiology (e.g. Zelen et al, 2015; 2016), the number of such studies is limited, as are the number of systematic reviews.

This section outlines and summarises the evidence in common wound aetiologies, identifying where there is strong evidence and associated guidance for use and where gaps may exist. Evidence summary boxes are included for DFUs, where the majority of relevant evidence currently exists.

Diabetic foot ulcers (DFUs)

Biological dressings (placental-derived products)

Based on their systematic review for the 'Guidelines on interventions to enhance healing of foot ulcers in people with diabetes', the IWGDF (IWGDF, 2023) have recommended the consideration of placental-derived products (biological dressings) as an adjunct to the best SOC when the ulcer has failed to respond (reduce in size) to SOC alone after 4 weeks.

This recommendation was based on several prospective RCTs across the subcategories of biological dressings (i.e. dHAMs, dHACMs and vCPMs).

A RCT conducted on the efficacy of a dHACM compared to SOC for achieving wound closure of non-healing DFUs (*n*=80) was conducted by DiDomenico (2018). After a 2-week screening period, patients with DFUs that were unresponsive to SOC were randomised into two groups; one patient group was treated with SOC alone and the other with weekly applications of a dHACM as an adjunct to SOC. At 12 weeks, 85% of the dHACM-treated DFUs healed, compared with 33% of the patients treated with SOC alone. The mean time to healing was also significantly faster for the dHACM-treated group (37 days) compared to SOC alone (67 days). When evaluating the cost to closure reported in the literature, the authors concluded that the investigated dHACM had the lowest cost over the 12 weeks at $1,771 (USD) per healed wound.

Similar results were obtained for the efficacy of a dHACM as an adjunctive treatment of DFUs, reported by Snyder et al (2016), who found that 33% of reported wound closure at/or before week 6 was in the dHAM group, compared to 0% in the SOC group.

A RCT (*n*=60) conducted by Zelen et al (2015) found that wound closure reported at week 6 was superior when treated with a dHACM (95%), compared to SOC with collagen-alginate dressing (35%) or a BLCC (45%). Median time to healing was also significantly faster with dHACM treatment (13 days), compared to treatment with a BLCC (49 days) or SOC (49 days). The mean number of grafts used and the graft cost per patient were lower for dHACM usage, at 2.15 grafts for $1,669 (USD) versus 6.2 grafts for $9,216 (USD), respectively.

A follow-up RCT conducted by Zelen et al (2016) compared clinical outcomes over a longer interval of time with a larger cohort (*n*=100). After a 12-week study period, the proportion of wound closure was greatest for the dHACM-treated group (97%) compared to the patient groups treated with a BLCC (73%) or SOC (51%). Additionally, the mean time-to-heal within the 12-week study period was lower for the dHACM-treated group (23.6 days) compared to those treated with a BLCC (47.9 days) or SOC (57.4 days). When investigating cost-effectiveness, the median number of grafts used and median graft cost per healed wound were lower for dHACM usage compared to BLCC, at 2.5 grafts for $1,517 (USD) compared to 6 grafts for $8918 (USD), respectively. The results of these studies suggest that dHACMs are superior in terms of clinical and resource utilisation to BLCC or SOC for the treatment of diabetes-related ulcers of the lower extremities.

Lavery et al (2014) conducted a RCT (*n*=97) to compare the efficacy of a vCPM (*n*=50) compared to SOC (*n*=47) for treating DFUs. The primary endpoint was the percentage of patients with complete wound closure after a 12-week treatment period, which was significantly higher for patients who received adjunctive treatment with a vCPM (62%) than those treated according to SOC alone (21%). Secondary endpoints included the median time to

Box 3. Evidence for use of biological dressings for DFUs/venous leg ulcers (VLUs)
The following studies were considered 'low-risk-of-bias' by the Agency for Healthcare Research and Quality, USA.

Dehydrated human amnion/chorion membrane (dHACM)

- RCT (*n*=80) reported at 12 weeks, 85% of the DFU in the dHACM group achieved healing compared with 33% of the DFU in the SOC group (Zelen et al, 2015)
- RCT (*n*=60) reported on wound closure at 6 weeks of 95% for the dHACM group, 45% for BLCC (cellular biological matrix) and 35% for SOC (Zelen et al, 2015)
- RCT reported that the proportion of wound closure was the greatest for the dHACM-treated group (97%) compared to the patient groups treated with a BLCC (73%) or SOC (51%; Zelen, 2016)

Hypothermically Stored Amniotic Membrane (HSAM)

- RCT (*n*=76) reported complete wound closure of 60% at 12 weeks in the HSAM group compared to 38% in the SOC group (Serena et al, 2020)

Cryopreserved placental membrane with viable cells (vCPM)

- RCT (*n*=97) reported wound closure at 12 weeks was 62% in the vCPM group and 21% in the SOC group (Lavery et al, 2014)

Dehydrated human amnion membrane (dHAM)

- RCT (*n*=29) reported wound closure at/or before week 6 was 33% in the dHAM group and 0% in the SOC group (Snyder et al, 2016)

Dehydrated amnion chorion membrane (dACM)

- RCT (*n*=218) showed a 48% greater probability of wound closure in favour of the dACM group and, at 12 weeks, 50% of the DFU in the dACM group achieved healing, compared with 35% in the SOC group (Cazzell et al, 2024).

wound closure, which was 42 days for the vCPM group, compared to 69·5 days for the SOC group. Additionally, fewer adverse events were reported for vCPM patients (44% compared to 66%) and fewer with wound-related infections (18% compared to 36·2%). The results of this study indicate that vCPMs are a safe and more effective therapy for treating DFUs than standard wound therapy.

