Rethinking the Reconstructive Ladder:

Innovation in Autologous Cutaneous Multicellular Units for DFU Reconstruction

Supported by an educational grant from PolarityBio

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Faculty Disclosures

- **Erwin A. Kruger, MD**
  Advisory Board: PolarityBio
- **Robert Kirsner, MD, PhD**
  Consultant: Cell Constructs Inc.
- **Jason R. Hanft, DPM**
  Nothing to disclose in relation to this activity

Disclosures

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Learning Objectives

- Assess gaps in the reconstructive ladder for diabetic foot ulcers (DFUs), including limitations of flaps and grafts on the plantar surface, to improve durable wound closure
- Evaluate where autologous cutaneous multicellular therapy fits within the reconstructive ladder for DFUs, including its role in bridging gaps between traditional grafting and advanced reconstruction to promote tissue regeneration and wound closure
- Evaluate the scientific rationale and clinical evidence supporting autologous cutaneous multicellular units (ACMU), including Phase 2 outcomes demonstrating improved wound closure, alongside emerging late-breaking Phase 3 data supporting BLA submission in DFUs
- Evaluate clinical outcomes associated with ACMU through case-based analysis

DFU = diabetic foot ulcer; ACMU = autologous cutaneous multicellular units; BLA = Biologics License Application.

Autologous Cutaneous Multicellular Units (ACMU) are available for investigational use only.

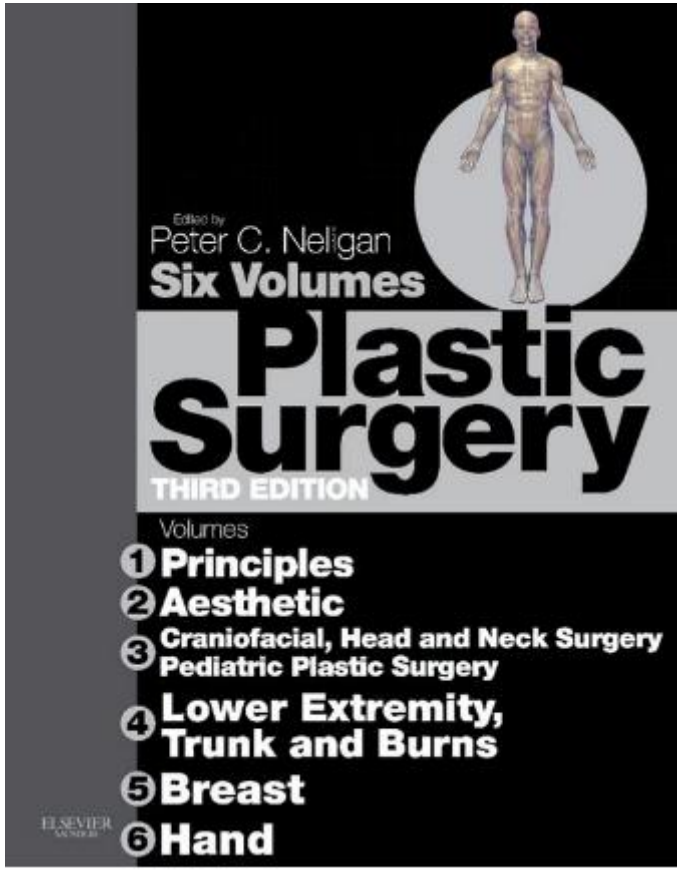
Rethinking the Reconstructive Ladder: A Novel Paradigm for Chronic Wounds

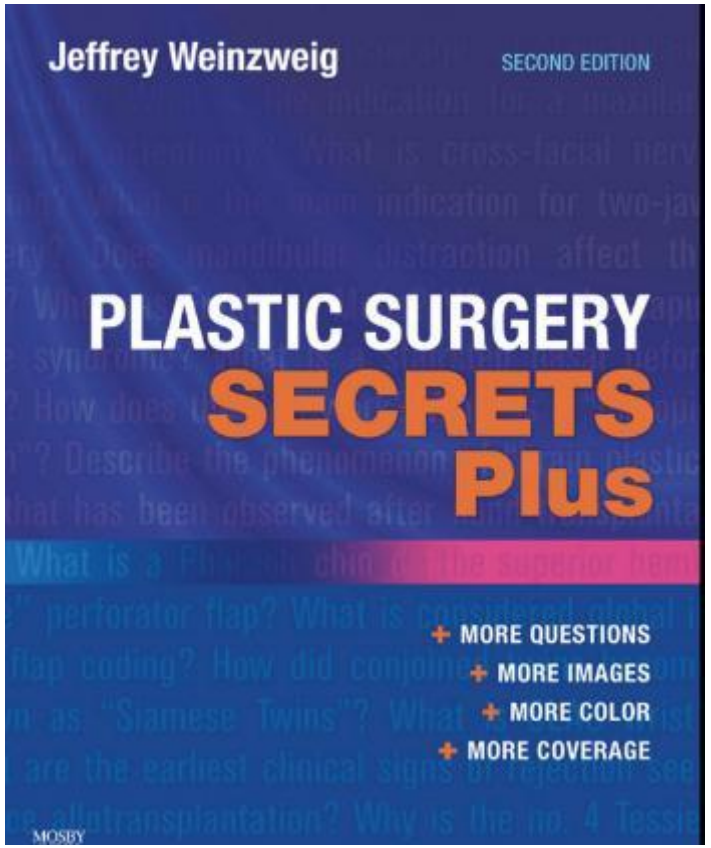
Erwin A. Kruger, MD

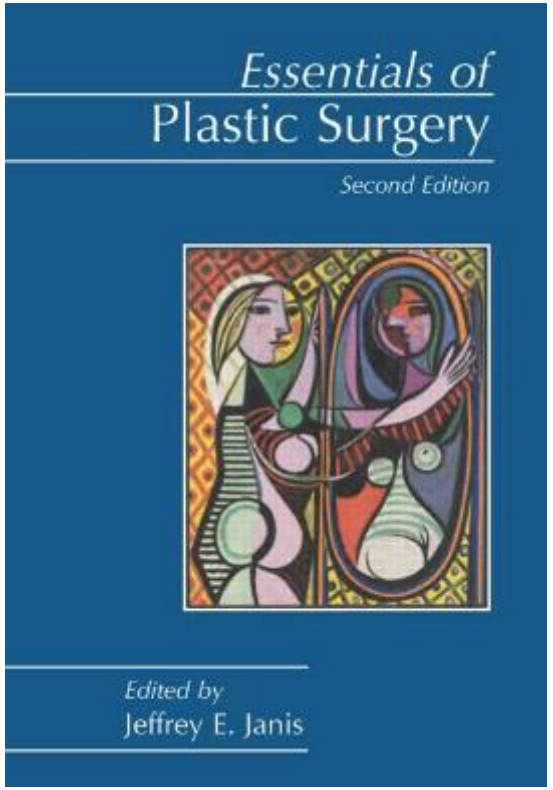
Plastic & Reconstructive Surgery

Phoenix, AZ

Plastic and Reconstructive Surgery







Plastic and Reconstructive Surgery

- In plastic surgery, the word ***plastic*** has nothing to do with synthetic plastic materials

- It comes from the Greek word ***plastikos*** (**πλαστικός**) meaning **“capable of being shaped, molded, or formed”**

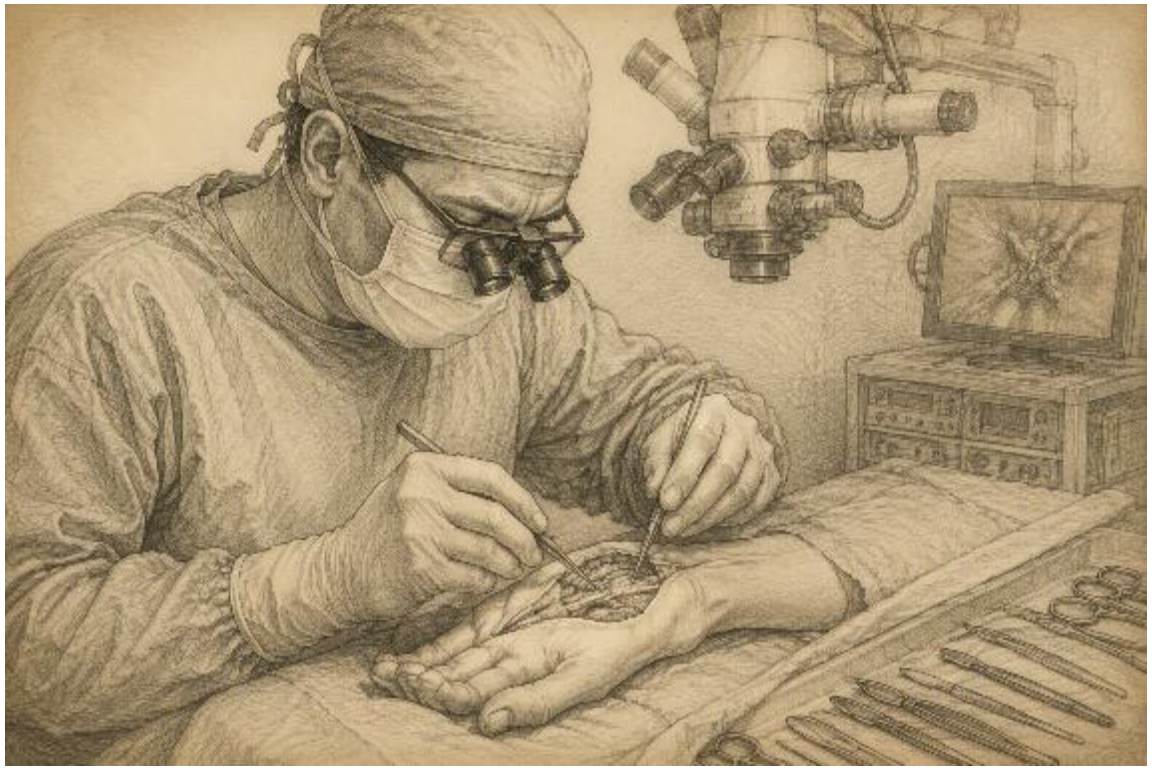
- The field of **plastic surgery** could be described as the **discipline of surgical reshaping and reconstruction of tissues with the purpose of restoring form and function**



Ancient Greek *sculptor*

Plastic and Reconstructive Surgery

- In plastic surgery, the word ***plastic*** has nothing to do with synthetic plastic materials
- It comes from the Greek word ***plastikos*** (**πλαστικός**) meaning **“capable of being shaped, molded, or formed”**
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Modern *plastic* surgeon

Plastic and Reconstructive Surgery — Complex Wounds



Hospital-Based Wound/Plastic Surgery Clinic

Surgical Wound Complications (SSI, dehiscence, infected mesh, seroma)	Hematomas	Abscesses
Traumatic Wounds	Necrotizing Fasciitis	Fournier's Gangrene
Necrotizing STIs	Infected Pressure Sores	Flaring Hidradenitis Suppurativa
Infected Vascular/DM Wounds	Acute Burns	Skin Tears (traumatic, surgical drapes)

SSI = surgical site infection; STI = soft tissue infection.

Hospital-Based Wound/Plastic Surgery Clinic

Diabetic Foot Ulcer (DFU)	Neuropathic Foot Ulcers
Vascular Wounds	Atypical Wounds (eg, vasculitis, vasculopathies)
Radiation Ulcers	Pyoderma Gangrenosum (PG)
Hidradenitis Suppurativa (HS)	Chronic Surgical Wound Complications

HS = hidradenitis suppurativa; PG = pyoderma gangrenosum.

General Management of Complex Wounds

- *Algorithmic* approach
- Full history and physical exam
- Wound evaluation
- Labs
- Imaging/diagnostic tests
- Assessment
- Surgical/therapeutic plan

The Reconstructive Ladder



Stage 4 PI



Exposed biologic mesh after liver transplant



DFU



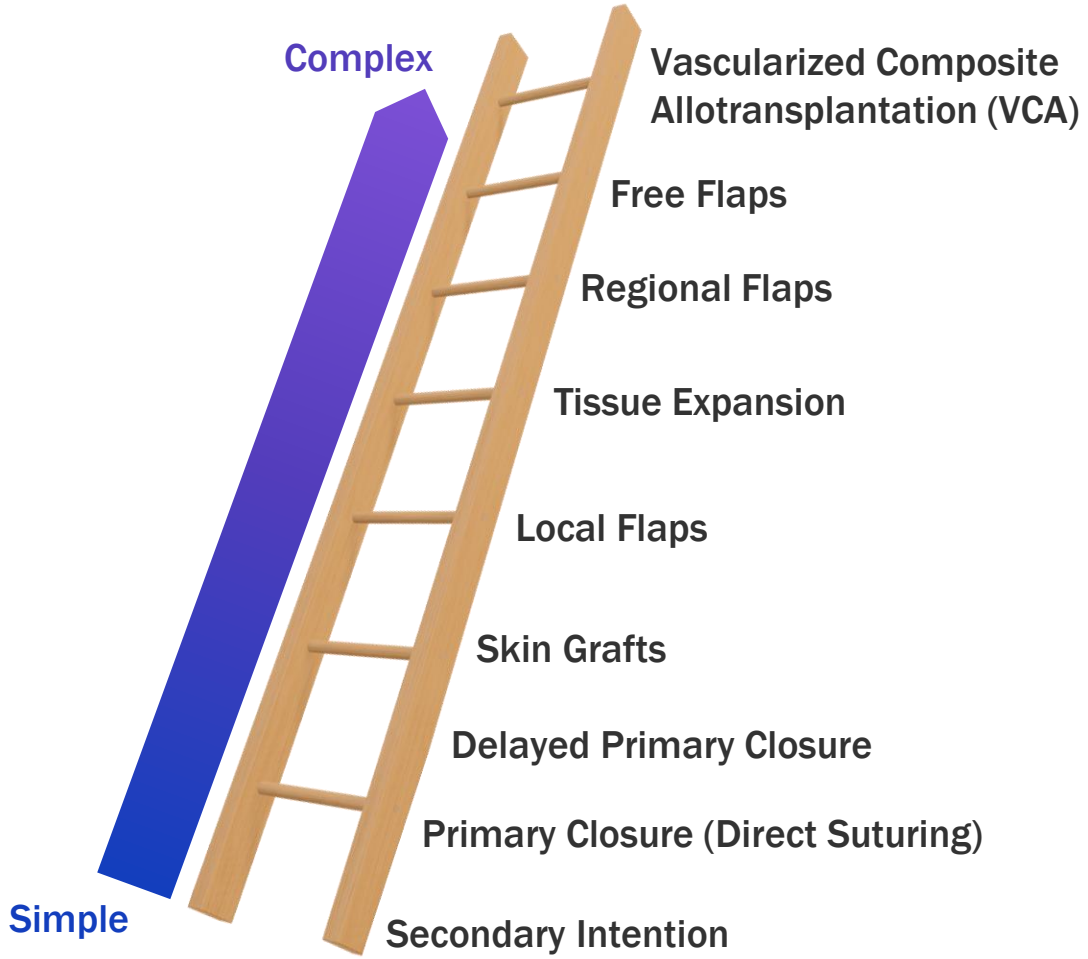
VLU

PI = pressure injury; VLU = venous leg ulcer.

