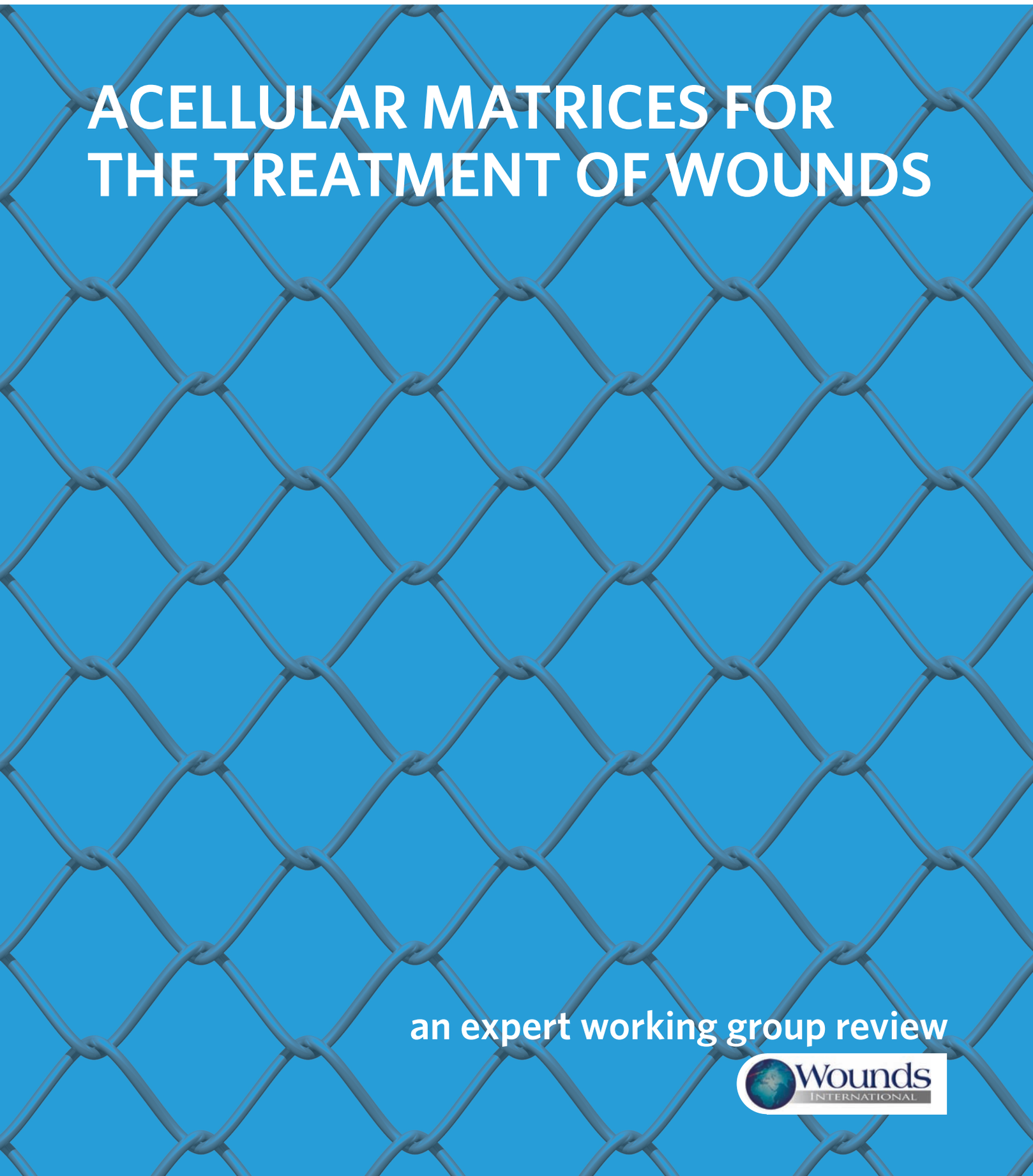
INTERNATIONAL
CONSENSUS

ACELLULAR MATRICES FOR THE TREATMENT OF WOUNDS



an expert working group review

Wounds International

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FOREWORD

Currently there is no definitive paper or guideline on the use of acellular matrices in acute and chronic wounds. To begin to address this, an expert working group convened in New York, USA in July 2010 to review current knowledge of acellular matricies and their rationale for use.

The recommendations in this document are based on the consensus opinion of the group and the available evidence. They aim to help both generalist and specialist clinicians decide when to use and how to select an appropriate acellular matrix. This document also aids understanding of how these products may be classified within the rapidly growing range of tissue-engineered products that are indicated for wound healing.

Acellular matrix products can be used in a wide variety of applications, including burns and reconstructive surgery, soft tissue and abdominal wall repair and as internal implants for orthopaedic use in joint resurfacing and tendon repair. This document focuses on the use of acellular matrices (or scaffolds) in hard-to-heal wounds such as diabetic foot ulcers, venous leg ulcers and pressure ulcers.

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Acellular matrices and wound healing

Wound healing is a dynamic process involving interactions between cells, extracellular matrix (ECM) and growth factors that reconstitutes tissue following injury[1].

Tissue engineering

Tissue engineering is the use of mechanical and chemical processing of materials to manufacture products that are intended to improve or replace body tissue function.

The extracellular matrix (ECM) plays an important role in tissue regeneration and is the major component of the dermal skin layer. The composition of ECM includes proteoglycans, hyaluronic acid, collagen, fibronectin and elastin. As well as providing a structural support for cells, some components of the ECM bind to growth factors, creating a reservoir of active molecules that can be rapidly mobilised following injury to stimulate cell proliferation and migration[2]. In many chronic wounds, increased levels of inflammatory cells lead to elevated levels of proteases that appear to degrade the ECM components, growth factors, protein and receptors that are essential for healing[3].

Recognition of the importance of the ECM in wound healing has led to the development of wound products that aim to stimulate or replace the ECM. These tissue-engineered products comprise a reconstituted or natural collagen matrix that aims to mimic the structural and functional characteristics of native ECM[4]. When placed in the wound bed, the three-dimensional matrix provides a temporary scaffold or support into which cells can migrate and proliferate in an organised manner, leading to tissue regeneration and ultimately wound closure.