In addition to the literature reviewed by the IWGDF (2023), Serena et al (2020) conducted a multi-centre RCT comparing HSAM to SOC in patients with DFUs. The primary endpoint was complete wound closure (CWC), within a 16-week period (12-week treatment phase and 4-week follow-up phase). The findings resulted in a statistically significant difference between the two patient groups (HSAM 60% versus SOC 38% at week 12 and HSAM 63% versus SOC 38% at week 16). The probability of wound closure increased by 75% in the HSAM group, and when assessing secondary endpoints, significantly more DFUs achieved greater reduction in ulcer area, depth, and volume with HSAM than SOC within the 16-week study period.

Cazzell et al (2024) conducted a prospective, multi-centre RCT comparing dACM plus SOC to SOC alone in patients with complex DFUs (DFU extending into dermis, subcutaneous tissue, tendon, capsule, bone or joint). The primary efficacy endpoints were time to and frequency of complete wound closure by or at 12 weeks. The cohort comprised 218 patients (*n*=109 in dACM plus SOC, and *n*=109 in SOC alone). Cox analysis showed the estimated frequency of wound closure for dACM compared to SoC was statistically significantly improved at week 4 (12% versus 8%), week 6 (22% versus 11%), week 8 (31% versus 21%), week 10 (42% versus 27%), and week 12 (50% versus 35%; *p*=0.04). The computed hazard ratio of 1.48 (confidence interval: 0.95, 2.29) showed a 48% greater probability of wound closure in favour of the dACM group. Median time to wound closure for dACM-treated ulcers was 84 days compared to 'not achieved' in the SOC-treated group (i.e. ≥50% of SOC-treated DFUs failed to heal by week 12; *p*=0.04).

Box 3 summarises the clinical evidence highlights.

Cost-effectiveness evidence for the use of dHACMs for lower extremity diabetic ulcers

In addition to the cost-effectiveness findings from Zelen et al (2015; 2016) discussed above, a handful of studies have been conducted, which examine the cost-effectiveness of dHACMs in treating lower extremity diabetic ulcers (LEDUs).

Tettlebach et al (2022a) conducted a health economic study to compare the cost-effectiveness and clinical outcomes of dHACM treatment to SOC for patients with LEDUs. The study showed that dHACM usage for LEDUs not only improved patient outcomes but also reduced costs. Over one year, dHACM use saved an average of $3,670 (USD) per patient compared to SOC while improving patient quality of life. Over 5 years, the total savings increased to $4,777 (USD) per patient. It was also found that a health plan with one million members could save $21.94 (USD) per member per year, or

Box 4. Cost-effectiveness evidence for the use of biological dressings for LEDUs

Dehydrated human amnion/chorion membrane (dHACM)

- RCT (*n*=60) reported the mean number of grafts used and the graft cost per patient was lower for dHACM usage compared to BLCC usage, at 2.15 grafts for $1,669 (USD) versus 6.2 grafts for $9,216, respectively (Zelen, 2015)
- RCT (*n*=100) reported the median number of grafts used and median graft cost per healed wound at 2.5 grafts for $1,517 (USD) for dHACM compared to 6 grafts for $8918 (USD) for BLCC (Zelen et al, 2016)
- Retrospective analysis revealed that over one year, dHACM use saved an average of $3,670 (USD) per patient compared to SOC while improving patient quality of life. Over 5 years, the total savings increased to $4,777 (USD) per patient. A health plan with one million members could save $21.94 (USD) per member per year, or $1.83 (USD) per member per month (Tettlebach et al, 2022a).

$1.83 (USD) per member per month, by implementing the use of dHACM. These savings were due to the reduction of costly events such as amputations and hospital admissions, which DHACM helps to prevent. The study strongly supports the adoption of dHACM in routine practice, which, when used according to recommended protocols, could reduce the clinical and economic burden on both patients and the healthcare system.

Box 4 summarises the cost-effectiveness evidence for the use of dHACM for the treatment of LEDUs.

Biological matrices

The same systematic review (IWGDF, 2023) found 23 RCTs for biological matrices. Cellular biological matrices assessed in the systematic review include DSS and BLCC.

A RCT by Veves et al (2001) involving 208 patients compared the efficacy and safety of BLCC (*n*=112) versus SOC (*n*=96) in treating non-infected neuropathic DFUs. The primary outcome was complete wound healing (CWC) at 12 weeks, analysed via intention to treat. BLCC achieved 56% CWC compared to 38% in the SOC group (*p*=0.0026). The median time to complete closure was shorter with BLCC (65 days) compared to SOC (90 days). Adverse events were lower with BLCC, with significantly fewer cases of osteomyelitis (2.7% versus 10.4%) and amputation (6.3% versus 15.6%).