Understanding the Reconstructive Ladder

- The ***reconstructive ladder*** is a **conceptual framework** that organizes wound closure strategies from **simplest to most complex;** you "climb" as needed

- The concept is widely attributed to the textbook tradition of plastic and reconstructive surgery, such as **Mathes and Nahai's** *Reconstructive Surgery: Principles, Anatomy, and Technique* (1997)



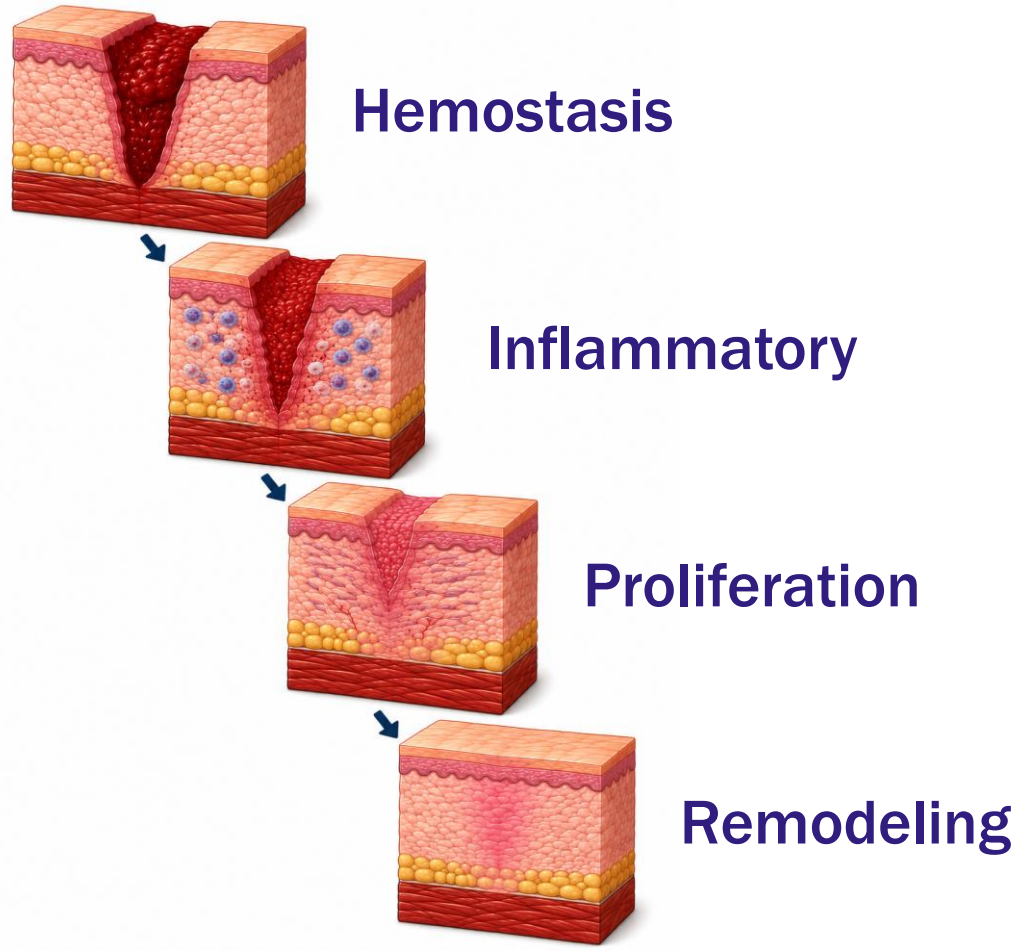
VCA = vascularized composite allotransplantation.

Mathes SJ, Nahai F. *Reconstructive Surgery: Principles, Anatomy & Technique*. New York: Churchill Livingstone; 1997

The Floor: Healing by Secondary Intention

Wound left open to heal by itself

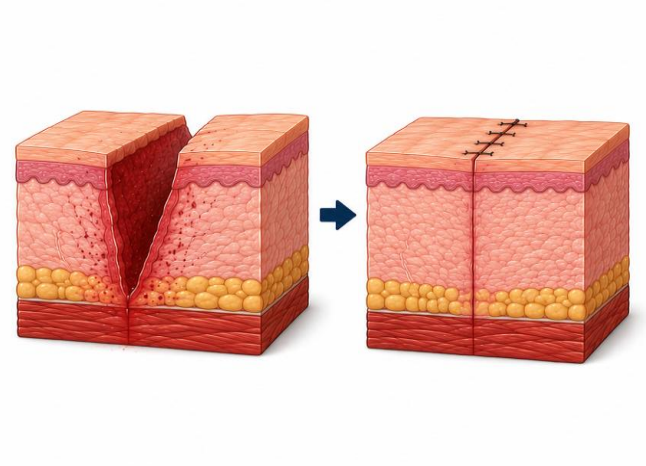
- Favored in patients with comorbidities at risk for general anesthesia
- Favored in wounds that can heal quickly on their own
- Can be unpredictable in chronic wounds

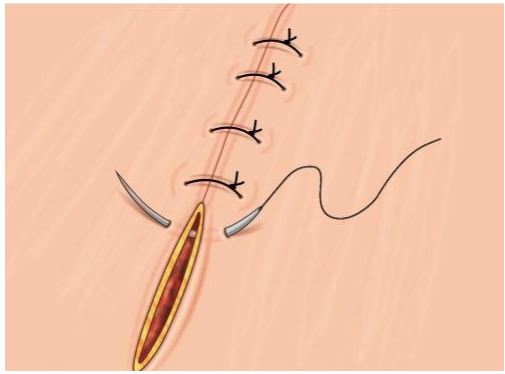


Primary Closure

Direct closure of the wound

- Favored for clean wounds with low tension
- Can include layered closure and/or undermining to relieve tension





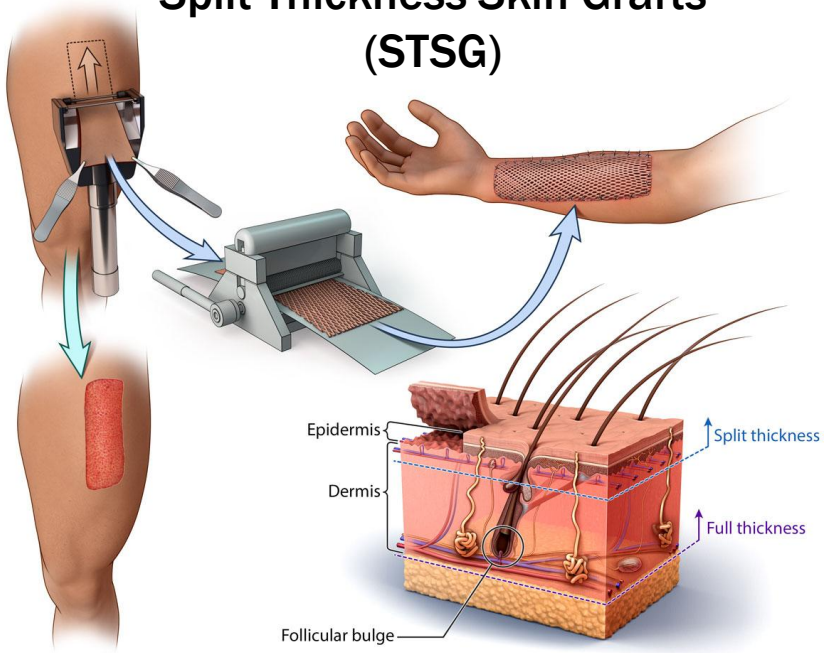




Skin Grafts

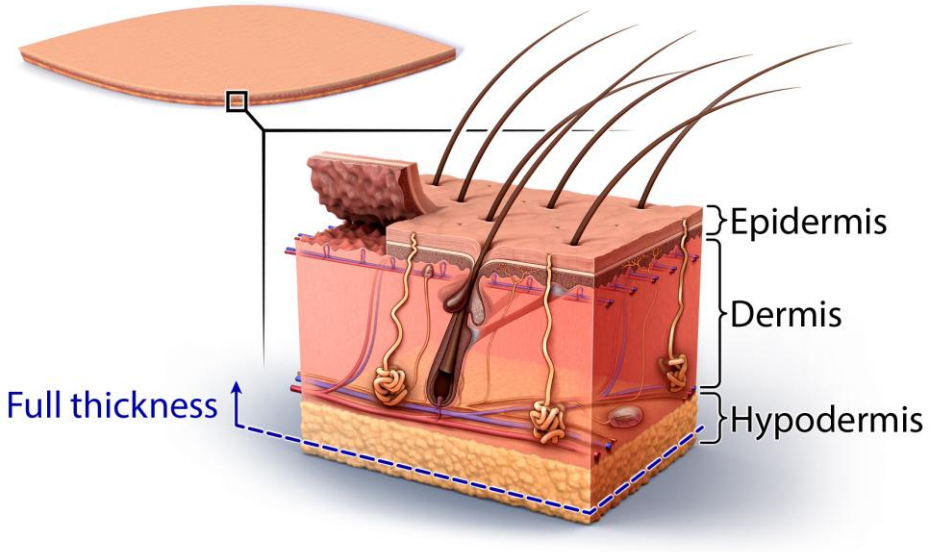
Transfer of skin from one part of the body to another without a vascular supply

Split-Thickness Skin Grafts (STSG)



- Favored in large wounds with a vascular wound bed not over functional or cosmetic regions
- Patient must be able to tolerate general anesthesia

Full-Thickness Skin Grafts



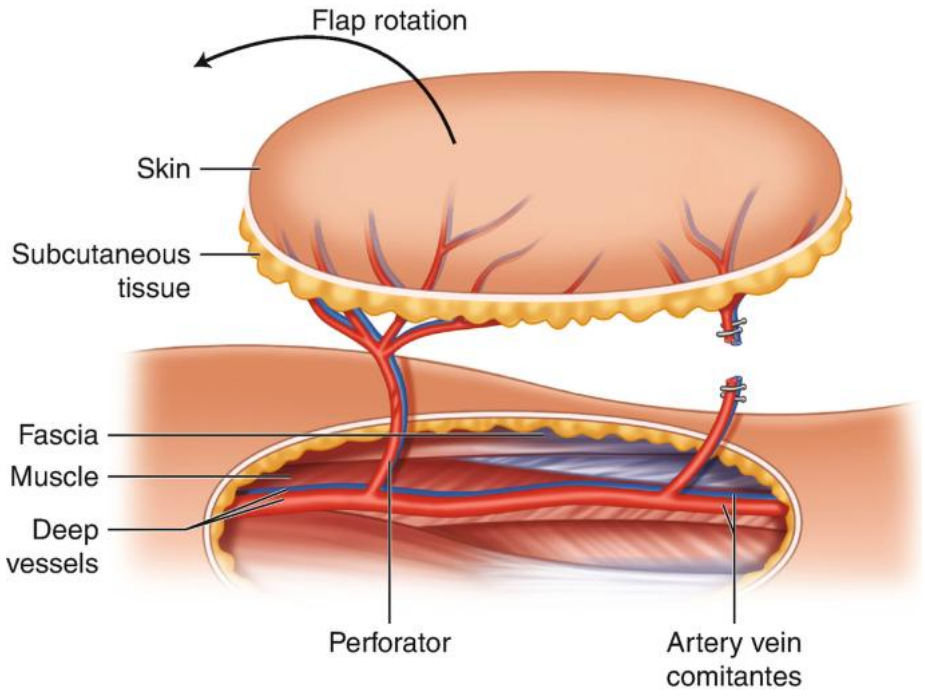
- Favored in smaller reconstruction where functional and aesthetic outcomes are critical (ie, hand and face)
- Wound bed must be highly vascular to ensure graft take

STSG = split-thickness skin graft.

Regional Flaps

Tissue transfer attached to a known blood supply

- Used for large defects that can't be closed locally in a region with a known, reliable flap
- Flaps become favored when avascular structures prevent skin grafting or tissue bulk is required for volume/function

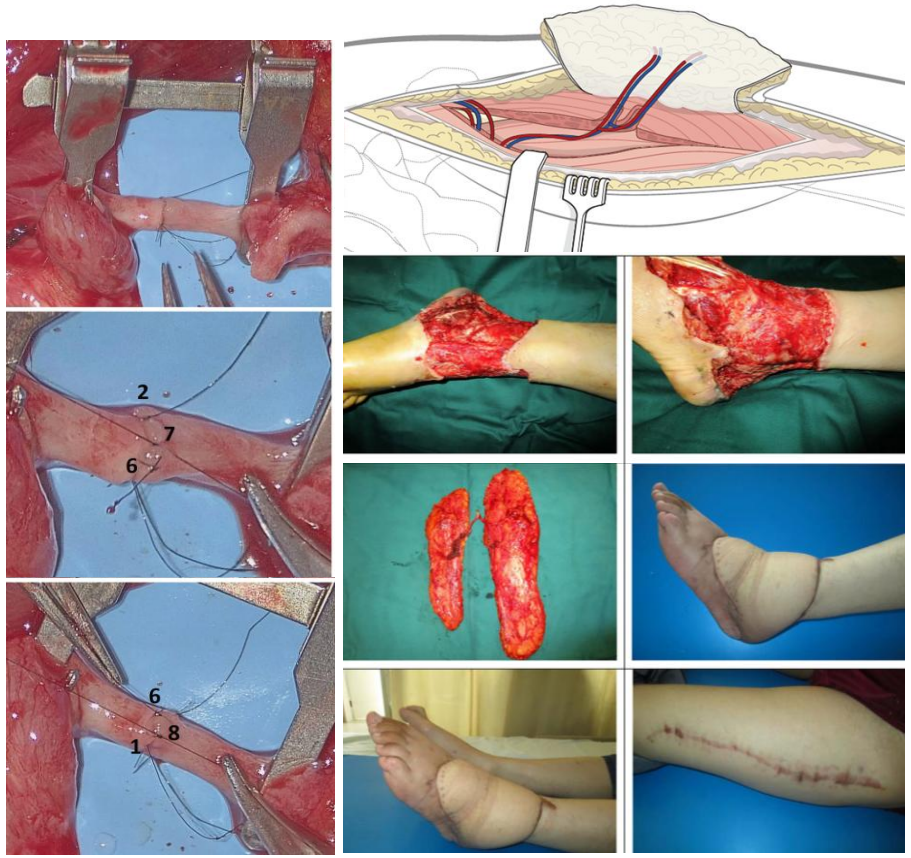




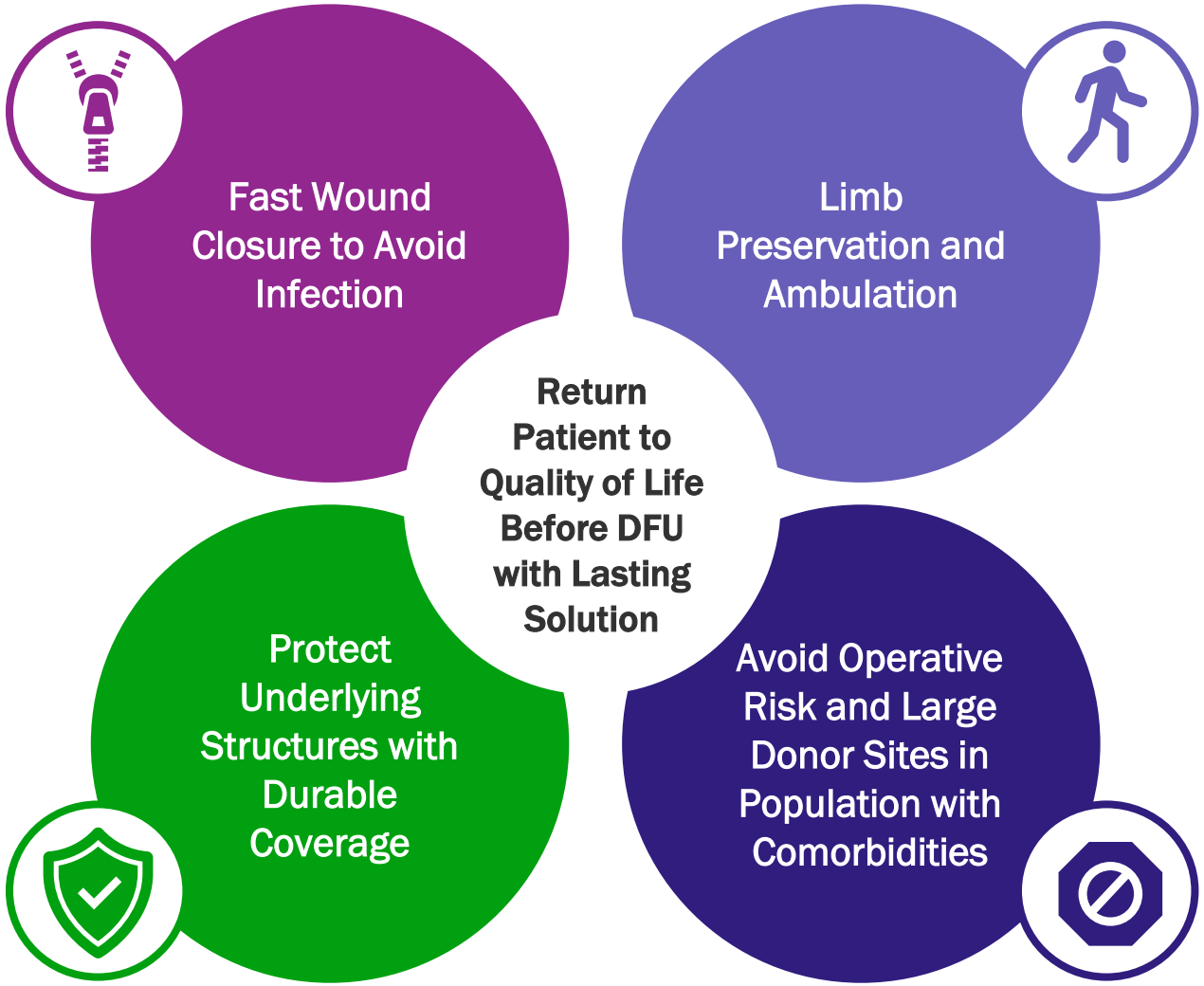
Free Flaps

Free tissue transfer with blood supply re-established through microvascular anastomosis