It is important to differentiate native ECM, a key component of the dermal layer, from a collagen matrix product that is applied to a wound bed

Tissue-engineered products may be **cellular** (contain living cells) or **acellular** (biologically inert) and sourced from:

- **Biological** tissue:
  - animal (eg equine/bovine/porcine)
  - human (eg cadaveric skin)
  - plant (eg containing oxidised regenerated cellulose/collagen)
- **Synthetic** materials
- **Composite** materials (containing two or more components, which may be biological or synthetic).

The terms **biological** (ie synthesised by nature), **synthetic** (ie derived from man-made materials) or **composite** (ie derived from a mix of materials of various origin) are preferable to general terms such as 'natural', 'organic', or 'biomatrix'.

Acellular matrices may be animal- or human-derived, with all cells removed during manufacture, or they may be synthetic or composite, where cells are naturally not present from the outset. These matrices or tissue scaffolds provide a collagen structure for tissue remodelling, while the removal of viable cells aims to minimise or prevent an inflammatory or immunogenic response[5].

Given current knowledge, the ideal acellular matrix is one that most closely approximates the structure and function of the native ECM it is replacing

Scaffold versus matrix

A matrix may be described as a tissue scaffold in that it provides a supporting structure into which cells can migrate. However, it should be noted that a scaffold does not have to be a matrix (eg it does not interact with cells to the same degree as a matrix). For example, fibronectin may act as a matrix, but is not necessarily a scaffold; similarly, polyglactin may act as a scaffold, but is not a matrix.

Skin substitutes

Skin substitutes is an umbrella term for a group of products. Depending on individual characteristics, they may substitute or replace all or some components that make up normal skin (eg epidermis and/or dermis, cells and matrix). They can be bi-layered, acellular or cellular, synthetic or biological and may consist of a synthetic epidermis and a collagen-based dermis to encourage formation of new tissue. In products that have a synthetic epidermis, this may act as a temporary wound covering.

PRODUCT CLASSIFICATION

Different types of tissue-engineered products exist and there is confusion around the terminology used. Products may be classified as skin substitutes, xenografts, allografts or collagen dressings. Alternatively, these products may be described as **biological dressings** in that they function as a protective wound cover. However, while most wound dressings need to be changed frequently, matrices provide a scaffold for tissue repair and therefore must remain in the wound for a sufficient length of time.

Product classification is determined by the product's primary mechanism of action[6]. In Europe, most acellular matrix products are classified as Class III medical devices and must be identified by the CE mark. In the US, the FDA regulates these as medical devices that require clearing via the 510(k) process to demonstrate safety (for definitions of medical devices in the US and Europe see Table 1). Those sourced from donated skin are classified as human bank tissue (eg Alloderm®, LifeCell). However, many new products do not fit into existing categories and matters are further complicated when a product combines two or more regulated elements (ie drug, device or biological product). At present there are no unified controls for combination products[5].

The regulation of products that combine two or more regulated elements remains a challenging and evolving area

One way in which acellular matrices may function is as a **biological modulator**. This term was introduced by the consensus group to help overcome confusion around different products. A biological modulator is a material or substance derived from biological or synthetic sources that influences biological processes such as wound healing (see page 5).

Table 1 | Definition of 'medical device'

US Food and Drug Administration	European Union Legal Framework
"an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is: ■ recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, ■ intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or ■ intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." *"Section 201(h) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 321(h))"*	"Any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for purpose of: ■ diagnosis, prevention, monitoring, treatment or alleviation of disease ■ diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap ■ investigation, replacement or modification of the anatomy or of a physiological process ■ control of conception and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted function by such means;" *Excerpt from Directive 2007/47/ec*

Product composition and processing

While tissue-engineered products offer increasingly important strategies for managing complex wounds, potential drawbacks include the risks of infectious agent transfer and immunological rejection[6]. Furthermore, the manufacturing process, transport, storage, etc, of these products have major cost implications, which mean that their current clinical use remains limited[5]. However, the development and introduction of more advanced products and better understanding of individual product characteristics will lead to better outcomes, enabling appropriate product selection and clearer assessment of cost-effectiveness.

In addition to clinical considerations, when selecting an acellular matrix product, clinicians should consider the following device-specific issues:

- Is the product animal/human-derived, synthetic or composite?
- How is the product manufactured?
- What is the rate of degradation of the product?
- Is the product sterile or aseptically processed?

Concerns for the clinician and patient include:

- Risk of possible viral transmission/infection, rejection/allergenic reaction
- Religious/cultural/social issues (eg objections to the use of animal products)
- Impurity of products (eg non-sterile).

Definitions

Allograft: A tissue from one species that is transplanted into the same species.

Autograft: An organ or tissue transplanted from one part of the patient to replace a part of the body (eg skin graft).

Xenograft: A tissue from one species that is used in a different species.

COMPOSITION

Acellular matrix products differ mainly in the source of cells and tissue materials and methods used during manufacture. A variety of animal- and human-derived products are available:

Products derived from animal sources (xenografts) are developed by harvesting living tissue (eg dermis, small intestine submucosa, pericardium, etc) from various donor animals (eg porcine, equine or bovine) at different stages of development. The tissue materials are subsequently processed to remove the cells (decellularisation), leaving the collagen matrix. Products derived from animal sources may consist of the tissue scaffold only (eg Unite® BioMatrix Collagen Wound Dressing, Synovis) or may be combined with **synthetic materials** to create a **composite** product (eg INTEGRA® Bilayer Matrix Wound Dressing, Integra LifeSciences).

Products derived from human sources, ie donated human cadaver skin (allografts), undergo various processes to remove the cells and deactivate or destroy pathogens (eg AlloDerm®, Lifecell; GraftJacket®, Wright Medical).

