## Appendix A. PRISMA 2020 Checklist

This checklist documents the reporting compliance of the present review with the PRISMA 2020 statement [17]. Adapted from Page MJ et al., BMJ 2021;372:n71, Table 1 (Creative Commons CC BY 4.0 license).

| Item # | Checklist Item | Where Reported | Status | Notes |
|---|---|---|---|---|
| 1 | Identify the report as a systematic review. | Title | Yes | |
| 2 | See the PRISMA 2020 for Abstracts checklist. | Abstract | Yes | |
| 3 | Describe the rationale for the review in the context of existing knowledge. | Introduction | Yes | |
| 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | Introduction | Yes | |
| 5 | Specify inclusion/exclusion criteria and how studies were grouped for syntheses. | Methods | Yes | |
| 6 | Specify all sources searched and last search date. | Methods | Yes | Search strategy in Methods. |
| 7 | Present full search strategies for all sources. | Methods | Yes | Detailed search strategy provided. |
| 8 | Specify study selection process (reviewers, independence, automation). | Methods | Yes | |
| 9 | Specify data collection process (reviewers, independence, verification). | Methods | Yes | |
| 10a | List and define all outcomes for which data were sought. | Methods | Yes | |
| 10b | List and define all other variables for | Methods | Yes | |

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| | which data were sought. | | | |
| 11 | Specify methods used to assess risk of bias. | Methods | Yes | |
| 12 | Specify effect measures used for each outcome. | Methods | Yes | |
| 13a | Describe processes used to decide which studies were eligible for each synthesis. | Methods | Yes | |
| 13b | Describe methods required to prepare data for presentation or synthesis. | Methods | Yes | |
| 13c | Describe methods used to tabulate or visually display results. | Methods | Yes | |
| 13d | Describe synthesis methods and rationale. | Methods | Yes | |
| 13e | Describe methods to explore heterogeneity. | Methods | Not applicable | |
| 13f | Describe sensitivity analyses conducted. | Methods | Not applicable | |
| 14 | Describe methods used to assess reporting bias. | Methods | Yes | |
| 15 | Describe methods used to assess certainty in the body of evidence. | Methods | Yes | GRADE applied. |
| 16a | Describe results of search and selection process (flow diagram). | Results | Yes | Figure 1 PRISMA Flow Diagram. |
| 16b | Cite excluded studies that seemed eligible and explain why excluded. | Results | Yes | Duplicates |
| 17 | Cite each included study and present its characteristics. | Results | Yes | |

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| 18 | Present assessments of risk of bias for each included study. | Results | Yes | |
| 19 | For all outcomes, present summary statistics and effect estimates. | Results | Yes | |
| 20a | Summarize characteristics and risk of bias among studies per synthesis. | Results | Yes | |
| 20b | Present results of all statistical syntheses conducted. | Results | Yes | |
| 20c | Present results of investigations of possible causes of heterogeneity. | Results | Not applicable | |
| 20d | Present results of sensitivity analyses conducted. | Results | Not applicable | |
| 21 | Present assessments of reporting bias for each synthesis assessed. | Results | Yes | |
| 22 | Present certainty assessments in body of evidence for each outcome. | Results | Yes | GRADE SoF Table. |
| 23a | Provide interpretation of results in context of other evidence. | Discussion | Yes | |
| 23b | Discuss limitations of the evidence. | Discussion | Yes | |
| 23c | Discuss limitations of the review process. | Discussion | Yes | |
| 23d | Discuss implications for practice, policy, and research. | Discussion | Yes | |
| 24a | Provide registration information or state not registered. | Other Info | Yes | |
| 24b | Indicate where protocol can be accessed or state not prepared. | Other Info | Yes | |

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| 24c | Describe and explain amendments to registration/protocol. | Other Info | Not applicable | |
| 25 | Describe sources of financial/non-financial support. | Other Info | Yes | |
| 26 | Declare competing interests of review authors. | Other Info | Yes | |
| 27 | Report availability of data, code, and materials. | Other Info | Yes | Evidence table and PRISMA checklist attached. |

# Appendix B. Evidence Summary Grid of Dermagraft VLU Study

| Study | Design | N | Wound Type | Intervention | Comparator | Key Outcomes | Limitations |
|---|---|---|---|---|---|---|---|
| Harding et al. 2013 | Prospective, multicentre, randomized controlled trial (open-label) | 366 patients (186 Dermagraft + compression; 180 compression alone) across 25 centers (UK, USA, Canada) | Chronic venous leg ulcers (VLUs) | Dermagraft (human fibroblast-derived dermal substitute) applied at weeks 0, 1, 4, and 8 + standard four-layer compression therapy plus Standard of care | Four-layer compression therapy alone plus standard of care | Primary endpoint: Complete closure by 12 weeks (34% Dermagraft vs 31% control; p = 0.235). Subgroup (ulcers ≤12 months): 52% vs 37% (p = 0.029). Ulcers ≤10 $cm^2$: 47% vs 39% (p = 0.223). Secondary outcomes: By 24 weeks, 52% vs 49% healed; median ulcer area reduction 83.7% vs 73.0%. Safety: No significant difference in adverse events or infections. | Open-label (no double blinding); primary endpoint not statistically significant; subgroup significance limited to shorter-duration ulcers; possible performance bias; large ulcer size may have limited effect size; study powered for modest difference. |

## Appendix C. Evidence-to-Decision Framework

| Domain | CMS Evaluation Question | Evidence Summary (Keramatrix) | GRADE Judgment |
|---|---|---|---|
| **Problem** | Is the condition of public-health importance? | DFUs/VLUs affect >8 million Medicare beneficiaries; high cost and amputation risk. | High |
| **Benefits** | Does Keramatrix improve important outcomes? | Accelerated epithelialization (RR 1.6); improved closure; reduced pain. | High |
| **Harms** | Are harms serious or frequent? | No serious AEs across 700+ wounds. | High |
| **Certainty of Evidence** | Overall confidence in effect estimates? | High (Davidson 2013); Moderate overall. | Moderate–High |
| **Values & Preferences** | Do patients value faster healing & fewer procedures? | High alignment: EB families report better QoL. | High |
| **Resource Use / Cost-Effectiveness** | Does it reduce resource burden? | 40–60 % lower total costs; fewer visits & hospitalizations. | Moderate |
| **Equity & Acceptability** | Is access equitable across settings? | Office, PAC, rural deployment feasible; high acceptability. | High |
| **Feasibility** | Can this intervention be implemented widely? | Requires minimal training; supply chain established. | High |
| **Recommendation** | Should CM S cover Keramatrix for DFUs/VLUs? | Benefits ≫ harms; High–Moderate certainty; strong patient preference. | Yes, CMS should cover Keramatrix for DFUs and VLUs with special consideration for |

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| | | | donor site wounds and EB. |