- Used for large, complex defects without adequate regional options
- Commonly used for complex wounds on the lower third of the leg and foot, head and neck, and breast reconstruction

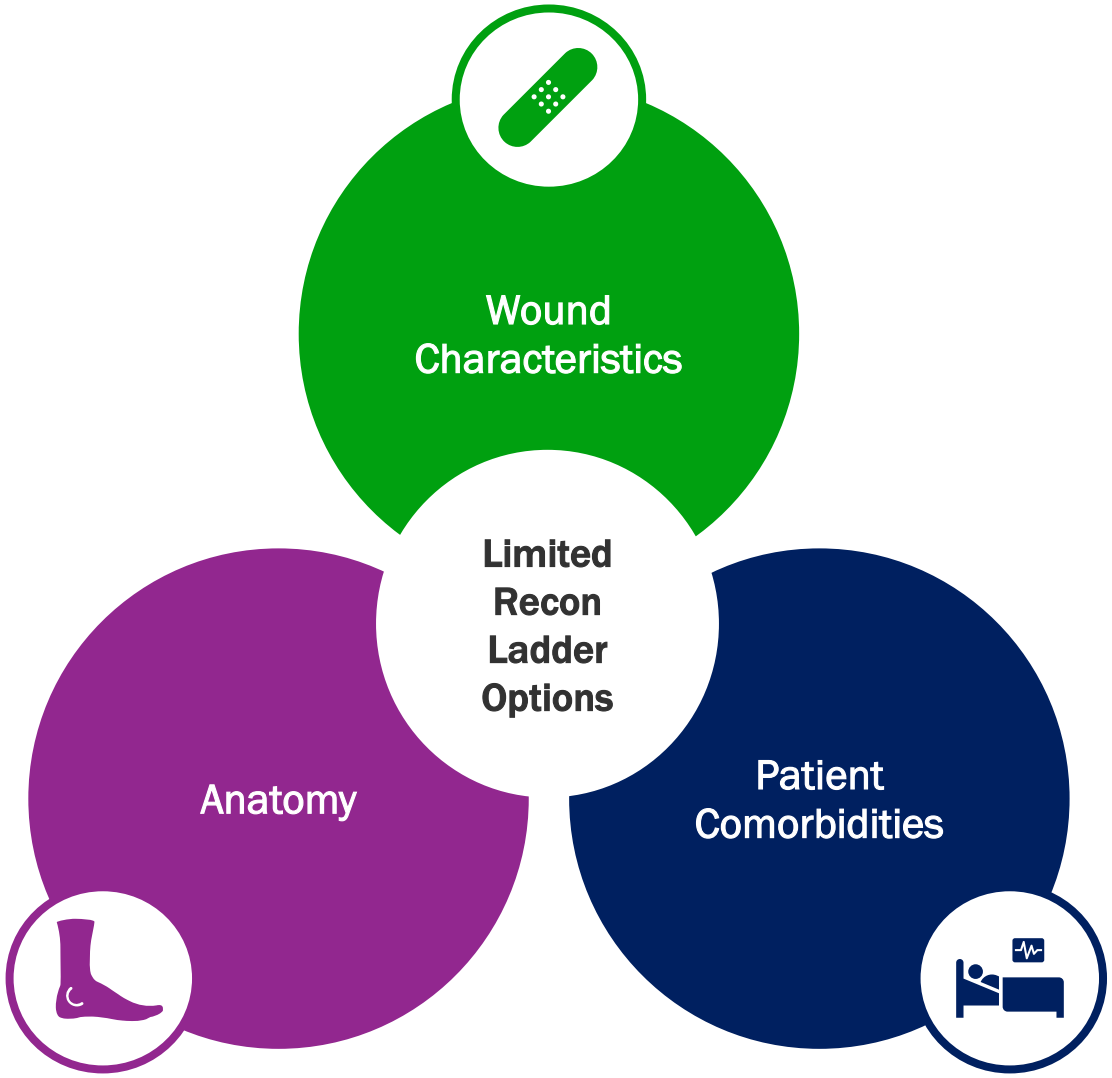


Goals of DFU Reconstruction





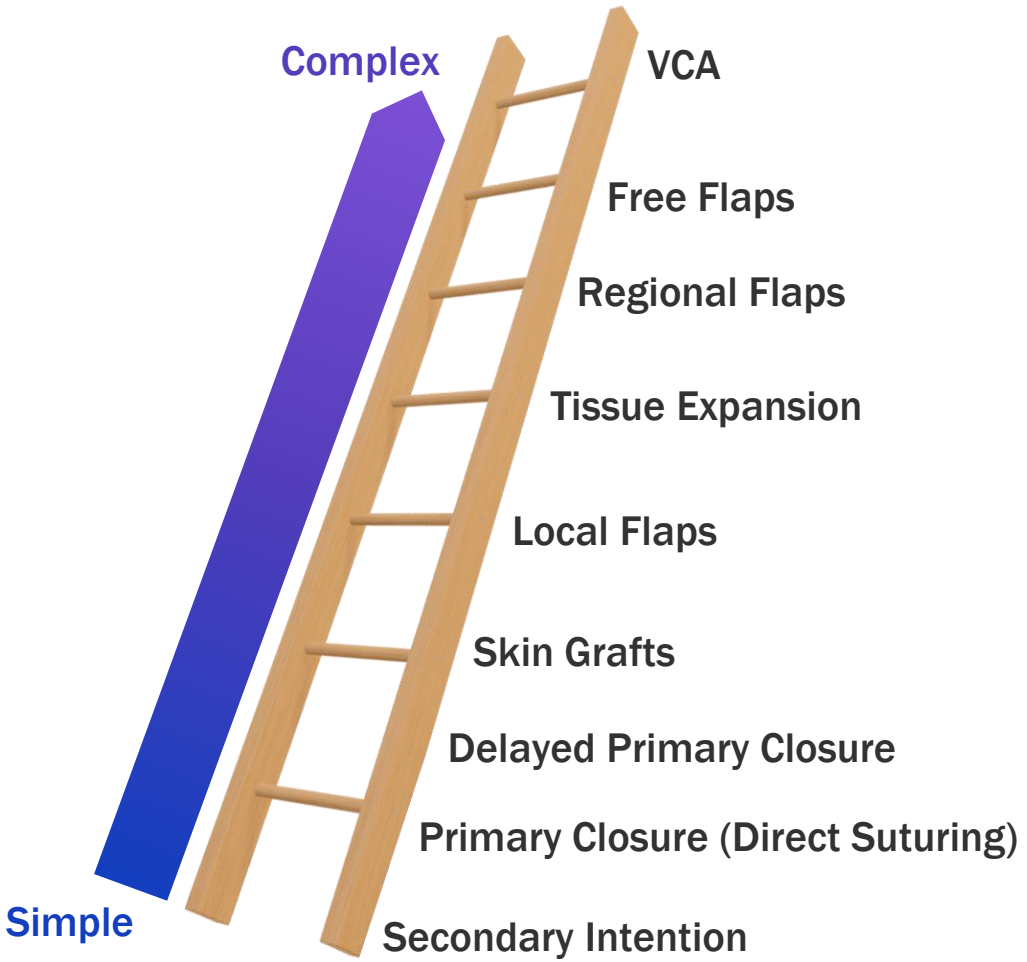
Unique Challenges of DFU Reconstruction



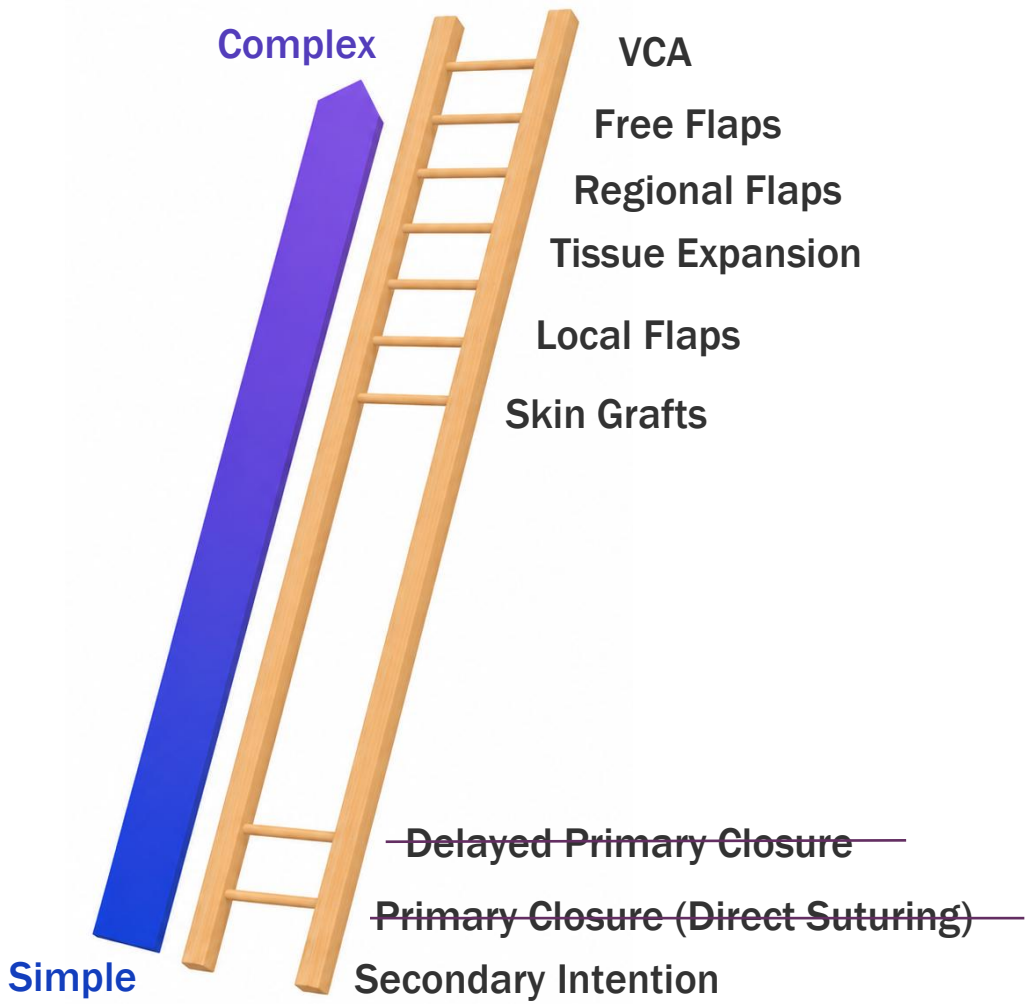


A Large Gap Emerges in the DFU Reconstructive Ladder

Traditional Recon Ladder



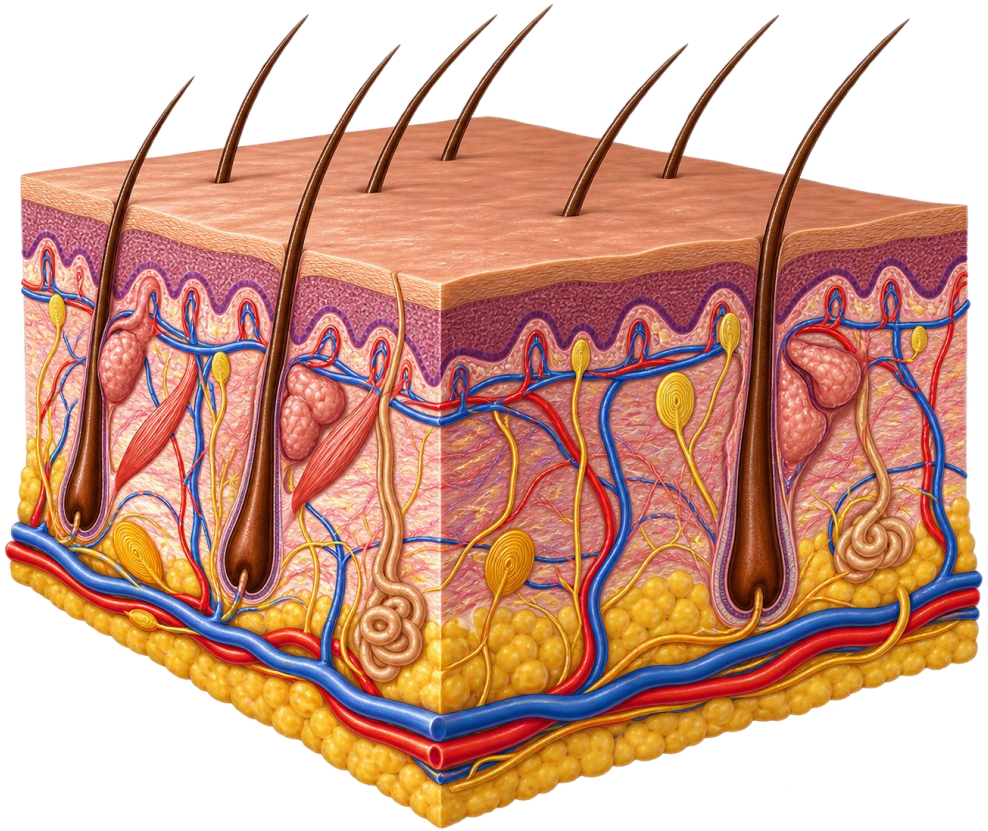
DFU Recon Ladder



Goals of Therapy to Fill the Gap in the DFU Recon Ladder

Design Goals for DFU Therapy

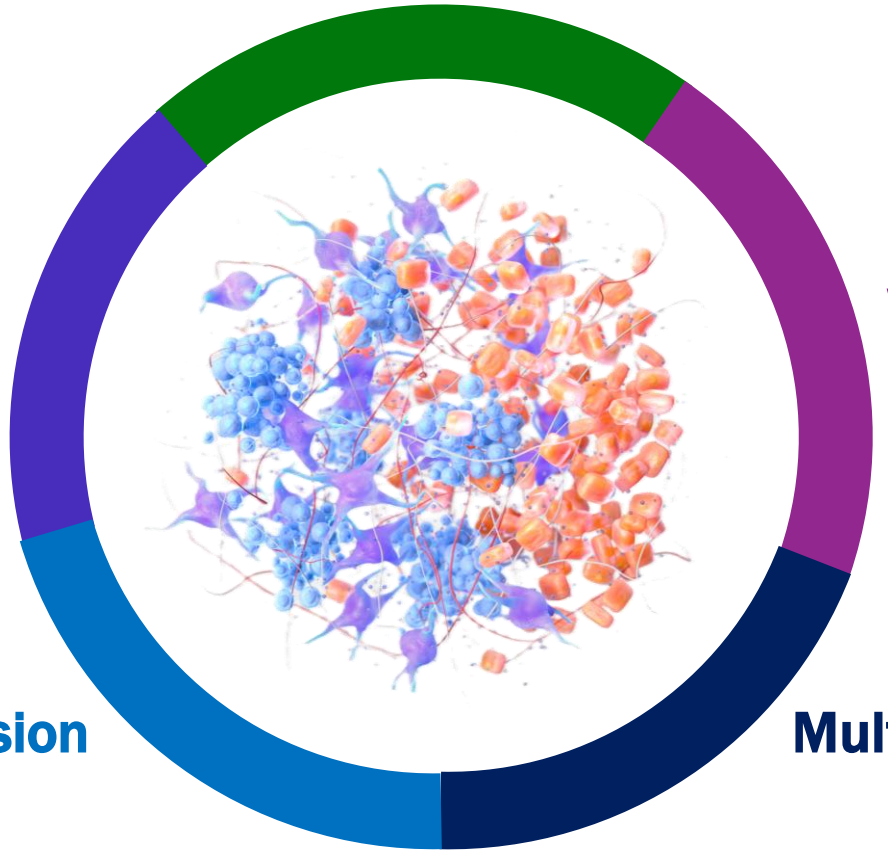
- Epithelium that prevents bacterial penetration and retains moisture
- Dermis that is durable, yet flexible
- Dermal appendages that facilitate moisture and thermal regulation and sensation
- Able to withstand austere wound environments
- Outpatient treatment