It is important that healthcare professionals know the constituents of individual products. They have a duty to explain to patients the nature and purpose of any proposed treatment, along with any risks attached. Where appropriate, informed consent should be obtained[7]

MANUFACTURING PROCESS

Acellular matrices are engineered using a range of chemical and mechanical processes. The ultimate goal is to remove all cellular components using a non-damaging process that maintains the structure and function of the source tissue. The more compatible the final product is to host ECM, the less likely it will elicit an adverse reaction[8]. The steps used in the manufacture of individual products, however, may degrade the structure of the source tissue or strip out growth factors that are bound to ECM components. This may result in rapid degradation and reabsorption of the matrix by the host and lead to scar tissue formation[8]. An adverse reaction

may be indicated by inflammation with accumulation of cells around the edges of the matrix, preventing cellular or vascular infiltration (encapsulation)[8]. The ideal response is minimal inflammation and gradual degradation of the matrix over time with complete integration with the host tissue. How a product is manufactured may therefore be more important to product function than the source, species and location from which the tissue has been taken. Manufacturing may involve the following processes.

Effects of crosslinking on host immune response

A recent study compared five products to assess their host immune response. When not chemically crosslinked, products are rapidly degraded after implantation. Chemical crosslinking provides increased strength and inhibition of degradation. However, degradation of the matrix contributes to tissue remodelling. Further work is needed to explore these biological processes and the variables that affect the host immune response[12].

Crosslinking

The process of stabilising collagen (crosslinking) involves the creation of links between individual strands of collagen. This inhibits degradation of the collagen by proteases (eg matrix metalloproteinases [MMPs]) and prolongs its presence in the wound[5]. The nature of the crosslinking bonds varies according to the processes used. Some traditional methods using chemical (eg aldehydes) or mechanical processes, heat or radiation may allow very little control over the degree of crosslinking. Such processes may produce bonds that are very short and inflexible, which may inhibit cell migration and vascular regeneration, while residual chemicals in the product may produce an inflammatory response causing the matrix to be rapidly reabsorbed[5].

Newer processes have been shown to produce elastic crosslinks that are more pliable and less prone to enzymatic breakdown[4]. Data from animal models also suggest that if a matrix is flexible rather than rigid, cells can migrate more rapidly and proliferate in an organised manner similar to normal tissue regeneration[9].

The type of crosslinking may therefore have a direct effect on product durability in the wound and treatment outcomes[10]. In a published case study, a stabilised xenograft was shown to withstand enzyme activity in a patient with a chronic ulcer and high level of infection and inflammation[10].

In comparison, non-crosslinked products may be degraded by proteases more quickly and replaced by scar tissue[5]. However some next generation products have been shown, when implanted, to be associated with rapid revascularisation without scar tissue formation and a low inflammatory or immunological response, but are not crosslinked[11].

Sterilisation processes

Terminal sterilisation: process of sterilising materials with the product in its final form
Aseptic technique: individual components are sterilised and brought together in a sterile environment

Sterilisation

Sterilisation is important to reduce the risk of disease transmission and is required for FDA clearance of all animal-derived products. However, residual chemicals used during the sterilisation process (eg ethylene oxide [EtO] or gluteraldehyde) may produce an inflammatory response within the host tissue and radiation may damage the matrix, causing it to be broken down and absorbed too quickly[5]. Newer sterilisation methods using a tested liquid chemical (ethylene dichloride [EDC]) are being developed that preserve the collagen structure in the tissue while eliminating the risk of disease[5]. Most human-derived acellular products are aseptically processed and are not terminally sterile.

Preservation and shelf-life

The preservation media or solution used will affect product stability and overall shelf-life. In addition, this may be affected by the regulatory conditions in individual countries as well as the known chemical degradation of the product. Shelf-life may vary from 18 months to five years. Products that have off-the-shelf availability, can be stored at room temperature and require minimal preparation, offer advantages to both clinicians and patients in decreasing operating time and avoiding donor site morbidity[13].

A saline rinse prior to application may help to minimise an inflammatory response in the host tissue by removing any residual chemicals used in the preservation process. Manufacturers' directions for preparation and use should be followed

Understanding mode of action

The mechanisms by which acellular matrices promote wound healing remain to be elucidated and there is ample scope for further research.

It is known from the literature that chronic or hard-to-heal wounds are characterised by a disrupted or damaged ECM that cannot support wound healing. Treatment strategies that are designed to replace the absent or dysfunctional ECM may be beneficial[3]. As a result, there is renewed interest in collagen-based advanced wound care products.

In chronic wounds, there is an excess of MMPs and reduced growth factor activity. Together these result in the degradation of the ECM. For wound healing to occur the balance between protease and growth factor activity needs to be adjusted[3]. Research has demonstrated that topically applied collagen-based products can initiate wound healing by binding to and inactivating harmful proteases, while encouraging angiogenesis and formation of granulation tissue[14].

Current information about the mode of action of acellular matrices is largely based on preclinical data, mainly from research focusing on a porcine-derived small intestinal submucosa (SIS) wound matrix. These data show that matrices may:

- Act as a scaffold to support cell ingrowth and granulation tissue formation[15]
- Have receptors that permit fibroblasts to attach to the scaffold[16]
- Stimulate angiogenesis[17]
- Act as a chemoattractant for endothelial cells[18]
- Contain/protect growth factors[19].

Biological modulator

A material or substance derived from biological or synthetic sources that influence biological processes such as wound healing.

When used as an implant, the acellular matrix appears to be fully incorporated into the wound. However, when used in a chronic wound, the matrix is eventually displaced and is not fully incorporated. As such, the role of acellular matrices in chronic wounds is not fully understood. It has been suggested that they act as a biological cover that modulates the wound environment to promote normal wound healing[20,21] (Figure 1).

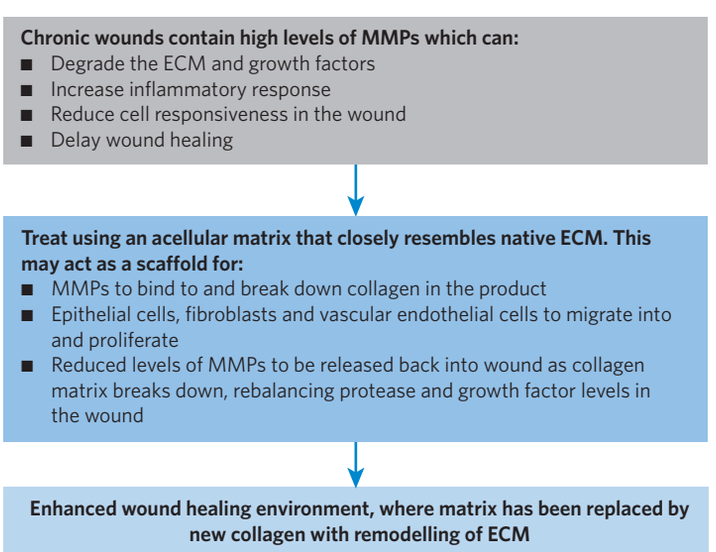

Figure 1 | Suggested mode of action of collagen-based acellular matrix products[20,21] Note: the optimal response will be achieved using a matrix that is closest to the tissue it is replacing.