Kirsner et al (2015) conducted a real-world comparative effectiveness analysis comparing BLCC to dHACM in 218 patients (226 DFUs) across 99 wound care centres. At 12 weeks, BLCC healed 48% of wounds compared to 28% with dHACM, with a median time to closure for BLCC of 13.3 weeks compared to 26 weeks for dHACM. BLCC also increased the probability of healing by 97%.

A RCT by Marston et al (2003) studied 245 patients, comparing DSS (*n*=130) to SOC (*n*=115) in treating chronic DFUs. By week 12, 30% of patients in the DSS group achieved wound closure, compared to 18.3% in the SOC group, confirming the safety and efficacy of DSS.

Kraus et al (2017) also compared DSS to dHACM in 122 patients (122 DFUs) across 72 wound care centres. By 12 weeks, DSS led to 55% wound closure versus 32% with dHACM. DSS increased the probability of wound closure by 107%, with a median time to closure of 7.4 weeks, 38% faster than dHACM.

The evidence from these RCTs and real-world observational comparative effectiveness analyses suggests that when used as an adjunct to SOC, both cellular and acellular skin substitutes may improve incidence of healing and reduce the time to healing in patients with diabetes-related foot ulcers.

See Box 5 for a summary of the evidence highlights.

Cost-effectiveness evidence for the use of biological matrices for DFUs

Retrospective health economics and outcomes research conducted by Rice et al (2015) evaluated the cost-effectiveness of BLCC and DSS, compared to SOC in Medicare patients with DFUs. The findings showed that patients treated with BLCC and DSS had significantly lower rates of lower-limb amputations

Box 5. Evidence for use of cellular and acellular biological matrices for DFUs

- RCT (*n*=208) reported wound closure at 12 weeks was 56% for BLCC group and 38% for the control/SOC group (Veves et al, 2001)
- Real-world comparative effectiveness analysis (*n*=226 DFUs) reported wound closure 48% for the BLCC group versus 28% for the dHACM group (Kirsner et al, 2015)
- RCT (*n*=245) reported wound closure at 12 weeks was 30% for DSS group and 18% for the control/SOC group (Marston et al, 2003)
- Real-world comparative effectiveness analysis (*n*=122 DFUs) reported wound closure at 55% for DSS group and 30% for dHACM group (Kraus et al, 2017)
- RCT (*n*=307) in which complete DFU closure during the treatment phase was significantly greater with acellular product treatment (51%) than control treatment (32%) at 16 weeks (Driver et al, 2015).

(27.6% lower for BLCC, 22.2% lower for DSS, compared to SOC) and reduced hospitalisations and emergency visits compared to those receiving SOC. Over an 18-month follow-up period, BLCC patients saved an average of $5,253 (USD), and DSS patients saved $6,991 (USD) compared to SOC patients. These results suggest that using BLCC and DSS for DFU treatment improves clinical outcomes and reduces overall healthcare costs, making these technologies a cost-effective alternative to conventional wound care.

Venous leg ulcers (VLUs)

Compared to the amount of data on the use of skin substitutes for the treatment of DFUs, limited studies have been published regarding their effectiveness in treating VLUs. Many studies did not have inclusion criteria or had insufficient information regarding randomisation techniques. In addition, withdrawals and adverse events were inadequately reported. Deficient data regarding withdrawals and the use of per-protocol analyses rather than intention-to-treat analyses suggest that the outcomes may be biased.

Biological dressings

Farivar et al (2019) conducted a RCT to compare the efficacy of a vCPM for the treatment of VLUs to SOC. The ulcers of all enrolled patients failed to heal after a 12-week treatment period, including weekly multilayer compression therapy and local wound care. Subsequently, the same group of patients received applications of a vCPM every 1 to 2 weeks as an adjunct to SOC. Outcomes of vCPM therapy were then compared to SOC, with each patient serving as their own control. Complete ulcer healing was achieved in 53% of VLUs refractory to treatment with SOC alone, after vCPM application commenced.

There was also a mean reduction in wound surface area by 79% compared with SOC after a mean treatment time of 10.9 weeks. Furthermore, 80% of VLUs were reduced in size by half compared with 25% treated according to SOC alone. The authors concluded that these results indicate that the application of vCPMs and treatment according to SOC provides superior healing rates in refractory VLUs.

A RCT by Bianchi et al (2018) was conducted to evaluate the efficacy of a dHACM as an adjunct to multilayer compression therapy for the treatment of non-healing full-thickness VLUs. After a 12-week treatment period, patients who received weekly dHACM application in addition to compression were significantly more likely to experience complete wound healing than those receiving standard wound care and compression (60% and 35%, respectively). A Kaplan–Meier analysis determined that time-to-healing in the dHACM was significantly improved. These results suggest that dHACMs used as an adjunctive to standard wound care and multilayer compression therapy for the treatment of non-healing, full-thickness VLUs significantly improve healing outcomes.