ACMU Design Characteristics

Autologous Skin

Designed to Include All Skin Cell Populations



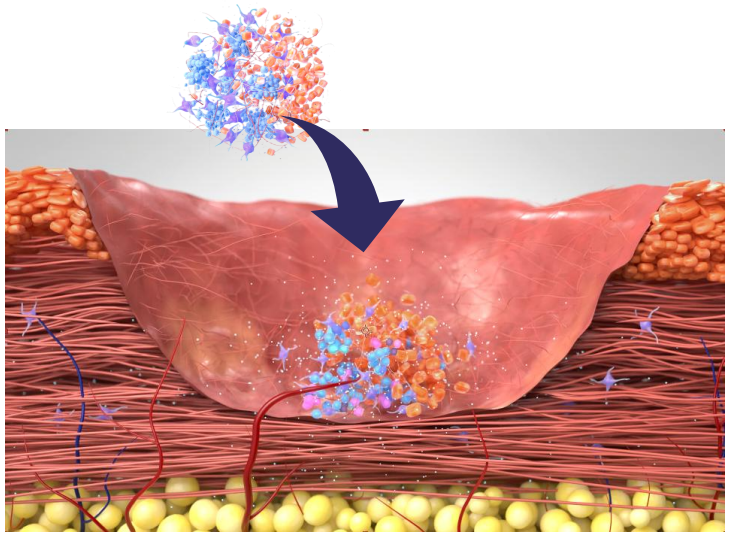
Designed to Activate Wound Healing Pathways

Size Designed for Nutrient & Waste Diffusion

Organoid-Like Multicellular Structure

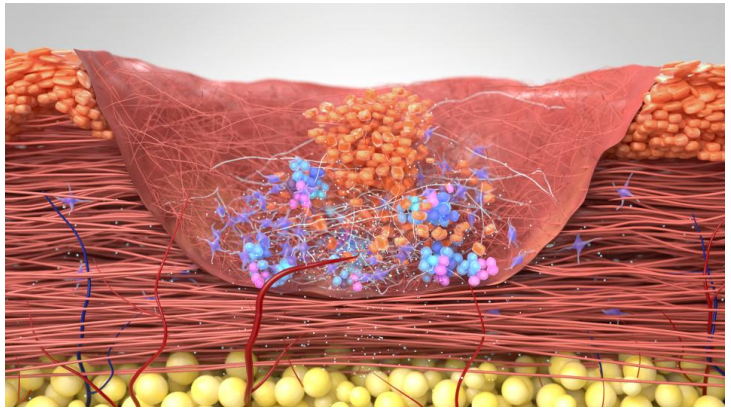
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Proposed Mechanism of Action for ACMU



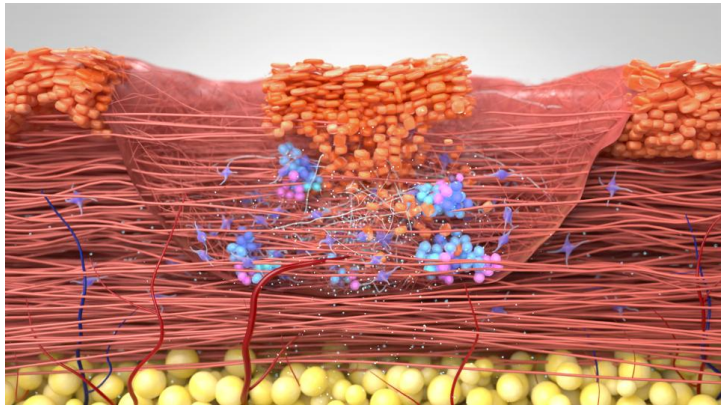
1

Engraftment



2

Proliferation & Migration



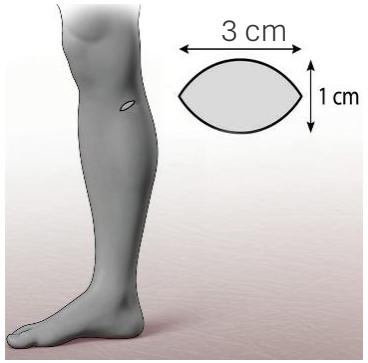
3

Release of Cytokines & Growth Factors

Autologous Cutaneous Multicellular Units (ACMU) are available for investigational use only.

ACMU Workflow

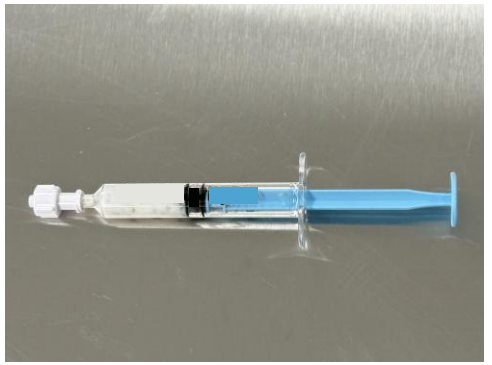
Workflow for ACMU in late-stage clinical development for the treatment of DFUs



Full-Thickness Skin Harvest by Provider



Skin Harvest Shipped to Manufacturing Facility



ACMU Returned to Provider

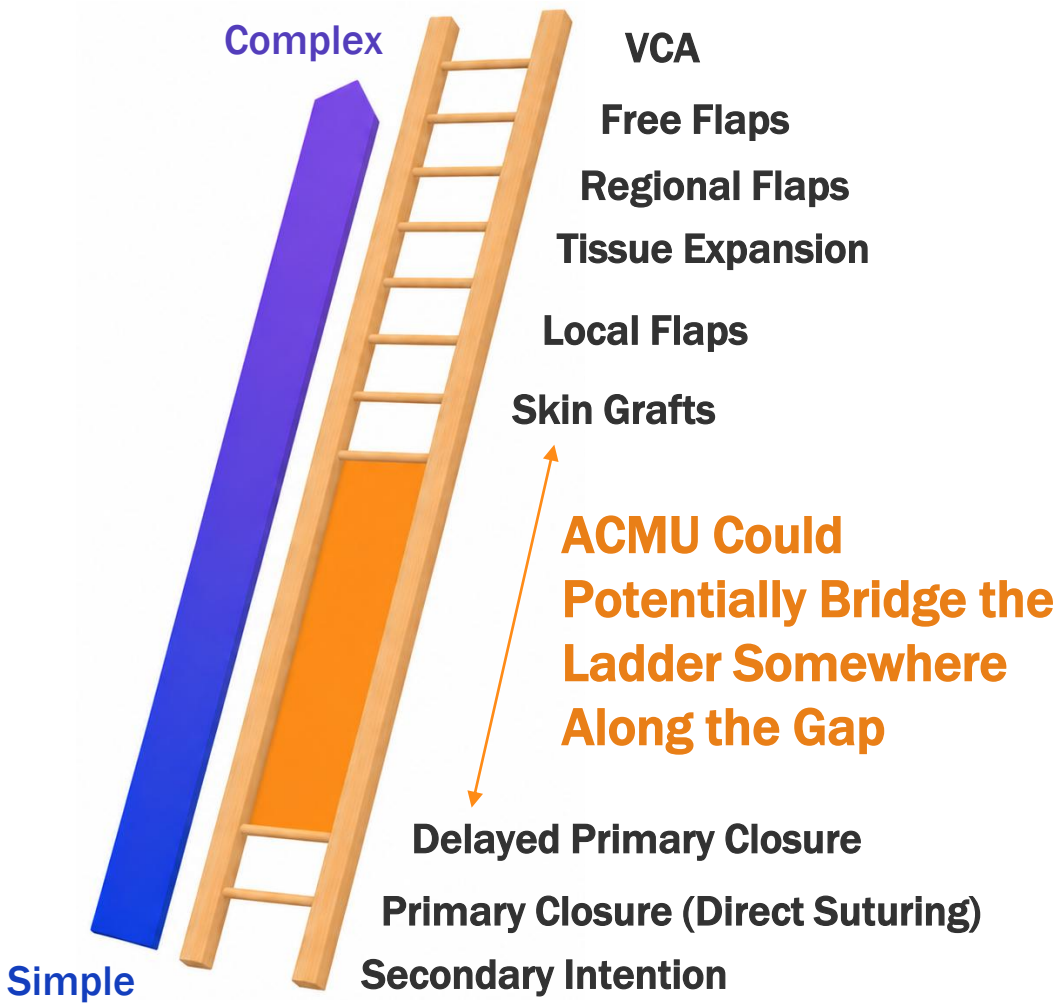


ACMU Applied to Wound

Autologous Cutaneous Multicellular Units (ACMU) are available for investigational use only.

ACMU Could Potentially Fit in the DFU Recon Ladder Gap

DFU Recon Ladder



What it means on the ladder

- On the traditional reconstructive ladder
- Above delayed primary closure
- Below skin grafts
- If approved, ACMU could potentially bring the autologous reconstructive ladder to office and outpatient settings for DFUs

Autologous Cutaneous Multicellular Units (ACMU) are available for investigational use only.

Summary

- The ***reconstructive ladder*** is a useful paradigm for an **algorithmic** approach to acute and chronic wounds, but the ladder is not the same for every wound type

- **DFUs** pose a difficult challenge for traditional reconstructive options (skin grafts, flaps) due to the microvascular, sensory, and mechanical needs for durable closure – creating a treatment gap in the DFU reconstructive ladder

- **ACMU,** if approved for treatment of DFUs, may potentially fit within the gap on the DFU reconstructive ladder by offering an autologous reconstructive option in the outpatient/office setting

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References and Further Reading

1. Mathes SJ, Nahai F. *Reconstructive Surgery: Principles, Anatomy & Technique*. New York: Churchill Livingstone; 1997
2. Buchanan P, Kung T, Cederna P. Evidence-Based Medicine: Wound Closure. *Plast Reconstr Surg.* 2016;138(3S):257S-270S.
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4. Janis JE, Kwon RK, Attinger CE. The new reconstructive ladder: modifications to the traditional model. *Plast Reconstr Surg.* 2011;127(Suppl 1):205S-212S. Erratum in: *Plast Reconstr Surg*. 2020;146(5):1212.
5. De Francesco F, Zingaretti N, Parodi PC, Riccio M. The Evolution of Current Concept of the Reconstructive Ladder in Plastic Surgery: The Emerging Role of Translational Medicine. *Cells*. 2023;12(21):2567.
6. Grosu-Bularda A, Hodea FV, Cretu A, Lita FF, Bordeanu-Diaconescu EM, Vancea CV, Lascar I, Popescu SA. Reconstructive Paradigms: A Problem-Solving Approach in Complex Tissue Defects. *J Clin Med*. 2024;13(6):1728.

The Scientific Rationale and Clinical Evidence Supporting ACMU

Robert Kirsner, MD, PhD

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Chief of Dermatology, University of Miami Hospital
Harvey Blank Chair in Dermatology, Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery,
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PHASE 2 TRIAL DATA

Multicenter RCT of ACMU in Non-Healing Wagner 1 DFUs

ACMU + SOC vs SOC alone

SOC = standard of care.

STUDY OVERVIEW

Phase 2 ACMU Trial Design

Objective:

Prospective, multicenter RCT evaluating ACMU + SOC vs SOC alone in the treatment of DFUs

Primary Endpoint:

Percentage of wounds closed by 12 wks defined as complete epithelialization without drainage or dressing requirements confirmed at 2 consecutive study visits 2 wks apart

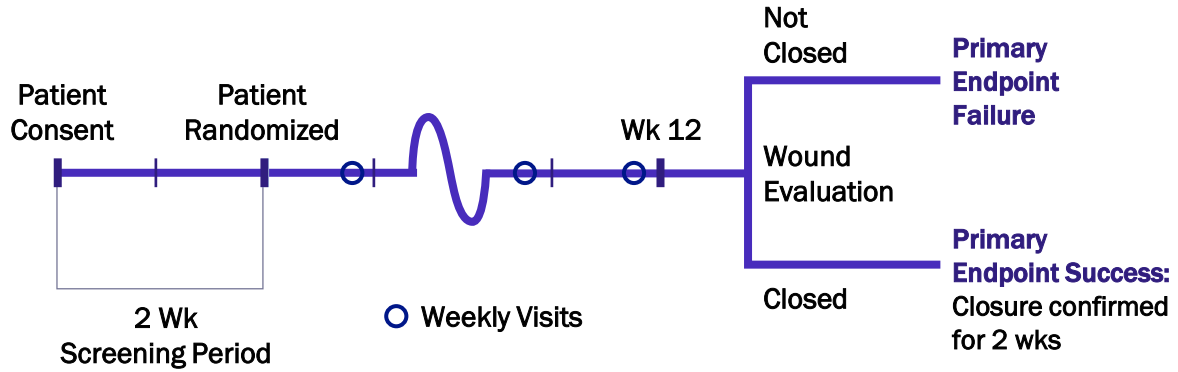
Closure Parameters:

- Initial closure determined unblinded on site
- 3 blinded validators confirm closure
- Wound must remain closed for 2 wks by initial process