In chronic wounds, an acellular matrix wound product should be in as complete contact as possible with the wound surface to be effective

Rationale for use

Currently available acellular wound matrix products are listed in the Appendix, page 13. It should be noted that this information is taken directly from the manufacturers' websites, and anyone using these products should always consult the specific manufacturer's instructions, taking into consideration important factors, such as allergy and wound infection.

All products should be used in conjunction with manufacturers' instructions and/or recommendations

Acellular matices should be considered in wounds that are unresponsive to traditional wound management modalities or present as a complex surgical wound. Factors to consider will be dependent on the wound type, underlying aetiology, patient suitability and treatment goal. In a non-healing chronic wound (eg diabetic foot ulcer), for example, an acellular matrix may be selected to replace the damaged ECM, fill the defect and optimise the wound environment for healing.

The use of different products is influenced by a number of external factors, including availability, single or multiple applications, ease of use and cost/reimbursement. In addition, it is important to consider the clinical setting in which the matrix is to be applied (eg in the operating theatre or outpatient clinic) as well as the expertise and level of training required (Table 2).

Wound bed preparation: TIME acronym, from[23]

T = Tissue management (eg debridement of non-viable tissue)
I = Inflammation and infection control
M = Moisture balance
E = Epithelial (edge) advancement.

APPLYING THE MATRIX

The following should be considered prior to application:

- Protocol for first application (eg wound bed preparation/TIME[22,23])
- Methods of attachment (ie sutures, Steri-strips or staples)
- The use of appropriate dressings to cover the matrix.

Table 2 | 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 social and cultural issues ■ **Exclude ischaemia/infection and uncontrolled bacterial burden/allergy** ■ **Address underlying aetiology to maximise healing potential** (eg control exudate/bacterial burden; ensure adequate offloading/compression/ pressure reduction; reduce steroids/inflammation) ■ **Perform adequate and appropriate wound bed preparation** (eg debridement) ■ **Ensure patient concordance** (eg those with diabetic foot problems, those requiring compression)	■ **Prevent/minimise product contamination and bacterial overgrowth** – Ensure correct handling of product according to manufacturer's instructions – Avoid intraoperative recontamination (eg change gloves between procedures) ■ **Secure matrix** using staples; Steri-strips (eg 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 (see also Use in large wounds p8) ■ **Ensure appropriate wound dressing selection** – The matrix should be covered with a non-adherent primary dressing, bolster and/or padding (eg in moderate to heavily exudating wound) – Use a secondary dressing to hold the matrix and wound dressings in place – Consider the use of an appropriate topical antimicrobial ■ **Consider fenestrated (meshed) product, eg:** – when the wound has a large surface area or is very deep, requiring negative pressure wound therapy (NPWT) – when it is necessary for fluid to drain, especially if heavily exudating	■ **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 a maximum of 14 days – Steri-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 (eg patients with diabetic foot ulcers need complete offloading 1 week post-application)

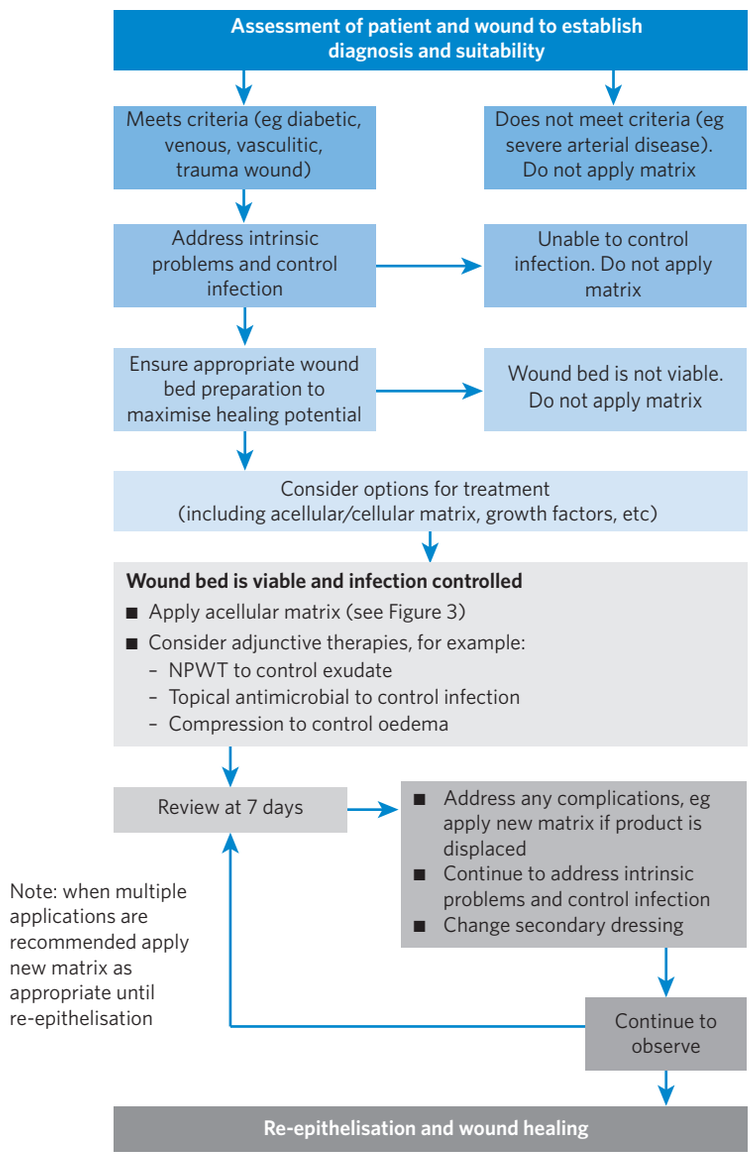

Figure 2 | Algorithm for application of acellular matrices in a chronic wound Previous studies have shown that reduction in the area of the chronic wound during the first four weeks of treatment is a predictor of complete healing at 12 weeks[24]. If no improvement is seen at this time, there should be further evaluation of the patient and current treatment strategy.