Cost-effectiveness evidence for the use of biological dressings for VLUs

This cost-effectiveness analysis evaluated the use of dHACM for treating VLUs in Medicare patients. The study found that DHACM was more effective and cost-saving than SOC, reducing per-patient costs by $170 (USD), while improving quality of life over 3 years. dHACM also lowered hospital admissions and resource use, particularly in patients with complex VLUs. The net monetary benefit per patient was $1,178 (USD), favouring dHACM as a cost-effective solution. Given these benefits, clinicians should consider dHACM as a primary treatment option

Evidence for use

(Continued)

for VLUs, and policymakers are encouraged to update reimbursement strategies to promote its use, reducing the overall burden of chronic wounds (Tettlebach and Forsyth, 2024).

Biological matrices

Mostow et al (2005) evaluated the efficacy of porcine SIS (an acellular biological matrix) as an adjunctive to compression therapy compared to compression therapy alone in treating chronic VLUs. At 12 weeks, 55% of the wounds in the SIS group were healed compared with 34% in the group treated with standard wound care and compression therapy (p=0.0196). There were no recurrences in the 6-month follow-up in the SIS-treated group.

A multi-centre, open-label RCT was conducted to evaluate the safety and efficacy of a human acellular dermal matrix product (D-ADM), compared with conventional wound care management in patients with VLUs (n=18 and n=10, respectively). There was a strong trend of reduction in percentage wound area for D-ADM patients, with an average reduction of 59.6% at 24 weeks versus 8.1% at 24 weeks for control patients (Cazzell et al, 2017).

A RCT (n=293) conducted by Falanga et al (1998) compared the efficacy and safety of BLCC compared to SOC in patients with chronic VLUs. Each patient with a venous ulcer received either compression therapy alone or compression therapy and treatment with BLCC. The patients were evaluated for BLCC safety, complete (100%) ulcer healing, time to wound closure and wound recurrence. At 24 weeks, significantly more patients healed in the BLCC group (63%) than in the SOC group (49%). The median time to complete wound closure was 61 days for BLCC versus 181 days for SOC.

In a RCT conducted by Stone et al (2017; 2020), the biological actions of BLCC on VLU pathophysiology compared to SOC/compression alone were evaluated. Mechanistically, VLUs treated with BLCC displayed three distinct transcriptomic patterns, suggesting that BLCC induced a shift from a non-healing to a healing tissue response, orchestrating a shift from a chronic non-healing ulcer microenvironment to one resembling that of an acute, healing wound.

Mixed arterial/venous and vasculitic ulcers

Ulcers of mixed aetiologies present particular challenges for clinicians and are costly to treat. These wounds are often slow to heal and are associated with high levels of pain, inflammation and tissue necrosis (Wounds International, 2011).

Romanelli et al (2007) investigated the effectiveness of a porcine SIS compared to a hyaluronic acid (HA) biomaterial in the treatment of mixed arterial/venous ulcers. The RCT found that, at 16 weeks, complete wound closure was achieved in 82.6% of patients within the SIS group compared to 46.2% for the HA group. Patients treated with SIS also reported significantly greater comfort and less pain compared to the HA group.

Future evidence

Currently, the majority of evidence in common wound aetiologies appears to be in the field of DFUs, with limited evidence available in VLUs and still less in other types of leg ulcers. While guidelines and the existing evidence suggest that these advanced therapies can be beneficial in all of these wound types, more evidence is needed for a wider range of wound aetiologies.

Key points

- Good-quality evidence is needed for advanced wound care products to inform practice and tackle the growing burden of chronic and non-healing wounds by improving outcomes for patients through facilitating use of advanced therapies
- While evidence exists, particularly in the field of DFUs, the panel identified a need for further evidence to fill the current gaps
- Advanced wound therapies should be used as per local guidance and availability, and guidance for specific wound types.

Guidelines for product selection

Selecting the appropriate product for the individual patient is key to clinical decision-making. In identifying patient suitability, it is important to view the full clinical picture, considering the patient, their wounds, their needs and preferences holistically (World Union of Wound Healing Societies [WUWHS], 2020).

All clinical decision-making, such as product selection, should begin with a full and accurate assessment. Communication with the patient is also paramount, explaining the product use and rationale as much as possible, and engaging the patient in collaborative decision-making that they fully understand (WUWHS, 2020).

Assessment and wound bed preparation

The panel agreed that thorough patient evaluation and wound assessment are crucial to accurately identify the wound aetiology, intrinsic conditions affecting healing (e.g. diabetes, venous disease) and potential infection, which should be addressed before application.

Appropriate wound bed preparation is vital for optimal patient outcomes with skin substitutes. A structured assessment tool, such as the TIMERS framework (Atkin et al, 2019) serves as a valuable tool for patient evaluation, wound assessment and underpinning best practice for wound bed preparation and ongoing treatment **[see Box 6]** The TIMERS assessment framework expands on the original TIME acronym (Dowsett and Ayello, 2004).