Grade 1
Wagner 1 DFU

Study Design and Timeline



100 Subjects

13 U.S. Sites

1:1 Randomization

12-wk duration per patient

Index Ulcer Criteria

Index ulcer area
1.0 – 25.0cm²

Index ulcer duration
≥4 wks

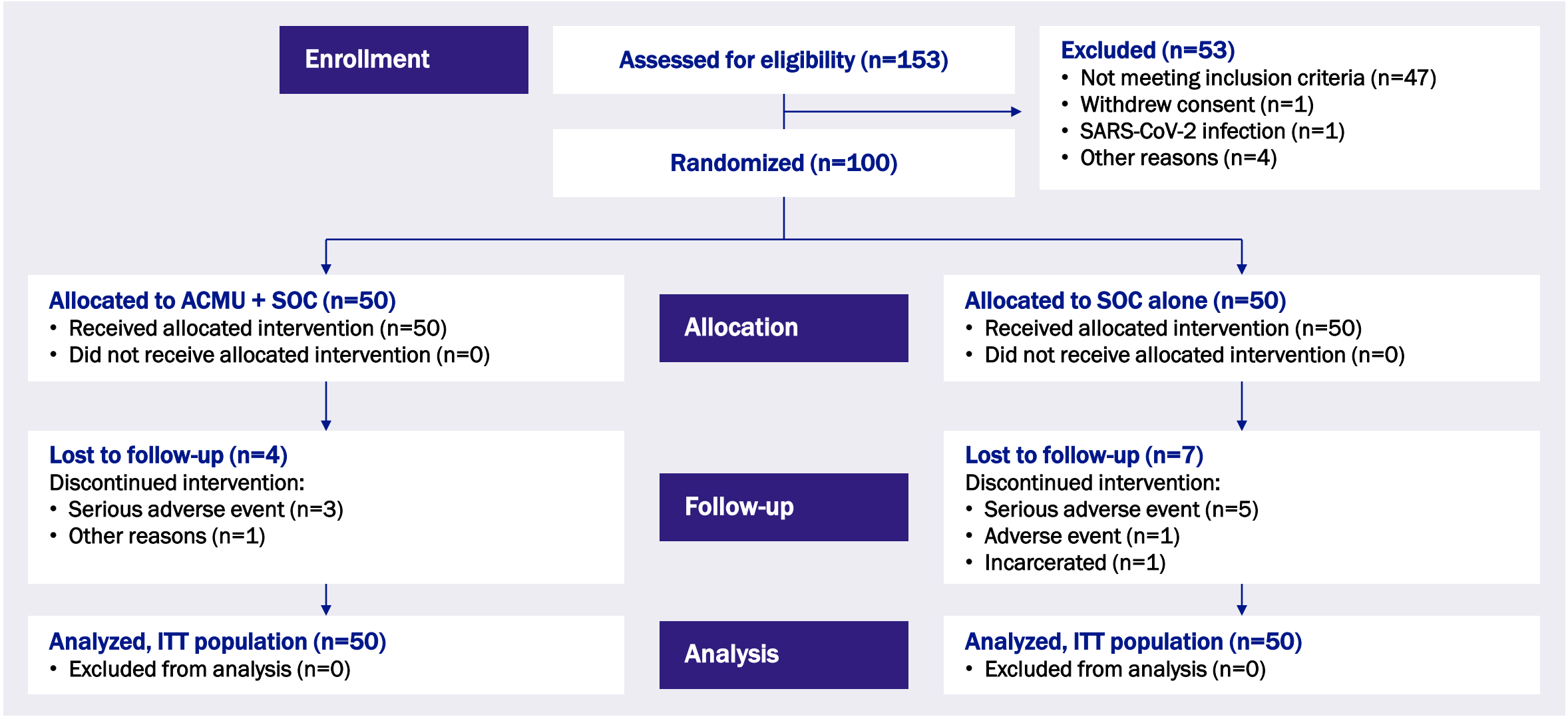
SOC run-in period
2 wks

Armstrong DG, et al. *Int Wound J*. 2023;20(10):4083-4096.

Autologous Cutaneous Multicellular Units (ACMU) are available for investigational use only.

STUDY OVERVIEW

Patient Flow (CONSORT)



Armstrong DG, et al. *Int Wound J*. 2023;20(10):4083-4096.

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DEMOGRAPHICS & WOUND CHARACTERISTICS

Baseline Demographics and Wound Characteristics

100 patients
50 ACMU + SOC • 50 SOC alone
13 sites across the U.S.

mean baseline wound area
3.5 vs 3.2cm²
ACMU vs SOC

mean baseline wound age
22.6 vs 24.3 wks
ACMU vs SOC

Demographics

Variable	ACMU + SOC (n=50)	SOC alone (n=50)	*p*
Age, yrs, mean (SD)	60.1 (9.8)	57.1 (11.4)	0.16
Body mass index, mean (SD)	32.7 (9.2)	33.7 (7.7)	0.56
Male sex, n (%)	36 (72.0)	36 (72.0)	1.0
Comorbidity count, mean (SD)	3.8 (2.7)	4.6 (3.3)	0.19
PAD / PVD, n (%)	4 (8.0)	5 (10.0)	1.0
Major foot deformity, n (%)	10 (20.0)	6 (12.0)	0.28
HbA1c, %, mean (SD)	7.4 (1.6)	7.7 (1.7)	0.37
Creatinine, mg/dL, mean (SD)	1.20 (0.49)	1.24 (0.49)	0.93
Alcohol use / history, n (%)			0.033
Current use	16 (32.0)	12 (24.0)	
Former use	6 (12.0)	17 (34.0)	
Never use	28 (56.0)	21 (42.0)	

Demographic, clinical, and wound characteristics were well balanced between groups; alcohol use was the only difference.

Wound Characteristics

Variable	ACMU + SOC (n=50)	SOC alone (n=50)	*p*
Wound area, cm², mean (SD)	3.5 (3.5)	3.2 (3.5)	0.46
Wound age, wks, mean (SD)	22.6 (26.8)	24.3 (22.6)	0.65
Plantar location, n (%)	41 (82.0)	44 (88.0)	0.40
Index ulcer is a recurrence, n (%)	20 (40.0)	16 (32.0)	0.41
Lifetime DFU count, mean (SD)	3.8 (3.2)	3.5 (4.3)	0.11
Prior amputation (any foot), n (%)	28 (56.0)	26 (52.0)	0.69
Offloading: CAM boot, n (%)	41 (82.0)	40 (80.0)	0.65

ACMU Applications

5 patients received a second application after inadvertent removal of ACMU (mean 1.1 applications per subject)
ACMU harvest sites all remained closed after primary closure

PAD = peripheral artery disease; PVD = peripheral vascular disease; CAM = controlled ankle movement.

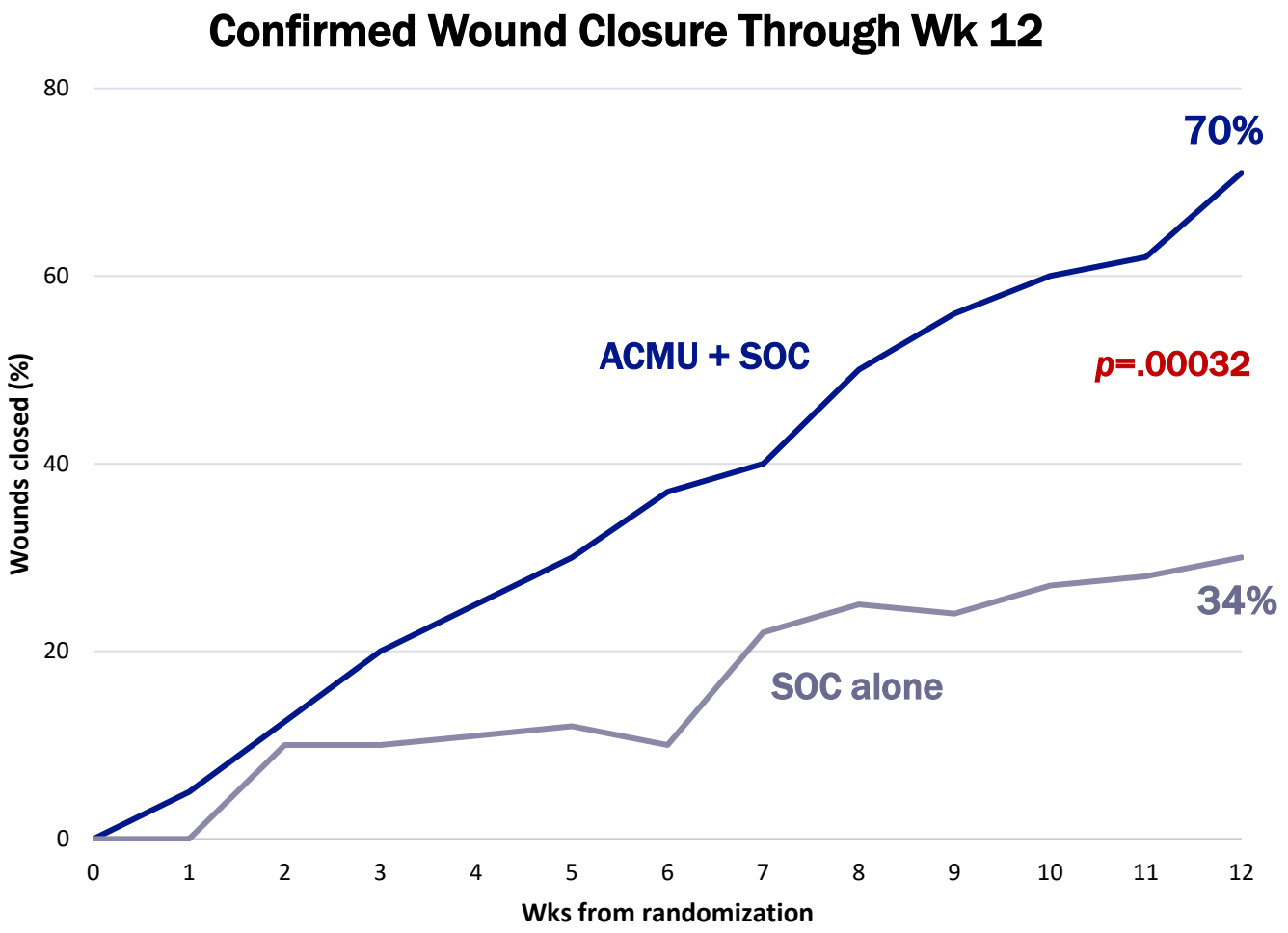
Armstrong DG, et al. *Int Wound J*. 2023;20(10):4083-4096.

Autologous Cutaneous Multicellular Units (ACMU) are available for investigational use only.

EFFICACY RESULTS

Primary Endpoint: Complete Wound Closure at 12 Weeks

Primary endpoint of incidence of complete wound closure within 12 wks met



70% wounds closed with ACMU + SOC at 12 wks (35/50)

34% wounds closed with SOC alone at 12 wks (17/50)

***p*=.00032**
between-group difference

OR 5.37
adjusted odds of healing

Variable	OR	95% CI	*p*
ACMU	5.37	1.94–14.89	0.001
Sex (male)	0.20	0.057–0.697	0.011
Blood glucose	1.01	1.002–1.017	0.017
Wound area at randomization	0.79	0.65–0.95	0.013
Comorbidity count	0.80	0.65–0.97	0.026
Body mass index	1.06	1.00–1.13	0.049
Hyperlipidaemia	5.06	1.23–20.80	0.025
Constant	0.38	—	0.428

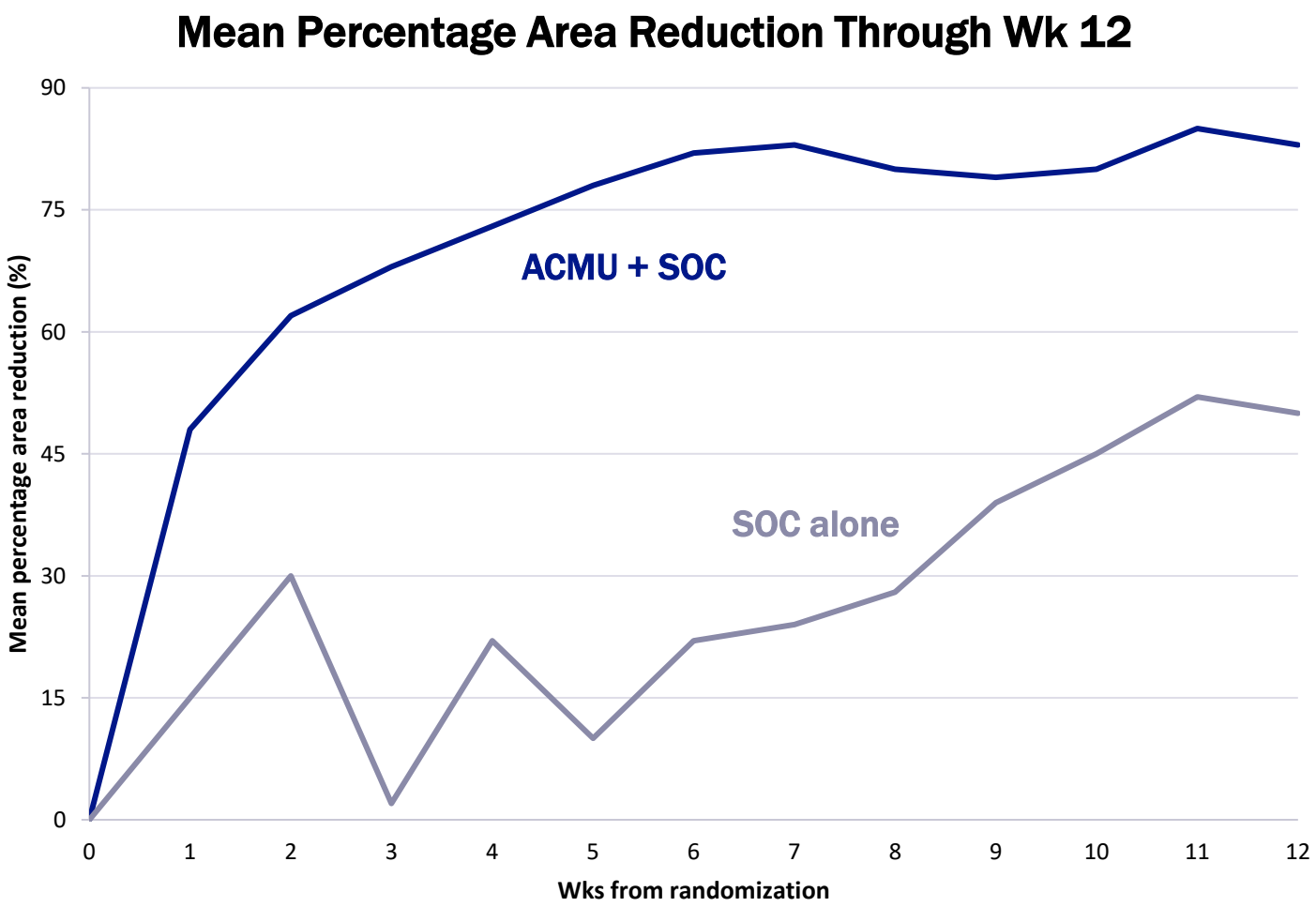
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EFFICACY RESULTS

Secondary Endpoint: Percentage Area Reduction (PAR)

Secondary endpoint of PAR met



84.3% mean PAR at 12 wks, ACMU + SOC

50.5% mean PAR at 12 wks, SOC alone

***p*=.009** group difference in PAR over 8 wks (linear mixed model)

Week	ACMU+SOC	SOC alone
4	74.0 (27.6)	22.0 (149.9)
6	82.9 (26.4)	21.2 (160.6)
8	80.7 (35.2)	26.8 (147.4)
10	79.7 (54.1)	45.6 (114.2)
12	84.3 (39.5)	50.5 (92.2)

PAR = percentage area reduction.

Armstrong DG, et al. *Int Wound J*. 2023;20(10):4083-4096.

Autologous Cutaneous Multicellular Units (ACMU) are available for investigational use only.

SAFETY

Safety Results

148 TEAEs
49 subjects experienced ≥1 adverse event (of 100 total)

66 TEAEs
21 pts (42%)
ACMU + SOC group • rate 1.32 per subject

2 ACMU Harvest Site TEAEs
1 cellulitis • 1 pain

82 TEAEs
28 pts (56%)
SOC alone group • rate 1.64 per subject

TEAEs Related to Study Intervention

Event type	ACMU + SOC	SOC alone
Related TEAEs, total	**3 (6%)**	**2 (4%)**
Index ulcer infection	1	0
Blister infection	0	1
Harvest site cellulitis	1	0
Harvest site pain	1	0
Bleeding episode	0	1

Index Ulcer Related TEAEs

Adverse event	ACMU+SOC	SOC alone	Total
Index ulcer infection			
No. patients (%)	3 (6)	6 (12)	9 (9)
Severity, no. events			
Mild	1	3	4
Moderate	2	2	4
Severe	1	1	2
Life-threatening	0	0	0
Index ulcer complications, not infection			
No. patients (%)	0 (0)	2 (4)	2 (2)
Severity, no. events			
Mild	0	1	1
Moderate	0	1	1
Severe	0	0	0
Life-threatening	0	0	0

TEAE = treatment-emergent adverse event.