Figure 3 | Application of the matrix. It is important to carefully contour the graft and ensure it is in contact with the wound bed.

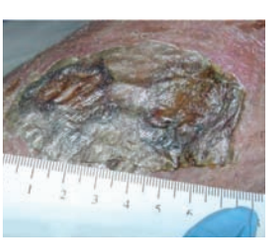

Figure 4 | Three weeks post application. The product is slowly detaching as the underlying wound surface progresses towards closure. Note the typical staining with silver dressing use.

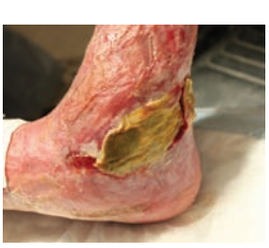

Figure 5 | Three weeks post application. The matrix appears macerated and is disassociating from the wound. Wound odour would also indicate infection.

The landmarks towards achieving a successful outcome include:

- No clinical signs of infection or bioburden, eg purulence, sliminess, unexpected malodour (Note: some products that contain keratin produce an odour when wet)
- Formation of granulation tissue, reduction in wound size and re-epithelisation
- Removal of the method of attachment (ie staples, sutures or Steri-strips).

When the matrix is still present in the wound bed, it may produce a different appearance to normal granulation (eg the tissue may not have the typical bright red appearance; if silver dressings are used, it may look dry, silver/black in colour with no signs of infection). It is important to know what the wound should look like when it is reviewed post-application and to be able to identify when the wound is **progressing normally** (Figure 4) and when **further intervention is needed** (Figure 5).

Complications

The actions below are recommended should the following complications occur:

- **Infection:** remove acellular matrix, control the infection and apply a new matrix following adequate wound bed preparation.
- **Detached or displaced matrix:** remove matrix and assess to establish the reasons for failure. Perform adequate wound bed preparation before applying a new matrix.
- **Excessive inflammation/allergic reaction:** remove and do not reapply a new matrix.
- **Failure to heal/lack of effect:** reassess the wound and the patient. When the wound is not healing the matrix may be displaced and there may be an increase in wound size.

A significant increase in pain after application may indicate a reaction to the product or infection

Use in large/exudating wounds

When the wound is very large, multiple sheets may be needed to cover the entire wound bed. There should be slight overlap with the wound edges and the matrix may need to be secured to reduce risk of displacement. Many chronic wounds are often accompanied by infection and excessive amounts of exudate, making matrix fixation difficult[25]. A fenestrated (meshed) acellular matrix can be used to allow the fluid to drain from the wound. The level of exudate will affect the choice of secondary dressing for an optimal moist wound environment[26]. 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.

Use with adjunctive therapies

The use of an acellular matrix combined with other treatments may permit progression to the next stage. For example, negative pressure wound therapy (NPWT) may help to control excessive exudate and hold the matrix in place to maximise contact with the wound bed[27]. When using NPWT a fenestrated (meshed) matrix should be application and a non-adhesive contact layer must be placed between the matrix and the foam dressing.

It is important to know whether other products can be used successfully in combination with the matrix

Achieving optimal outcomes

Appropriate and careful product selection is critical to achieve optimal patient outcomes. The decision to use a particular product may be based on a number of structural, biological and clinical factors (Table 3).

Table 3 | The ideal properties of an acellular matrix for hard-to-heal wounds

Structural	Biological	Clinical	
		Process	Outcome
■ Closely resembles native ECM (eg retains natural architecture and key components for wound healing) ■ Minimal storage/ preparation needed and long shelf-life ■ Terminally sterile (ie cannot transmit viral or other agents)	■ Provides barrier to infection (i.e. innate immunity) ■ Resistant to proteolytic enzyme degradation ■ Promotes optimal cell activity for rapid revascularisation and tissue regeneration	■ Single or infrequent application ■ Easy to handle/apply and secure ■ Cost-effective/ reimburseable ■ Consistent with standard of care ■ Minimal education and training to use ■ Different delivery methods available	■ No host immune response ■ Improves patient comfort/reduces pain ■ Reduction in wound size / complete closure ■ Reduced or no scarring and good skin durability ■ Low complication rate

Evaluating the clinical evidence for use

Box 1: **Wound Healing Society evidence levels**

Level I: Meta-analysis of multiple randomised clinical trials (RCTs) or at least two RCTs supporting the intervention. Another route would be multiple laboratory or animal experiments with at least two significant clinical series supporting the laboratory results.

Level II: At least one RCT and at least significant clinical series or expert opinion papers with literature reviews supporting the intervention. Experimental evidence that is quite convincing, but not yet supported by adequate human experience, is included.

Level III: Suggestive data of proof-of-principle, but lacking sufficient evidence such as meta-analysis, RCT, or multiple clinical series.

The Wound Healing Society guidelines are available at: http://www.woundheal.org

Acellular matrices have been used extensively in burns, when the primary goal is to restore function[28] and have an expanding role in the treatment of chronic wounds[21]. There is also an increasing range of acellular products for use as surgical implants in abdominal[29], plastic and reconstructive surgery.

Understanding the clinical advantages and limitations of individual products is crucial to effective use and patient outcomes. However, there is currently limited published data that reaches a sufficient level of evidence (see Box 1: Wound Healing Society guidelines for the treatment of chronic wounds) and few comparisons of products in different indications, in particular chronic and problematic wounds that are hard to heal.

HARD-TO-HEAL WOUNDS

The most common types of wound that fit into this category are:

- Diabetic foot ulcers
- Lower extremity venous ulcers
- Ulcers of mixed aetiology
- Pressure ulcers.