Patient history and communication

In addition to thorough assessment of the patient on presentation, a detailed patient history should be obtained and should include (adapted from WUWHS, 2016):

- Past medical and surgical history
- Management of any other concurrent conditions or illnesses (e.g. diabetes)
- Symptoms and signs of peripheral arterial or venous disease
- Symptoms and signs of peripheral neuropathy
- Musculoskeletal evaluation (e.g. for overall flexibility, range of movement in the ankle, foot shape)
- Systemic signs of infection

Box 6. Wound assessment and preparation – TIMERS (Atkin et al, 2019)

- **T** **Tissue** – removal of devitalised tissue via debridement
- **I** **Inflammation and infection** – control of infection and inflammation through debridement and antimicrobials and cleaning with surfactants
- **M** **Moisture** – maintenance of a moist environment conducive to healing
- **E** **Edges** – debridement to remove callus
- **R** **Repair/regeneration** – consider the application of advanced therapies such as skin substitutes to facilitate wound closure of stalled wounds
- **S** **Social and patient-related factors** – promote patient concordance and satisfaction with treatment by providing patient education, employing active listening and motivational interviewing.

- Pain (e.g. neuropathic pain, wound-related pain)
- History of trauma to the foot/limb
- History of wounds/ulceration and infection
- Medications
- Family history of underlying conditions.

Other issues such as wellbeing, quality of life and lifestyle factors should also be considered. These may include:

- Employment status/occupation
- General mobility
- Limitations to daily activities
- Psychological and social impact
- Socioeconomic circumstances
- Smoking status
- Nutrition status and weight.

Evidence-based decision-making and regulatory approval

While robust clinical and health economic evidence is available for the use of biological dressings and biological matrices for the treatment of DFUs and VLUs, product selection is largely driven by regulatory approval and coverage, as well as personal experience, in alignment with the current evidence and recommendations from national and international societies/committees.

Guidelines for product selection

(Continued)

Key points

- All treatment decisions should be underpinned by thorough and accurate assessment, using a structured assessment tool such as TIMERS (Atkin et al, 2019), considering the patient holistically in terms of their overall health, needs and preferences, as well as their wound
- It is important that clinicians are knowledgeable about the biomaterials within the product that they would like to use and the stage of wound healing that they would like the product to help modulate
- Wound bed preparation is also an important consideration in optimising product use and outcomes
- Wherever possible, clinical consideration needs to be based on evidence, to ensure best practice and consistency of care for patients; however, evidence may still be lacking in some areas, and local guidance along with clinical judgement should be used.

In the US, skin substitutes can be marketed in different ways. FDA regulates skin substitutes via section 351, section 361 or the medical devices pathway. The product testing requirements are vastly different for each of these regulations.

FDA regulation of medical device companies ensures that the devices they produce have the expected quality, safety, effectiveness and reliable performance. Implantable/non-implantable medical devices are subject to FDA review prior to release for patient use. While this review alone does not guarantee patient outcomes, it does hold companies accountable to a scientifically based selection of tests for biocompatibility, animal studies, and/or clinical studies.

Medical devices are also subject to design controls. This means that clinician input is used in the design, which is then tested and validated to ensure it works as intended for the patient. Risk management is applied throughout the design and manufacturing process to ensure patient safety. Any changes to the design or manufacturing of the device must go through a formal process to ensure that the modified device will still perform as intended for the patient. These mandatory processes help ensure that patients receive medical devices that are likely to provide real benefits.

Human cells, tissues, and cellular and tissue-based products (HCT/Ps) are required to comply with various FDA regulations (GTPs, 1271), and any additional medical device, biologic, or drug regulations, if that particular HCT/P is regulated as a device, biologic, or drug.

In the US, skin substitutes which are marketed as medical devices can be categorised based on the level of risk they pose and must go through one of two primary regulatory pathways accordingly to obtain FDA approval: Premarket Approval (PMA) or 510(k) clearance. While products marketed under the 510(k) clearance are indicated to be safe and effective, the evidence supporting these trials appears to be less stringent than that required for PMA, the FDA's comprehensive scientific and regulatory review process for evaluating the effectiveness of high-risk or Class III medical devices. Currently, only three biological matrices have received PMA:

- BLCC
- DSS
- DRTs.

Please refer to the appropriate regulatory agencies for guidance on which products are covered according to your particular setting. **Box 7** shows examples of regulatory agencies that approve medical products, including biomaterials

Box 7. Regulatory agencies approving biomaterials

- European Medicines Agency and European Commission
- FDA (US)
- Medicines and Healthcare products Regulatory Agency (MHRA; UK).

Important clinical considerations

In addition to cost-effectiveness, equity, and feasibility, several clinical considerations should be taken into account when selecting a skin substitute. These include the product's origin (i.e. whether it is human or animal-derived) and its sterility.

Sterility assurance levels (SAL) and ADMs

While the decellularisation process is thought to remove potentially immunogenic material, different ADMs have demonstrated varied levels of residual DNA content. A lower residual DNA content indicates a more thorough decellularisation process, enabling a desirable host response. An ADM's SAL is an important consideration, especially considering the threat of infection associated with DFUs.