Armstrong DG, et al. *Int Wound J*. 2023;20(10):4083-4096.

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PHASE 3 TRIAL DATA

COVER DFUS II Pivotal Phase 3 BLA Multicenter RCT of ACMU in Non-Healing Wagner 1 DFUs

ACMU + SOC vs SOC alone

STUDY OVERVIEW

COVER DFUS II Pivotal Phase 3 BLA Trial Design

Objective:

Prospective, multicenter RCT evaluating ACMU + SOC vs SOC alone in the treatment of Wagner 1 DFUs

Primary Endpoint:

Proportion of wounds closed by 12 wks defined as complete epithelialization without drainage or dressing requirements confirmed at 2 consecutive study visits 2 wks apart

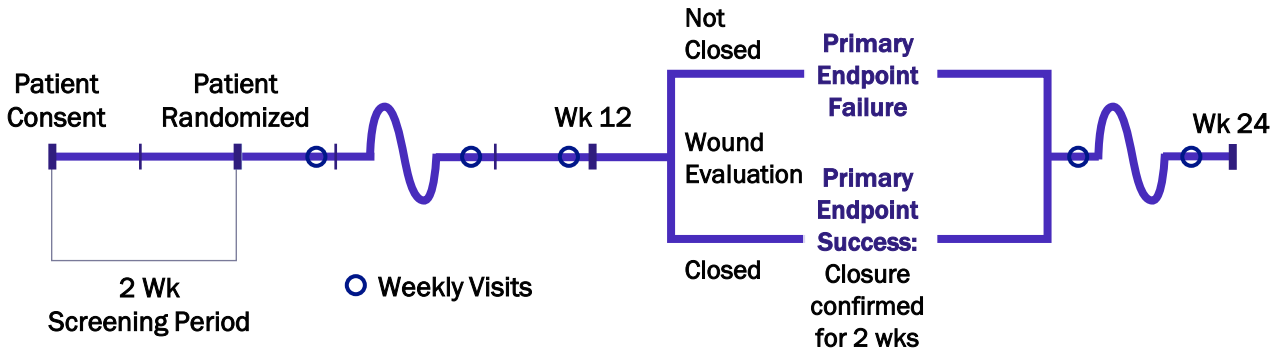
Closure Parameters:

- Initial closure determined unblinded on site
- 3 blinded validators confirm closure
- Wound must remain closed for 2 wks by initial process



Grade 1
Wagner 1 DFU

Study Design and Timeline



120 Subjects

19 U.S. Sites

1:1 Randomization

24-wk duration per patient

Index Ulcer Criteria

Index ulcer area
1.0 – 15.0cm²

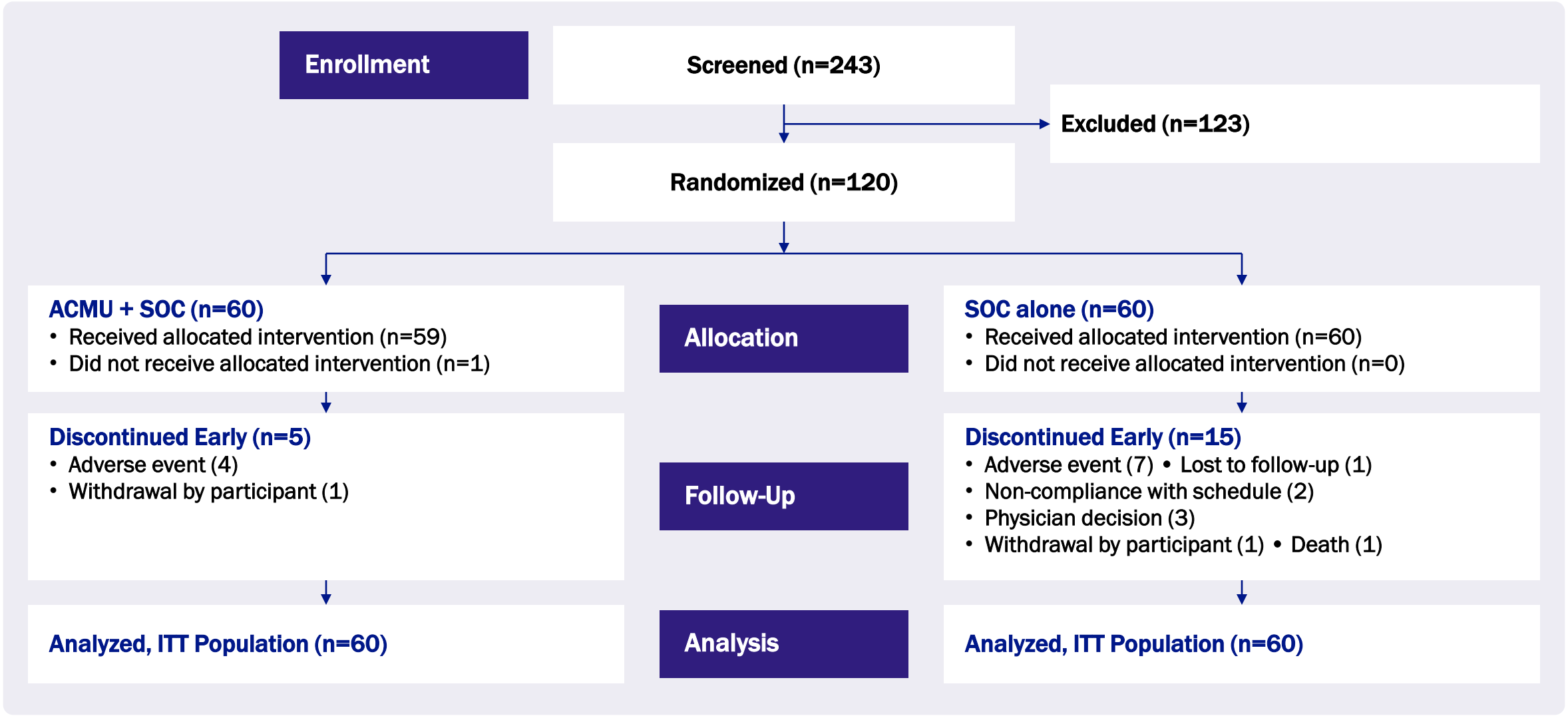
Index ulcer duration
≥4 wks

SOC run-in period
2 wks

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STUDY OVERVIEW

Patient Flow (CONSORT)



ITT = intention to treat.

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DEMOGRAPHICS & WOUND CHARACTERISTICS

Baseline Demographics and Prognostic Characteristics

120 patients

60 ACMU + SOC • 60 SOC alone

Mean HbA1c
≈8%

No. of Previous DFUs
2.6 vs 1.9
ACMU vs SOC

History of Amputations
≈60%

Category	ACMU+SOC (N=60)	SOC (N=60)
Sex		
Female, n (%)	13 (21.7)	11 (18.3)
Male, n (%)	47 (78.3)	49 (81.7)
Age (years)		
n	60	60
Mean (SD)	58.4 (9.76)	58.8 (8.40)
Median	59.5	59.0
Min, Max	36, 88	41, 83
Race		
White, n (%)	51 (85.0)	52 (86.7)
Black/African American, n (%)	7 (11.7)	7 (11.7)
Asian, n (%)	2 (3.3)	1 (1.7)
Ethnicity		
Hispanic or Latino, n (%)	23 (38.3)	26 (43.4)
Not Hispanic or Latino, n (%)	37 (61.7)	34 (56.7)
BMI (kg/m²)		
n	60	59
Mean (SD)	31.73 (6.02)	32.28 (6.83)
Median	30.50	31.90
Min, Max	22.1, 48.8	22.6, 62.3

Category	ACMU+SOC (N=60)	SOC (N=60)
Baseline HbA1c (%)		
n	59	60
Mean (SD), Median	8.03 (1.63), 7.90	8.33 (1.62), 8.30
Min, Max	4.6, 10.7	4.2, 11.5
Total No. of Previous DFUs		
n	60	60
Mean (SD), Median	2.6 (2.93), 2.0	1.9 (1.85), 1.5
Min, Max	0, 14	0, 8
Foot Deformity/Dermatologic/Fungal/Other		
Yes, n (%)	18 (30.0)	19 (31.7)
No, n (%)	42 (70.0)	41 (68.3)
History of Charcot Foot		
Yes, n (%)	6 (10.0)	8 (13.3)
No, n (%)	54 (90.0)	52 (86.7)
Any Amputation or Lower-Extremity Surgery		
Yes, n (%)	40 (66.7)	40 (66.7)
No, n (%)	20 (33.3)	20 (33.3)
History of Amputations		
Yes, n (%)	38 (63.3)	34 (56.7)
No, n (%)	22 (36.7)	26 (43.3)

Baseline characteristics were well balanced except for a higher proportion of active smokers (18.3% vs 8.3%) and alcohol users (40.0% vs 23.3%) in the ACMU group.

DEMOGRAPHICS & WOUND CHARACTERISTICS

Baseline Wound and Ulcer History

Baseline Wound Area
3.36 vs 3.25cm²
mean, ACMU vs SOC

Wound Age
310 vs 266 days
mean, ACMU vs SOC

Prior Index Ulcer Infection
≈27%

Prior Index Ulcer Osteomyelitis
≈17%

Category	ACMU+SOC (N=60)	SOC (N=60)
Area of Index Ulcer (cm²)		
n	60	60
Mean (SD), Median	3.36 (3.32), 1.75	3.25 (2.78), 2.30
Min, Max	1.0, 14.8	0.9, 13.9
Additional Ulcers Present		
Yes, n (%)	13 (21.7)	6 (10.0)
Duration of Current DFU (days)		
n	60	60
Mean (SD), Median	309 (640.5), 142.5	266 (270.5), 197.0
Min, Max	28, 4730	30, 1384
Prior Treatments on Index Ulcer		
Yes, n (%)	24 (40.0)	28 (46.7)
No, n (%)	36 (60.0)	32 (53.3)
History of Index-Ulcer Recurrence		
Yes, n (%)	11 (18.3)	16 (26.7)
No, n (%)	49 (81.7)	44 (73.3)
Recurrences: Mean (SD), Med	2.3 (1.49), 2.0	1.9 (1.34), 1.5
History of Soft-Tissue Infection / Cellulitis		
Yes, n (%)	16 (26.7)	17 (28.3)
No, n (%)	44 (73.3)	43 (71.7)
History of Index-Ulcer Osteomyelitis		
Yes, n (%)	10 (16.7)	10 (16.7)
No, n (%)	50 (83.3)	50 (83.3)

Additional Ulcers Present
21.7% vs 10.0%
ACMU vs SOC

ACMU Applications & Harvest

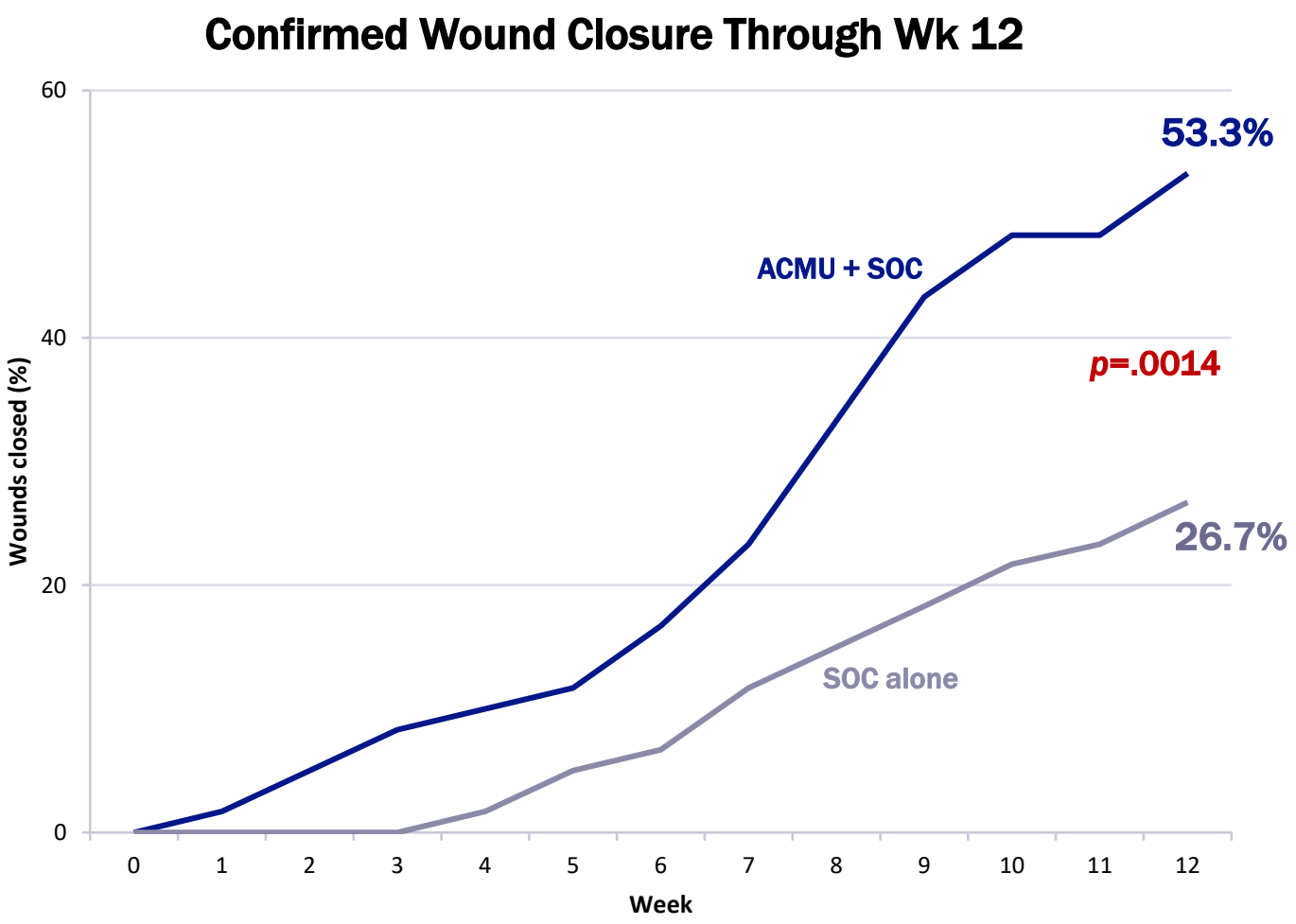
- 11 (18.3%) underwent a second application
- A second application was allowed for inadvertent removal of ACMU or insufficient PAR at wks 4, 6, and 8