Appropriate treatment using an acellular matrix may result in faster or more complete healing than standard treatment in hard-to-heal wounds[30]. This is further supported by a retrospective evaluation of the use of an acellular collagen product derived from equine pericaridum in chronic full-thickness wounds of varying aetiology. Despite being unresponsive to previous treatment approaches, all wounds achieved complete closure without complications[21].

The low complication rate supports the theory that acellular matrices are less likely to cause an immunological response than cellular products that contain cross-species cellular components. Both acellular xenografts and allografts appear to modulate the wound environment by reducing the inflammatory activity to stimulate tissue regeneration[21]. However, more extensive and controlled clinical studies are needed to provide a better understanding of their mechanisms of action and role in the treatment of hard-to-heal wounds.

Diabetic foot ulcers (DFUs)

A number of studies have been performed in patients with diabetes and lower extremity ulcers (foot, ankle or leg) using porcine collagen derived from small intestine submucosa (SIS) and a human-derived dermal matrix (Table 4). A more recent prospective series has studied the use of equine pericardium in neuropathic diabetic foot ulcers (DFUs)[31]. These studies suggest acellular matrices may promote wound healing when compared to conventional treatments. However, there are no large-scale studies and it is difficult to make direct comparisons of the results. All studies have shown that these products are safe and can achieve complete wound closure in both partial and full-thickness wounds, including when bone and/or tendon are exposed (Table 4). In addition, they may be used with split-thickness skin grafts to achieve complete closure in deep wounds[32]. Long-term studies are needed to assess the quality of the regenerated tissue and re-ulceration rate in all wound types[33].

Prior to application, appropriate debridement of non-viable tissue is vital for optimal wound healing. For deep wounds that are irregular, or demonstrate tunnels or undermining, a flowable tissue matrix (micronised) can be applied with a syringe into tunnels or extensions[34]. When using a sheet-form matrix, this will need to be cut to size so that it overlaps the wound margins. In addition, NPWT may be used in combination with an acellular matrix to promote healing in the management of non-healing diabetic foot ulcers[27]. Appropriate offloading is also necessary to achieve wound healing[30].

Table 4 | Summary of evidence for diabetic foot wounds

Product used	Wound type	Publication	Type of study	Outcomes
Human-derived allograft (GraftJacket®) vs hydrogel wound dressing (Curasol®)	Diabetic lower extremity wounds	Brigido SA et al *Orthopedics* 2004; 27 (1 Suppl): s145-49	Prospective randomised single blind, pilot (n=40)	All patients were treated with sharp debridement. 20 patients were given one application of the allograft. At 4 weeks, there was a statistically significant reduction in ulcer size in the allograft treated group compared with the debridement only group (controls); wound closure was 73% vs 34%. At 12 weeks, 85% of patients in the allograft group were healed compared with only 5% in controls.
Porcine small intestine submucosa xenograft (Oasis®) vs becaplermin wound gel (Regranex®)	DFUs (chronic, full-thickness)	Niezgoda et al. *Adv Skin Wound Care* 2005; 18(5): 258-66	Prospective, randomised controlled, multicentre (n=73)	At 12 weeks 49% (18/37) of patients receiving SIS xenograft were healed vs 28% (10/36) of patients receiving daily treatment of the gel (p=0.055). Subgroup analysis showed that in patients with wounds on the plantar surface, 53% of SIS xenograft patients healed compared with 14% of gel-treated patients. No significant difference was found in mean time to healing between treatment groups (p=0.245).
Human-derived allograft (GraftJacket®) + moist wound therapy	DFUs (neuropathic)	Martin BR et al. *Int Wound J* 2005; 2(2): 161-65	Prospective case series (n=17)	82.4% (14) of wounds, measuring mean 8.9±3.2cm^2 healed in the 20-week evaluation period.
Silicone membrane/ reconstituted bovine collagen matrix (INTEGRA™ Bilayer Matrix) and split-thickness skin grafts (STSG) to replace silicone layer	DFUs (with exposed bone and tendon)	Silverstein G. *J Foot Ankle Surg* 2006; 45(1):28-33	Retrospective case series review (n=5)	All 5 patients with diabetes had extensive soft tissue defects. Following surgical debridement a non-fenestrated version was applied. Dressing changes were carried out weekly until appropriate to proceed to STSG (usually 4–6 weeks). Despite 2 grafts failing, all wounds healed completely and patients were able to remain ambulatory.
Human-derived allograft (GraftJacket®) vs hydrogel wound dressing (Curasol®)	Diabetic lower extremity wounds	Brigido SA. *Int Wound J* 2006; 3(3):181-87	Prospective, randomised controlled (n=28)	All patients were treated with sharp debridement. At week 16: 12/14 allograft treatment group healed vs 4/14 in control group. Ulcer area, depth, volume and number of ulcer healed achieved statistical significance in favour of the allograft treatment arm (p≤0.001).
Human-derived allograft (GraftJacket®) + mineral oil soaked compression bandage	Diabetic lower extremity wounds (including wounds penetrating to bone or joint)	Winters CL et al. *Adv Skin Wound Care* 2008: 21(8): 375-81	Retrospective multicentre (n=75)	Total 100 wounds of which 91 (91%) in 67 patients healed. Patients treated with multiple modalities to attain wound closure. No significant differences were observed for matrix incorporation, 100% granulation and complete healing. Mean time to complete healing was 13.8 weeks.
Human-derived allograft (micronised) (GraftJacket® Xpress Scaffold)	DFUs with sinus tract	Brigido SA et al. *Foot Ankle Spec* 2009; 2(2):67-72	Retrospective series (n=12)	At 12 weeks 10/12 patients achieved complete healing. Average time to healing was 8.5 weeks.
Human-derived allograft (GraftJacket®) + silver-based non-adherent dressing vs standard of care	DFUs	Reyzelman et al. *Int Wound J* 2009; 6(3): 196-208	Prospective randomised controlled multicentre (n=86)	12 week study in which 47 patients were randomised to allograft group and 39 patients to control group. Complete healing was 69.6% (p=0.0289) and mean healing time 5.7 weeks for allograft group; 46.2% and 6.8 weeks for control group.
Silicone membrane/ reconstituted bovine collagen (INTEGRA™ Bilayer Matrix)	Infected DFU with exposed bone and tendon	Clerici et al. *Int J Lower Extrem Wounds* 2009; 8(4)209-12	Case report	62 year old female patient with an acute deep foot infection. Following surgical debridement, NPWT and amputation of the distal metatarsal, a collagen bilayered matrix was applied. At 8 weeks there was complete healing. A 3-month review revealed no stump complications with preservation of maximal foot length.
Equine pericardium xenograft (Unite®)	DFUs (neuropathic)	Fleischill et al. *J Am Pod Med* 2009; 99(4): 301-05	Prospective pilot case study	23 consecutive patients with 34 foot wounds. Surgical debridement prior to application of xenograft. At time of xenograft removal (mean 2.9 weeks), 30 (94%) wounds had improved. 15 wounds (47%) healed at 12 weeks.
Bovine-derived xenograft (MATRIDERM®)	DFU	Cervelli et al. *Int Wound J* 2010; 7(4):291-96	Prospective case report	A 65 year old male patient with DFU. Following treatment with antibiotics and surgical debridement, xenograft applied. There was immediate pain reduction; complete wound healing was achieved, which was associated with an excellent aesthetic result.
Silicone membrane/ reconstituted bovine collagen (INTEGRA™ Bilayer Matrix)	DFUs (lower extremity salvage)	Iorio M et al. *Plast Reconstr Surg* 2010; 8 [Epub ahead of print]	Retrospective review (n=105 patients with 121 wounds)	Collagen bilayer matrix found to be a viable option when used for reconstruction and stable closure in patients at low risk of amputation. For patients at high-risk of amputation, the rate of salvage may not be improved with the use of a collagen bilayer matrix.