These biological matrices may then be tested for sterility. If terminally sterilised by a validated method, the skin substitute may have a Sterility Assurance Level (SAL) of 10^{-3}, indicating a 1 in 1,000 probability that a packaged implant contains a viable microorganism, while a SAL of 10^{-6} indicates a 1 out of 1,000,000 chance. The latter, SAL of 10^{-6}, is the expected level for a sterile-labelled implantable medical device (Cazzell et al, 2017).

Guidelines for product application

While application guidelines will vary depending on the individual product, patient and clinical scenario, there is some general guidance that will help to ensure best practice. Following holistic assessment using a structured framework such as TIMERS (Atkin et al, 2019), the panel agreed that effective wound bed preparation is vital to optimising ongoing treatment.

It is also important to note that all products should be used in accordance with the manufacturer's instructions, guidelines or recommendations.

Initial considerations

Prior to application, practical factors about the appropriate individual method for treatment should be considered. These include (Wounds International, 2011):

- Protocol for first application (i.e. wound bed preparation, use of assessment framework)
- Methods of attachment (i.e. sutures, wound closure strips or staples)
- The use of appropriate dressings to cover the matrix, based on the individual needs of the patient and their wound, following failure to respond to the SOC after 4 weeks of treatment.

Treatment goals

Goals and objectives for treatment should be identified at the start of treatment. Ideally, this should be a collaborative process with the patient, so that they understand the rationale and are more engaged with their treatment (WUWHS, 2020).

These goals, and their progress, can be revisited with ongoing assessment, considering whether progress is being made or if a change of regimen is needed. The milestones towards achieving a successful outcome may include:

- No clinical signs of acute infection or bioburden (e.g. purulence, sliminess or unexpected malodour)
- Formation of granulation tissue
- Re-epithelialisation
- Reduction in wound size
- Successful removal of the method of attachment (i.e. staples, sutures or wound closure strips).

It is generally accepted that reduction in size after 4 weeks of treatment is a predictor of healing; therefore, if no improvement is seen at this time, there should be further review of the patient and current treatment strategy.

Key points

- It is important to carry out all treatment in accordance with the manufacturer's instructions and guidelines or recommendations
- Prior to commencing treatment, practical factors and treatment goals should be considered
- Treatment goals should be reviewed and progress assessed as treatment continues.

Control and optimisation of the wound environment

Optimising the wound environment involves addressing several critical factors, including controlling exudate, managing bacterial burden, reducing inflammation and removing non-viable tissue.

Exudate control

Chronic wounds often produce excess exudate, which contains proinflammatory cytokines, proteases, and microorganisms that can damage surrounding tissue and promote infection. Unmanaged exudate can lead to further complications, including bacterial growth, biofilm formation and damage to the periwound skin. Absorbent dressings, negative pressure wound therapy (NPWT) or fluid collection devices (e.g. ostomy/fistula appliances) may be employed to manage high exudate levels, helping maintain a balanced wound environment that supports healing (WUWHS, 2019).

Initial debridement

Once the assessment is complete and any underlying conditions have been effectively addressed, wound bed preparation with adequate wound debridement is required before applying the skin substitute. Failure to do so would allow necrotic tissue and debris to remain within the wound, acting as a physical barrier to proper contact between the wound bed and the substitute. Debridement reduces bacterial load through the removal of microorganisms and biofilms, as well as removing pro-inflammatory cytokines and proteases, which halt progression through the wound healing cascade (Schultz et al, 2003; Demidova-Rice et al, 2012). Wound debridement also helps to restart wound healing by creating an acute injury to initiate the haemostatic phase and movement through to the inflammatory phase (Dayya et al, 2022).

'Adequate' debridement is regarded as the most efficient method that can be tolerated by the patient, considering patient pain levels, haemostasis, available equipment, and scope-of-practice constraints. A significant barrier to achieving adequate debridement is a lack of agreement among clinicians over the definition of the term. Major international organisations strongly recommend regular, sharp debridement when blood flow is adequate for stalled DFUs. Sharp debridement is the removal of devitalised tissue in a non-surgical setting using a scalpel, scissors and/or forceps to just above the viable tissue level (Vowden and Vowden, 2011).

A range of debridement types may be available depending on the care setting. Forms of debridement may include:

- Autolytic
- Biosurgical
- Hydrosurgical
- Mechanical
- Sharp
- Surgical
- Ultrasonic.

All forms of debridement require varying levels of expertise and have their advantages and disadvantages in terms of time taken, patient acceptability and ease of use. Clinical judgement should be used depending on the clinician's expertise and experience, and the option that best suits the patient, their wound and the clinical scenario.

Evidence for debridement in use of skin substitutes

In a recent study on the influence of adequate debridement with placental-derived products (e.g. dHAMs) for treating DFUs, Tettlebach et al (2022b) found that the quality of debridement had a major impact on wound closure. Prospectively collected data showed that, when the debridement performed was adjudicated as inadequate, wound closure rates dropped to 30%. No wound closure occurred when SOC alone was provided alongside inadequate debridement.

Post-application debridement

A retrospective analysis found that debridement intervals of 7 days (or less) demonstrated the best outcomes (i.e. lower amputation rates and hospital utilisation rates; Tettlebach et al, 2022b). While the impact of debridement and treatment with biological matrices is independent, a synergistic effect was observed.