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EFFICACY RESULTS

Primary Endpoint: Index Ulcer Healed by Week 12

Primary endpoint of incidence of complete wound closure within 12 wks met



53.3% index ulcers healed by Wk 12, ACMU + SOC

26.7% index ulcers healed by Wk 12, SOC alone

***p*=.0014** 26.7-point absolute improvement (one-sided 97.5% CI lower bound: 9.8)

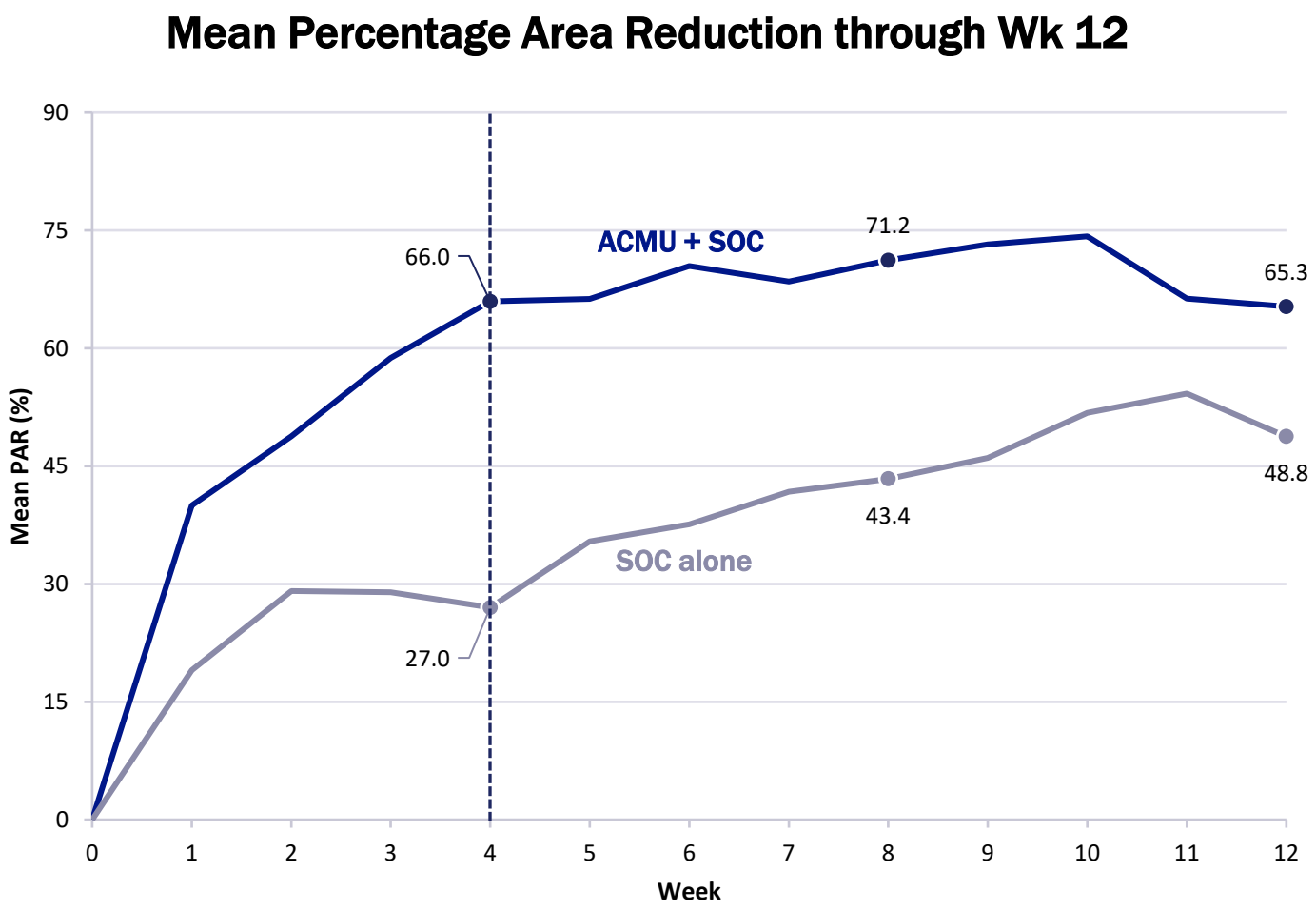
Sensitivity / supporting analyses	Result
CMH test, adjusted for wound-area stratum	*p*=.0013
Odds ratio, ACMU vs SOC	3.35
Index ulcers healed by Wk 24	63.3% vs 46.7%

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EFFICACY RESULTS

Secondary Endpoint: Percentage Area Reduction (PAR)

Secondary endpoint of PAR across wks 4, 8, and 12 met



66.0% mean PAR at Wk 4, ACMU + SOC

27.0% mean PAR at Wk 4, SOC alone

***p*=.0028** secondary endpoint met — mean PAR across 12 wks (MMRM, one-sided)

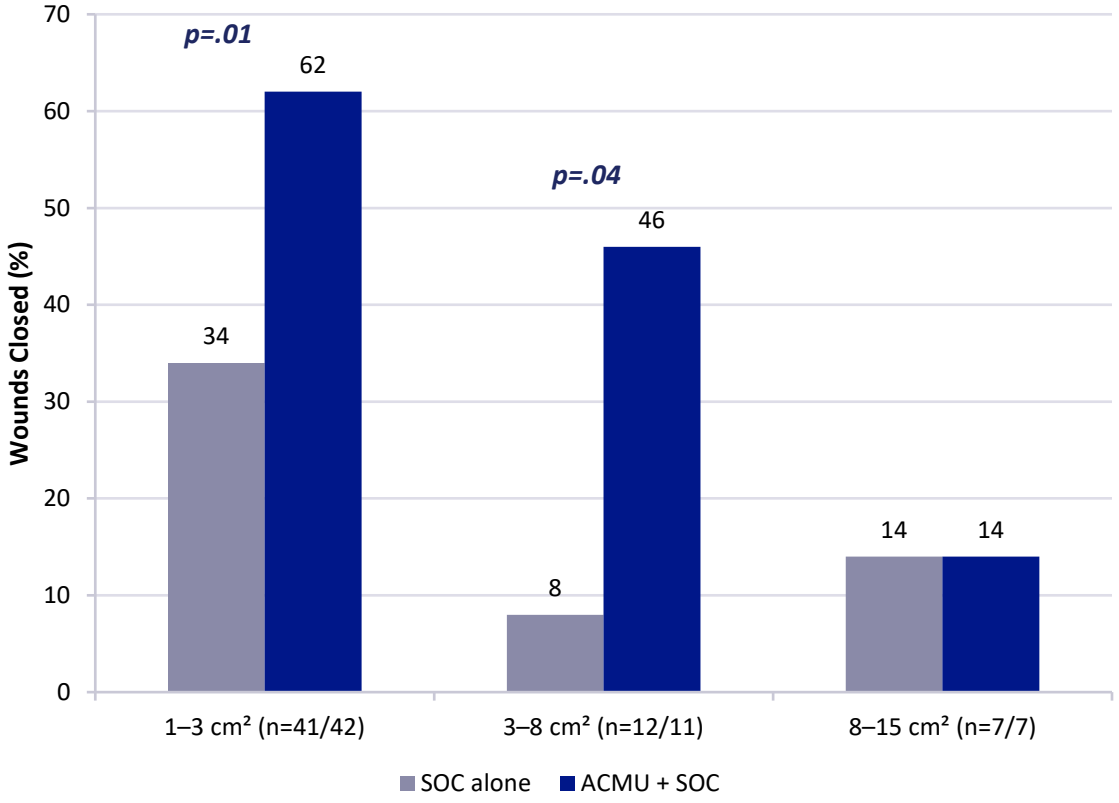
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EFFICACY RESULTS

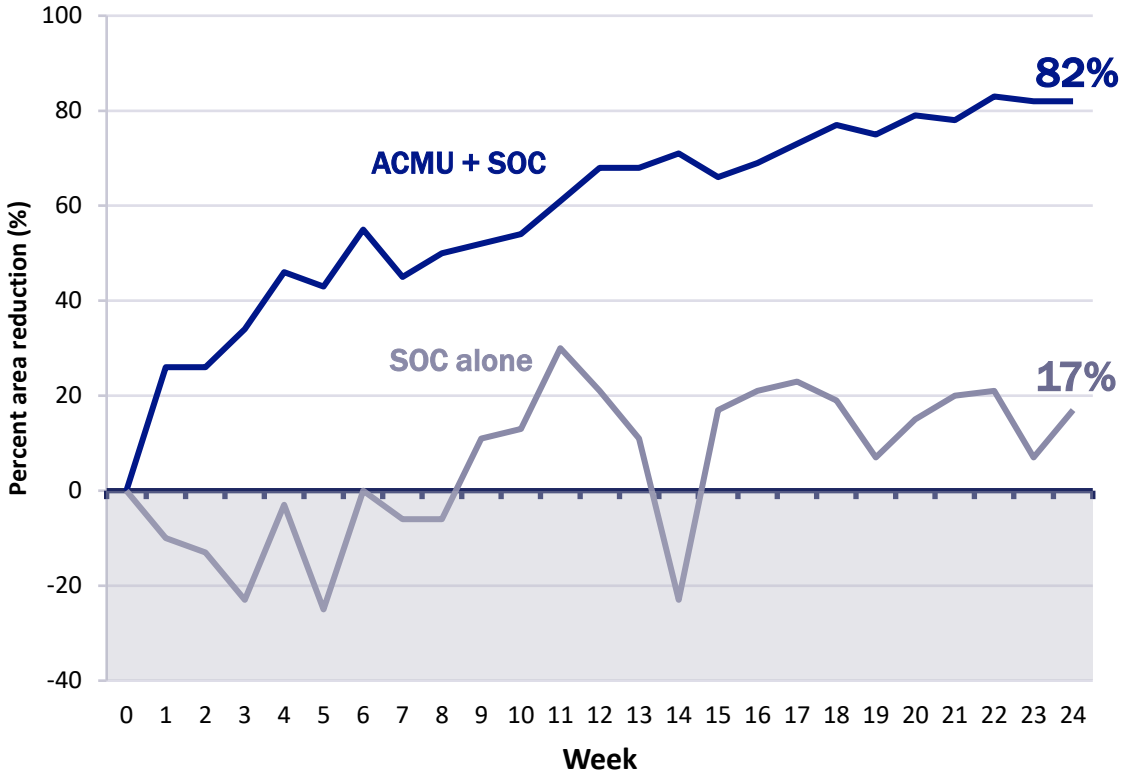
Closure Across Wound Size Strata and Subgroups

ACMU nearly doubled Wk 12 closure in small wounds (1-3cm²: 61.9% vs 34.1%) and exceeded a five-fold advantage in medium wounds (>3-8cm²: 45.5% vs 8.3%). Despite equal 12-wk closure rates in the largest stratum (>8-15cm²: 14.3% each), 24-wk PAR strongly favored ACMU (82% vs 17%)

12-Wk Closure Rate by Wound-Area Stratum



Percent Area Reduction Over 24 Wks: DFUs 8-15cm²



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SAFETY

Safety Results

ACMU-Related TEAEs
None

no TEAE of any grade, serious, fatal, or leading to discontinuation was related to ACMU

Any TEAE
67.8% vs 63.3%

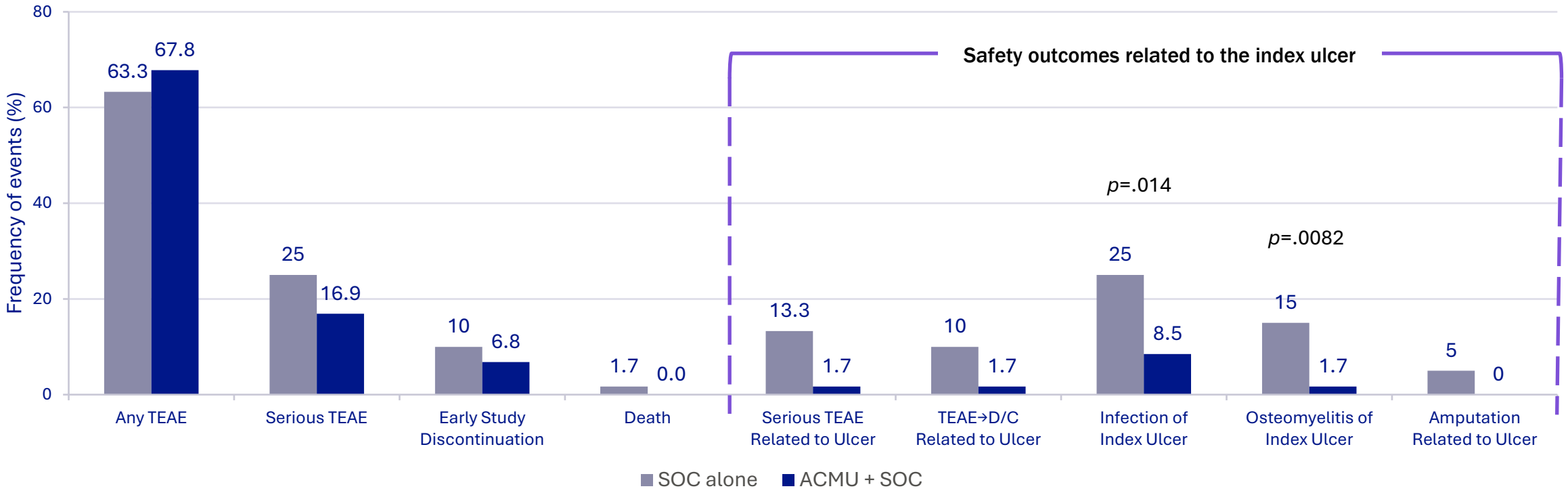
ACMU + SOC vs SOC alone — comparable overall rates

Index Ulcer Infection
8% vs 25%

ACMU + SOC vs SOC alone (p = 0.0143)

Index Ulcer Osteomyelitis
2% vs 15%

ACMU + SOC vs SOC alone (p = 0.0082)



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CLINICAL & ECONOMIC IMPACT

Clinical and Economic Impact of Fewer Complications

≈2x

wound closure at 12 wks

53.3% ACMU + SOC vs 26.7% SOC; *p*=.0014

Average DFU cost:

$20k–$40k per patient annually[1]

66%

relative reduction in index ulcer infection

8.5% ACMU + SOC vs 25.0% SOC; *p*=.0143

Infection requiring hospitalization:

$15k–$30k per episode[2]

89%

relative reduction in index ulcer osteomyelitis

1.7% ACMU + SOC vs 15.0% SOC; *p*=.0082

Amputation & rehabilitation:

$30k–$60k per episode; 5-yr survival <40%[3]

0% vs 5.0% index-ulcer-related amputation

No index-ulcer-related amputations occurred in the ACMU + SOC group vs 5.0% in the SOC-alone group

1. Chan B, et al. *J Wound Care*. 2017;26(sup4):S4-S14. 2. Gordois A, et al. *Diabetes Care*. 2003;26(6):1790-5. 3. Franklin H, et al. *J Rehabil Res Dev*. 2014;51(8):1325–1330.