NB: Studies listed in date order

Venous leg ulcers

A systematic review of randomised controlled trials (RCTs) of a variety of wound dressings for chronic venous ulcer[35] was conducted to determine whether more modern advanced wound dressings further improve the healing of venous ulcers over simple wound dressings. This found that of the 20 RCTs identified, five showed significance for ulcer healing, including a study by Mostow and colleagues using a porcine collagen matrix derived from small intestine submucosa (SIS)[36] (Table 5).

Mixed arterial/venous and vasculitic ulcers

Ulcers related to numerous underlying aetiologies may present particular challenges for clinicians and are costly to treat. These wounds are often slow to heal and associated with high levels of pain, inflammation and tissue necrosis[10]. The use of an acellular matrix has been shown to be effective in this subset of patients with lower extremity ulcers and can help to reduce the level of pain and increase quality of life[10,37] (Table 6).

Pressure ulcers

There is currently limited evidence on the use of acellular matrices in patients with pressure ulcers. Typically, non-healing pressure ulcers may present as partial or full-thickness wounds with or without exposed bone and tendon. In wounds with undermined areas a micronised injectable acellular matrix may provide an alternative to surgical treatment of pressure ulcers[38].

Table 5 | Summary of evidence for venous leg ulcers

Product used	Wound type	Publication	Type of study	Outcomes
Porcine small intestine submucosa (SIS) xenograft (Oasis®) + compression therapy vs compression therapy alone (standard of care)	VLUs	Demling et al. *Wounds* 2004; 16(1): 18-22	Interim analysis. Prospective randomised controlled multicentre (n=84)	At 12 weeks 71% of ulcers healed with SIS xenograft (applied weekly) compared to 46% with the compression therapy only group (p=0.018).
Porcine small intestine submucosa (SIS) xenograft (Oasis®) + compression therapy vs compression therapy alone	VLUs (> 1 month duration)	Mostow et al. *J Vasc Surg* 2005; 41(5): 837-43	Prospective, randomised controlled multicentre (n=120 with at least 1 VLU)	At 12 weeks 55% of the wounds in the SIS xenograft group were healed compared with 34% in the standard care group (p=0.0196). There were no recurrences in the six-month follow in the SIS treated group.

Table 6 | Summary of evidence for mixed arterial/venous ulcers and other aetiologies

Product used	Wound type	Publication	Type of study	Outcomes
Porcine small intestine submucosa (SIS) xenograft (Oasis®) vs hyaluronic acid (HA) biomaterial (Hyaloskin)	Mixed arterial/ venous ulcers	Romanelli et al. *Int Wound J* 2007; 4(1): 3-7	Randomised prospective single centre (n=54)	50 patients completed the study. At 16 weeks, complete wound closure achieved in 21 patients (82.6%) in SIS xenograft group compared to HA group. Patients treated with SIS xenograft reported significantly greater comfort (p<0.01), less pain (p<0.05) and less frequent dressing changes (p<0.05) compared to HA treated group.
Equine pericardium xenograft (Unite®) vs human acellular dermal matrix (GraftJacket®)	Vasculitic ulcer	Mulder G, Lee D. *Int J Lower Extremity Wounds* 2009; 8(3): 157-61	Case report	56 year old man with bilateral foot ulcers associated with severe cryoglobulinaemia and vasculitis. Surgical debridement and application of xenograft to all lateral and right medial wounds; half of left medial covered with allograft. Pain reduction at 1 week. At week 4, all xenograft sites improving. All xenograft-treated wounds healed by week 7. Further 3 months to heal left medial wound.
Equine pericardium (Unite®) plus injectable collagen glycosaminoglycan matrix (INTEGRA™ Flowable Matrix) for largest defect and use of a silicone free collagen-glycosaminoglycan product (INTEGRA™ Wound Dressing) for areas of exposed tendon	Lower extremity ulcers associated with scleroderma and Raynaud's Disease	Mulder G, Lee D. *Wounds* 2009; 21(11):297-301	Case report	39 year old man with bilateral full thickness ulcers associated with scleroderma. Surgical debridement and application of xenograft (plus combination therapy where applicable). Dressings left intact for 1 week. Patient had significantly less pain. At 12 days all wounds were progressing toward closure. At 8 weeks following surgery all but the largest of wounds had fully closed without complications

NB: Studies listed in date order

FUTURE RESEARCH

There is a need for comparisons of clinical effectiveness and cost to enable appropriate use of products and to challenge current gold standard treatments.