General tips for application

While following the manufacturer's instructions for individual products, there are some agreed general

tips for use that may be useful in practice.

- It is important to carefully contour the product and ensure it is in contact with the wound bed
- When the wound is very large, multiple sheets may be needed to cover the entire wound bed; in which case, there should be slight overlap with the wound edges, and the matrix may need to be secured to reduce risk of movement
- If the wound has significant volume of exudate, a fenestrated (meshed) acellular matrix can be used to allow the fluid to drain from the wound
- If there is excessive moisture, such as maceration of the wound edges, the matrix should not be applied until the exudate level has been controlled
- The level of exudate will affect the choice of secondary dressing for an optimal moist wound environment on reapplication frequency
- Many of these products are reapplied weekly to twice per week; it is important to follow the manufacturer's instructions
- It is important to investigate whether other products can be used successfully in conjunction with the matrix – for example, NPWT for exudate control, a topical antimicrobial for infection control, or compression therapy to manage oedema, as appropriate.

Potential complications

There are complications that may occur over the course of treatment that require action to be taken. These may include:

- **Infection:** remove the matrix, control the infection and apply a new matrix following adequate reassessment and wound bed preparation
- **Detached or displaced matrix:** remove the matrix and assess to establish the reasons for failure; perform adequate wound bed preparation before applying a new matrix
- **Excessive inflammation/possible allergic reaction with xenografts and synthetic matrices:** remove and do not reapply a new matrix
- **Failure of the wound to heal/lack of progression:** reassess the wound and the patient, considering any possible underlying causes; when the wound is not healing the matrix may be displaced and there may be an increase in wound size
- **Pain:** a significant increase in pain after application may indicate presence of infection, or a reaction to the product, which needs to be assessed urgently.

Key points

- Debridement/wound bed preparation is an important factor in treatment success
- Products should be used in conjunction with other therapies as necessary and appropriate, to manage other wound factors such as exudate or infection control, or to treat oedema
- It is important to know potential complications to look out for and to take appropriate action when necessary.

Pathway for care in practice

The need was identified for clear guidance in practice to aid clinicians in decision-making, to ensure that products are selected and used correctly, and patient outcomes optimised. The overall aim of this guidance is to increase clinician knowledge and confidence in practice.

Table 1 provides a summary of experienced practitioner tips for the pre-application, application and post-application stages of skin substitute application, so that guidance is broken down for every stage of treatment.

Figure 1 provides a clear step-by-step decision-making algorithm for skin substitute application in chronic wounds.

Table 1. Experienced practitioner tips for each stage of the procedure

Pre-application	Application	Post-application (maintenance period)
Assess patient suitability • Perform a comprehensive assessment of the patient and the wound • Establish a diagnosis • Address barriers to care (e.g. social and cultural issues). **Exclude ischaemia/infection and uncontrolled bacterial burden/allergy. Address underlying aetiology to maximise healing potential** (e.g. control exudate/bacterial burden; ensure adequate offloading/compression/ pressure reduction; reduce steroids/ inflammation) **Perform adequate and appropriate wound bed preparation** (e.g. debridement) **Ensure patient concordance** (e.g. those with diabetic foot problems, those requiring compression) **Address and co-manage wounds with the appropriate specialist** (Patients with chronic comorbid conditions should be co-treated to ensure best wound healing outcomes)	**Prevent/minimise product contamination and bacterial overgrowth** • Ensure correct handling of product according to manufacturer's instructions • Avoid intraoperative recontamination (change gloves between procedures). **Secure matrix** Using staples; wound closure strips (e.g. for patients with sensitive surrounding skin); sutures (caution is needed not to lift or pucker skin/disrupt product). Consider anaesthesia **Size matrix** Excess matrix should be trimmed using scissors **Ensure appropriate wound dressing selection** • The matrix should be covered with a non-adherent primary dressing, bolster and/or padding (e.g. in moderate to heavily exuding wound) • Use a secondary dressing to hold the matrix and wound dressing in place • Consider the use of an appropriate topical antimicrobial • Consider a fenestrated (meshed) product • When the wound has a large surface area or is very deep, requiring NPWT • When it is necessary for fluid to drain, especially if heavily exuding.	**Disrupt as little as possible** • Minimise dressing changes (should not be disturbed for at least 1 week; early inspection increases the risk of displacement) • If displaced, remove and apply a new matrix • Staples should not be left in for more than 1 week (7 days) • Sutures can be left for maximum of 14 days • Wound closure strips can be left for 1–2 weeks • Trim the edges of the product that dry and lift during the healing process. **Reduce bacterial burden** **Prevent recurrence** Ensure adequate compression/offloading, appropriate shoes/continued pressure reduction (patients with diabetic foot ulcers need complete offloading 1 week post-application)