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Clinical Outcomes Associated with ACMU through Case-Based Analysis

Jason R. Hanft, DPM, FACFAS
Founder/CEO, Defender Operations
Director, Doctors Research Network
South Miami, FL

Harvest Procedure

Harvest Procedure

1. Activate NanoCool™ temperature-controlled shipping system first

1. Place lid on a flat surface, then press the button underneath to start cooling



2. Logo turns blue, lid is cold; close lid snugly

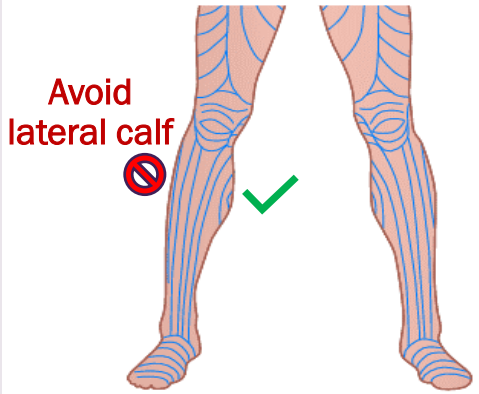


If the engine does not cool, replace the temperature-controlled shipping system

2. Selection of Harvest Site

Choose healthy skin, in order of preference

1. Medial proximal superior calf (avoid lateral calf)
2. Medial lower thigh near the knee
3. Thigh
4. Groin
5. Contralateral limb



Incisions should follow Langer lines

Avoid harvesting from

- Periwound skin
- Previous surgical sites
- Areas of scar tissue
- Inflamed or edematous skin
- Areas with moles or skin tags

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Harvest Procedure

3. Harvest: Site Preparation — Non-Sterile

1. Place and hold the provided template at the harvest location, following Langer lines

Shave the area, if needed, prior to beginning



2. Trace around template, measuring 3cm x 1cm, using skin marker; allow ink to dry



3. Inject anesthetic under and around marked 3cm x 1cm ellipse

Before injecting, prep twice using 2 chlorhexidine swabs



4. Ensure transport media for the harvest has no leaks



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Harvest Procedure

4. Harvest: Surgical Procedure — Sterile

1. Sharply excise a full-thickness specimen, including the fat-containing hypodermal layer (include ≈5mm of hypodermis to ensure full-thickness skin harvest)



Using scalpel, first incise the skin along the outer edge of the elliptical shape

Avoid use of electrocautery to excise harvest tissue — can be used for hemostasis, post-harvest



Using forceps, lift the incised edge and release the harvest tissue

Do not remove hypodermal fat or deeper adipose structures from harvest tissue (as would normally be done in full-thickness skin grafting)

Harvest Procedure

4. Harvest: Surgical Procedure — Sterile (continued)

2. Place harvest in shipping media

Seal tightly and invert 5 times to ensure tissue is fully submerged



3. Close site primarily

Ensure hemostasis; close with suture in a simple, interrupted pattern





4. Apply dressing

Apply dry dressing to harvest site



5. Apply Compression Dressing

- Must cover from base of toes to 2cm below the fibular head
- Must cover harvest site (if below knee)



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Application Procedure

Application Procedure

1. ACMU Application: Wound Bed Preparation

1. Debride all non-viable tissue to healthy, bleeding tissue – mandatory at the time of ACMU application



Excise thickened, rolled, or scarred wound edges to expose healthy, viable wound margins. Ensure any non-viable tissue is removed.

2. Ensure hemostasis

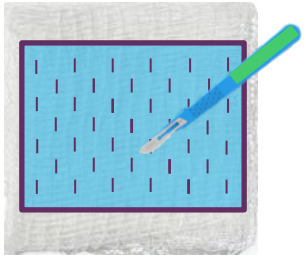


3. Irrigate thoroughly with normal saline

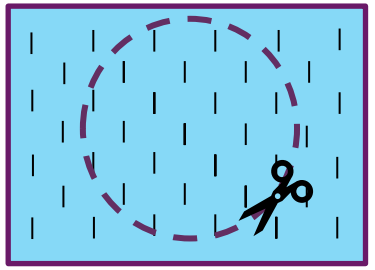
2. Prepare Silicone and Apply Skin Protectant

1. Place silicone sheet on top of opened gauze tray

Perforate with scalpel every 5mm



2. Cut fenestrated silicone to size of wound with 0.5-1cm overlap on periwound skin



3. Protect periwound skin by applying 2 applications of skin prep from the wound edge outward 5cm



Skin prep protects skin from maceration under silicone and allows better adhesion of adhesive skin closure strips

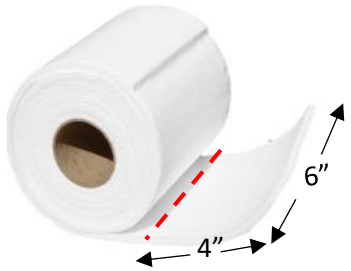
Autologous Cutaneous Multicellular Units (ACMU) are available for investigational use only.

Application Procedure

3. Prepare Local Offloading and Dressings

1. Prepare felt for local offloading

Cut a piece of felted foam large enough to cover the entire plantar surface of the foot



2. Cut felt to shape of foot

a) Hold felt close to foot with backing toward patient; cut felt to contour of foot in wound location

b) Ensure that felt edges are not positioned over bony prominences



Heel Forefoot Midfoot

3. Finish customization

a) Cut out area for wound, as shown, leaving ≈2-3mm margin around the periwound

b) Bevel all felt edges



2nd – 4th MTPs | 1st and 5th MTPs | Central midfoot | Medial/lateral mid and dorsal foot | Heel

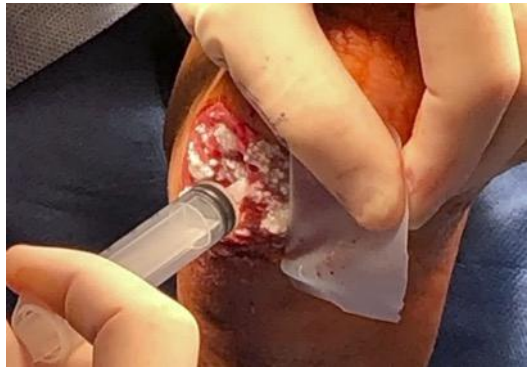
Autologous Cutaneous Multicellular Units (ACMU) are available for investigational use only.

Application Procedure

4. ACMU Application

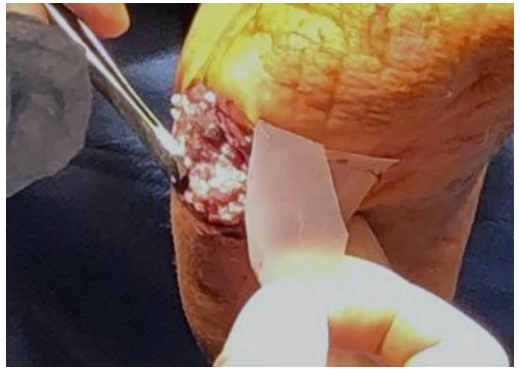
1. Apply ACMU to wound bed with a syringe

Avoid applying excess ACMU. Do not apply to periwound, as this can macerate surrounding tissue



2. Distribute ACMU evenly over entire surface of the wound

Apply 2mm layer over entire wound bed and all surfaces of tunneled or undermined areas



3. Apply silicone with 0.5-1cm overlap on periwound skin



4. Affix silicone to skin with adhesive skin closure strips (strips should align on each corner, overlapped)



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Application Procedure

5. Local Offloading and Dressing Application

1. Remove backing of prepared felted foam and apply to foot; use paper tape to further secure, if needed



2. Cut a section of foam dressing to fit into the open portion of felt and apply to the wound



3. Use remaining foam, or new piece of foam, to apply a larger second layer on top of first foam piece



4. Hold in place with cloth tape and gauze roll



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Application Procedure

6. Apply Compression Dressing

- Must cover from base of toes to 2cm below the fibular head
- Must cover harvest site (if below knee)



7. Apply Offloading Boot

Fitting Tips



Step 1

- Deflate the air cell by pushing the silver button
- Place patient in a tall diabetic sock that extends above mid-calf
- Place patient's heel firmly into the back of the boot

Scan QRCode
YouTube Patient Instruction Link



Step 2

- Apply front AFO closure, starting with hook & loop near toes, work your way up
- Be sure that top straps are not too tight, allowing for a 2-finger gap at the shin
- Note that the boot is not intended to fit tightly

▸ JUST RIGHT

- Note the AFO angle to the tibia (shin)



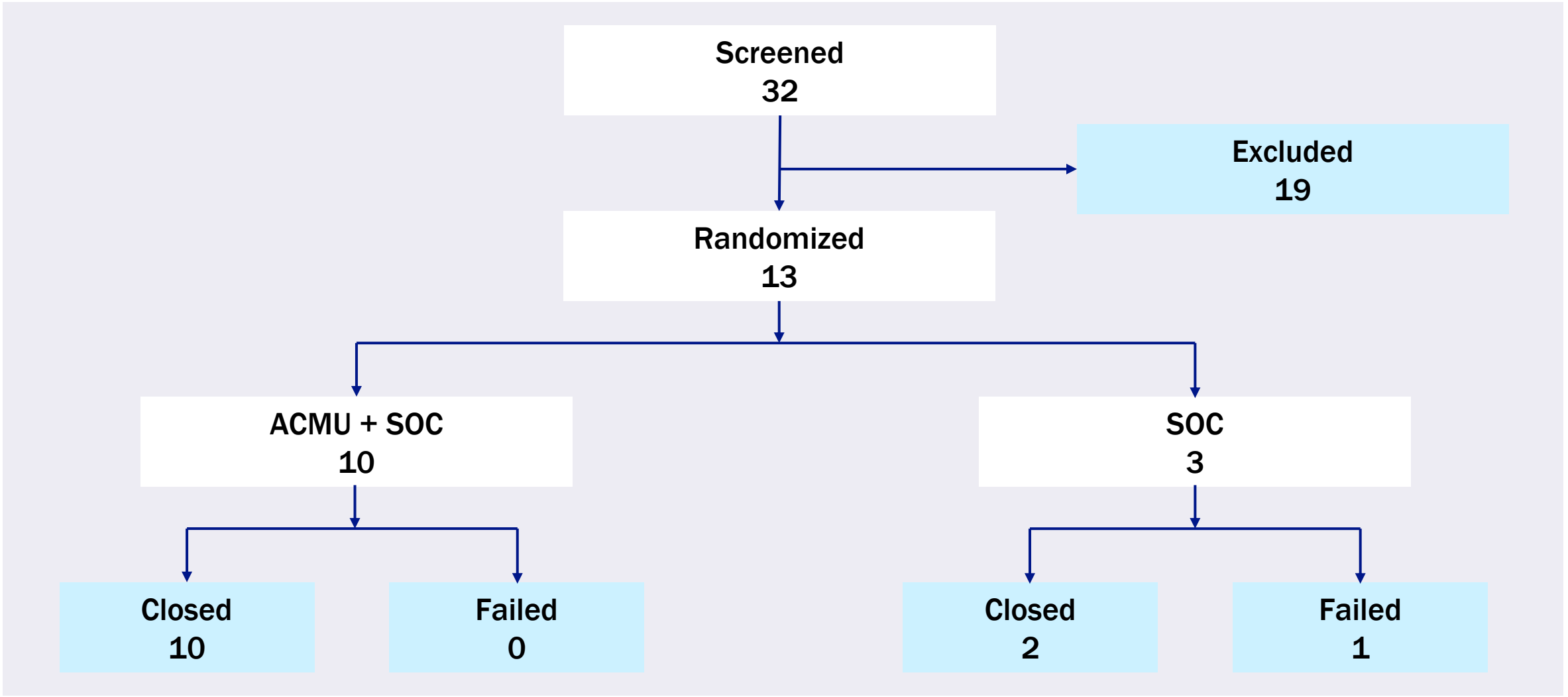
X TOO TIGHT

- Wrong angle to the tibia



COVER DFUS II Trial
Experience and Case Presentations

Our Site's COVER DFUS II Trial Experience



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Case Study 1

Case Study 1: 59y Female with right lateral midfoot DFU



- 59y Hispanic Female with medical hx significant for T2DM, bilateral PN, DL, HTN, and s/p 5th metatarsal partial excision
- Presented with 3.4cm^2 Wagner 1 DFU on right lateral midfoot (80 days old at time of screening); hx of 4 previous DFUs with no hx of recurrence of the index ulcer and no hx of prior infections of the index ulcer
- On presentation, HbA1c was 10.6, eGFR was 91, and ABI was 1.0

T2DM = type 2 diabetes mellitus; PN = peripheral neuropathy; DL = dyslipidemia; HTN = hypertension; ABI = ankle-brachial index.

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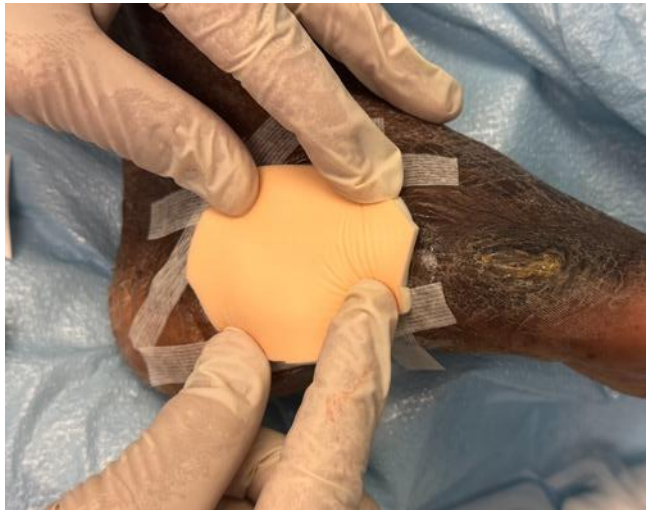




Autologous Cutaneous Multicellular Units (ACMU) are available for investigational use only.



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Autologous Cutaneous Multicellular Units (ACMU) are available for investigational use only.









Autologous Cutaneous Multicellular Units (ACMU) are available for investigational use only.

Case Study 1: Healing Progression



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Case Study 2

Case Study 2: 60y Male with large dorsal Wagner 1 DFU

- 60y Male, medical hx significant for T2DM, diabetic PN, HTN, DL, and 10 pack-yr former smoking hx; Presented with 7.4cm^2 Wagner 1 DFU on dorsal left forefoot (98 days old at time of screening)

Post-Debridement Day 0



Day 0



Wk 1



Wk 2



Wk 3





Wk 4



Wk 5



Closure Wk 7



Closure Wk 9

Closure Confirmation Wk 9



Case Study 3

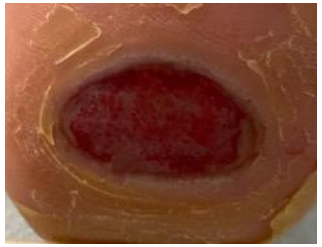
Case Study 3 : 62y Hispanic Female with a plantar heel Wagner 1 DFU

- 52y Hispanic Female, medical hx significant for T2DM, diabetic PN, 6 prior DFUs, HTN; presented with 5.4cm^2 Wagner 1 DFU left plantar heel (146 days old at time of screening) with 3 previous recurrences

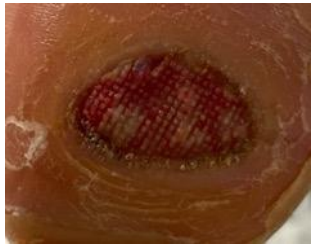
Post-Debridement Day 0



Day 0



Wk1



Wk 2

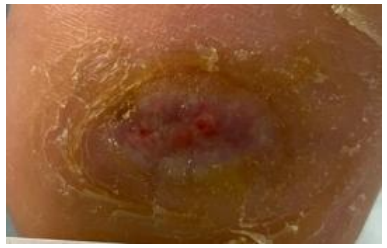


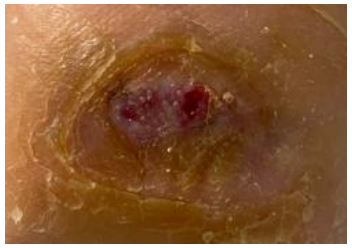
Wk 3



Closure Confirmation Wk 8

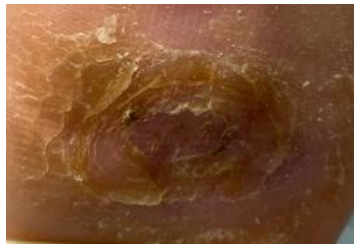






Wk 4

Wk 5



Closure Wk 6



Closure Wk 8

Autologous Cutaneous Multicellular Units (ACMU) are available for investigational use only.

Summary and Recommendations

5 procedures and steps that all need significant attention

1 Skin Harvest	Surgical procedure that must be done correctly to both avoid complications and receive enough product
2 Wound Bed Prep	ACMU is an autograft and requires the wound bed to be prepared in the same manner as a traditional skin graft
3 Dressing Prep and Local Offloading	Pre-cut all dressings and local offloading material (fenestrated silicone, foam, felted foam) for efficient application and to prevent product loss after applying
4 Application of ACMU	Crack the syringe before applying, have silicone partially secured, prone positioning for plantar DFUs, hedge towards using 2-3 layers of felted foam for plantar DFUs
5 Compression and Offloading Boot	Compression secures bolster and prevents harvest site complications, while the offloading boot minimizes direct pressure to the graft; education is key

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