Wounds that fail to heal can impact negatively on the patient's quality of life and have important cost implications for health services. Where wounds are less likely to heal with routine standard of care, there may be a role for advanced wound therapies such as acellular matrices. Potential benefits and low complication rates of these products, which when combined with the cost advantages of a single or infrequent application, minimal preparation/storage and long shelf-life, may make them a viable treatment option for patients with chronic ulcers.

Achieving the appropriate level of evidence

Future data to be sought from:

- Prospective, multicentre, randomised controlled trials
- Comparative studies between 2 or more products
- Long-term follow up studies
- Economic studies
- Effectiveness and efficacy studies (life experience)

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APPENDIX | Acellular wound matrix products available in US and/or Europe

Company/manufacturer	Product	Source	Indicated for		Shelf-Life*/Storage	Crosslinking	Sterilisation process
			Acute wounds	*Chronic wounds*			
Xenograft Collagen Grafts							
Acell Inc/Medline	MatriStem™ Wound Care Matrix	Porcine urinary bladder matrix	+	+	2 years Room temperature	None	Electron beam irradiation
AM Scientifics/Brennen Medical	EZ-DERM™	Porcine dermis	+	+	Room temperature	Aldehyde	Sterile (method undocumented)
Cook Medical	Biodesign® (Surgisis®) Hernia Graft	Porcine small intestine submucosa (SIS)	+	–	18 months Room temperature	None	Ethylene oxide
Covidien	Permacol	Porcine dermis	+	–	Room temperature	HDMI	Gamma irradiation
Davol Inc/Bard	CollaMend* Implant	Porcine dermis	+	–	Room temperature	EDC	Ethylene oxide
Davol Inc/Bard	XenMatrix™ Surgical Graft	Porcine dermis	+	–	Room temperature	None	Electron beam irradiation
Dr. Suwelack Skin & Health Care AG/ Eurosurgical	MATRIDERM®	Bovine dermis	+	+	5 years Room temperature	None	Gamma irradiation
Dr. Suwelack Skin & Health Care AG/Medline	Puracol® Plus Microscaffold Collagen *(Puracol® Plus Ag)*	Bovine collagen *(plus antimicrobial Ag)*	+	+	3 years Room temperature	None	Supplied sterile (method undocumented)
Euroresearch	BIOPAD® Collagen Wound Dressing *Note: Biospray also available for minor burns and superficial wounds*	Equine flexor tendon	+	+	Store in a dry place away from heat sources	None	Gamma irradiation
Healthpoint Ltd/ Cook Biotech, Inc	OASIS® Wound Matrix	Porcine small intestine submucosa (SIS)	+	+	2 years Room temperature	None	Ethylene oxide
Integra LifeSciences	INTEGRA™ Matrix Wound Dressing	Bovine tendon collagen and glycosaminoglycan	+	+	2 years Room temperature	Glutaraldehyde	Ethylene oxide
LifeCell	Strattice™ Reconstructive Tissue Matrix	Porcine dermis	+	–	Room temperature	None	Electron beam irradiation
Mesynthes	Endoform™ Dermal Template	Propria-submucosa layers of ovine forestomach	+	+	Room temperature	None	Ethylene oxide
Synovis Orthopedic and Woundcare, Inc.	Unite® Biomatrix Collagen Wound Dressing	Equine pericardium	+	+	3 years Room temperature	EDC	EDC
Synovis Orthopedic and Woundcare, Inc.	Veritas® Collagen Matrix	Bovine pericardium	+	–	Controlled room temperature	None	Sodium hydroxide
TEI Biosciences	PriMatrix™ Dermal Repair Scaffold	Fetal bovine dermis	+	+	3 years Room temperature	None	Ethylene oxide
TEI Biosciences	SurgiMend®/SurgiMend® Inguinal Hernia Repair Matrix	Fetal bovine dermis	+	–	3 years Room temperature	None	Ethylene oxide
Allografts							
ADI Medical/HANS Biomed	SureDerm™ Acellular Dermal Graft	Human dermis	+	–	2 years Refrigeration necessary	None	Supplied sterile
Davol Inc/Bard	AlloMax™ Surgical Graft	Human dermis	+	–	No refrigeration required	None	Tutoplast® process and low-dose gamma irradiation
LifeCell	AlloDerm® Regenerative Tissue Matrix *Also available as a micronised version (Cymetra®)*	Human dermis	+	–	2 years Freeze dried, refrigerate upon receipt	None	Aseptically processed
Mentor	NeoForm™	Human dermis	+	–	5 years Room temperature	None	Tutoplast® process and low-dose gamma irradiation
Musculoskeletal Transplant Foundation/ Ethicon	FlexHD® Acellular Hydrated Dermis	Human dermis	+	–	Ready to use Room temperature	None	Aseptically processed (passes the US Pharmacopeia Standard 71 for sterility)
Musculoskeletal Transplant Foundation/ Synthes CMF	DermaMatrix Acellular Dermis	Human dermis	+	–	3 years Freeze dried Room temperature	None	Aseptically processed (passes the US Pharmacopeia Standard 71 for sterility)
Wright Medical Technology, Inc	GraftJacket® Regenerative Tissue Matrix Ulcer Repair *Also available as a micronised version (GraftJacket® Xpress® Flowable Soft-Tissue Scaffold)*	Human dermis	+	+	2 years Freeze dried, refrigerate upon receipt	None	Aseptically processed
Synthetic Acellular Dermal Replacements							
Integra LifeSciences	INTEGRA™ Bilayer Matrix Wound Dressing	Bi-layered: bovine tendon collagen and glycosaminoglycan with a polysiloxane (silicone) membrane	+	+	2 years Room temperature	Aqueous glutaraldehyde	Irradiation
Integra LifeSciences	INTEGRA™ Dermal Regeneration Template	Bi-layered: bovine tendon collagen and glycosaminoglycan with a polysiloxane (silicone) membrane	+	–	2 years Store flat and refrigerate	Glutaraldehyde	Gamma irradiation
*All information has been checked against manufacturers' websites. Please refer to individual product literature for use. *Shelf-life is cited when known.*							

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