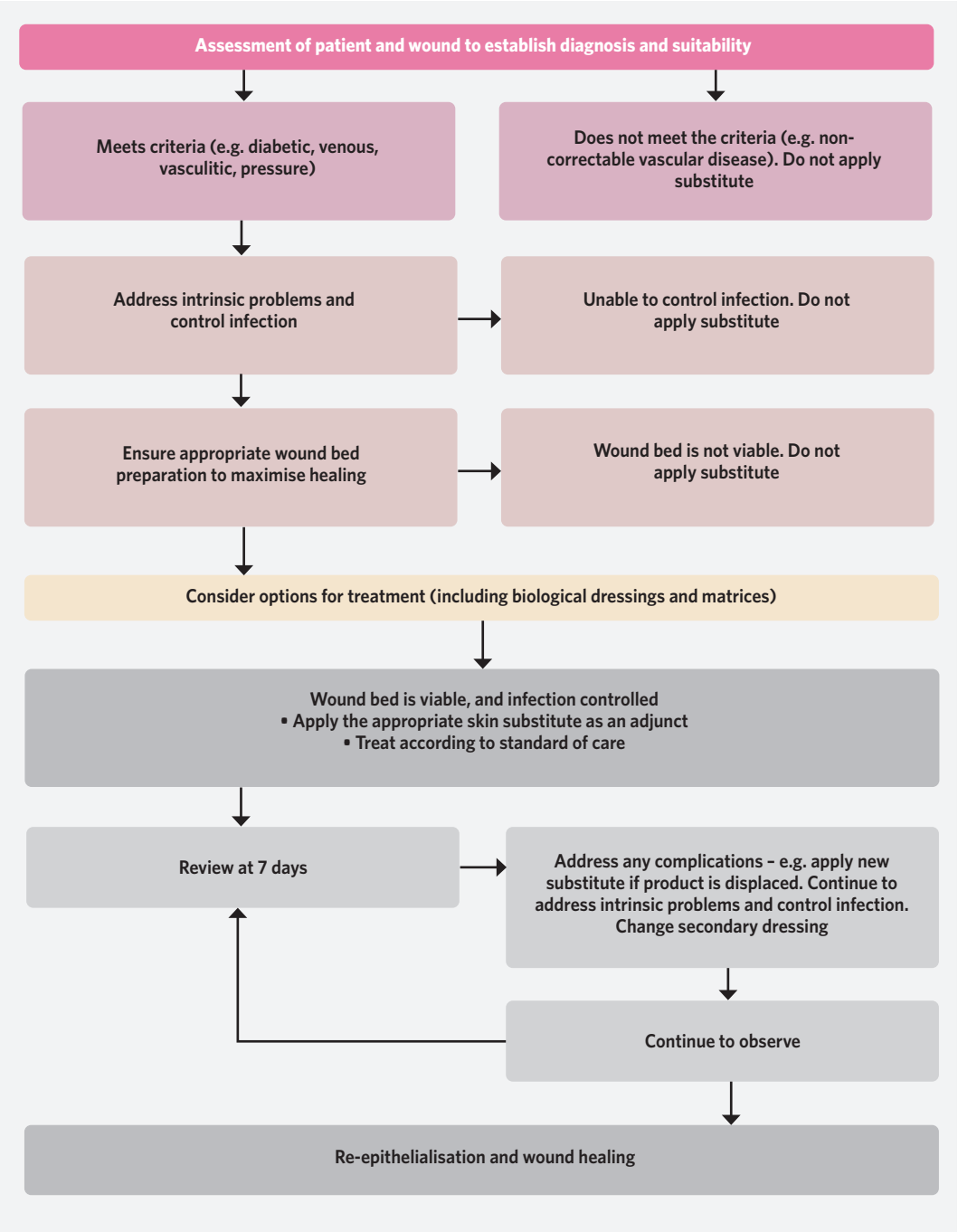

Figure 1. Decision-making algorithm for skin substitute application in chronic wounds

Conclusion

In recent years, advances in technology and a growing understanding of the importance of the ECM in wound healing has led to the development of products, many of which contain a 'dermal' component that stimulates and replaces the function of the affected ECM.

There is now a vast range of products on the market, including those that are animal/human-derived, synthetic, or composite. These products have been found to provide a useful management tool, particularly in wounds that are unresponsive to traditional wound management modalities (chronic or hard-to-heal wounds).

The need for broader education of multiple levels of healthcare practitioners on product selection and usage, and how to use these advanced therapies to best optimise patient outcomes was identified.

This consensus document has highlighted and outlined the following areas:

- The role of the ECM in wound healing and introduction to advanced therapy categories and options in skin substitute products
- Current use in practice and rationale for use
- Evidence for use in a range of wound aetiologies
- Guidelines for product selection
- Guidelines for product application
- Pathway for care in practice.

The need was also identified for additional and ongoing research to add to the existing evidence base, particularly in wound types where there is less evidence currently available (e.g. in different types of leg ulcers).

Overall, the aim is to give clinicians the knowledge, skills and confidence they need in decision-making so that these advanced therapies can be used as part of best practice for the appropriate patients and wounds in practice. The pathway for care in practice is designed to encourage informed decision-making and for clinicians to be able to use their experience and clinical judgement within a structured framework for consistent care.

Ultimately, the aim is to improve outcomes and experiences for patients, and consequently to reduce the pressure on clinicians and healthcare systems.

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