## Appendix B
### Evidence Table: Acute Wounds

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Design</th>
<th>Demographics</th>
<th>Intervention, outcome measures; instruments</th>
<th>Results</th>
<th>Control group</th>
<th>Methodological Comments</th>
</tr>
</thead>
</table>
| Trowbridge, 2005 | Prospective, nonrandomized, unblinded, single center | N= 2259 divided into 3 groups:  
- PRP: n= 382  
- No PRP: n= 948  
- Historical control: n=929 | ~70% of patients received PRP produced using the CATS (Terumo Cardiovascular Systems Corp) system  
~15% of patients received PRP produced using the SmartPRPe (Harvest Technologies, Inc) system  
~15% of patients received PRP produced using a COBE Cardiovascular Inc system | Rate of infection:  
Superficial—0.3  
Deep sternal—0.0 | Rate of infection:  
No PRP | Retrospective analysis design without benefit of randomization or blinding provides for less robust evidence to support net health outcome decisions. |
| | Inclusion= all patients >19 years old undergoing cardiac surgery from Oct 2002 to June 2005 | Mean (SD) age=  
- PRP: 64 (14)  
- No PRP: 64 (13)  
- Historical control: 65 (13) | PRP was applied first to the subcutaneous area and then to the cutaneous incision.  
Outcome= rate of superficial and deep sternal wound infections  
Subgroup data analysis to determine risk factors for infection | | | |
| | Exclusion= none stated | Gender=  
- PRP: 66% M  
- No PRP: 65% M  
- Historical control: 64% M | Low rate of infection precluded a subgroup analysis. | | | |
| | Wound types: sternal, vein and artery harvest sites | 3 groups were studied:  
- PRP applied  
- Concurrent control— No PRP  
- Historical control (surgical patients from the 18 months prior to start of study) | | | | |
| | Retrospective analysis design without benefit of randomization or blinding provides for less robust evidence to support net health outcome decisions. | Small sample size.  
Very difficult to determine which wounds received which intervention.  
Poor reporting of results. Results appeared to be pooled across groups despite the fact that each group received different treatment.  
Age range not representative of Medicare population.  
Healthy status not representative of Medicare population. | |
| Hom, 2007 | Prospective, controlled, pilot study with blinded photographic assessment | N= 8 (80 wounds)— 5 full-thickness wounds on each thigh in each volunteer | Magellan (Medtronic Inc) system used to produce PRP  
Each of the 5 sets of bilateral thigh wounds were assigned to one of 5 groups:  
Phase 1  
<table>
<thead>
<tr>
<th>Group</th>
<th>PRP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Applied on Day 0 + petrolatum ointment</td>
<td>Topical antibiotic</td>
</tr>
<tr>
<td>2</td>
<td>Applied on Day 0</td>
<td>None</td>
</tr>
</tbody>
</table>
* all wounds covered with a semi-occlusive dressing | RESULTS APPEAR TO BE POOLED ACROSS GROUPS  
Day 21: 63% PRP-treated wounds had full closure  
Day 24: 81% PRP-treated wounds had full closure  
Day 28: 88% PRP-treated wounds had full closure |  
The average time to achieve complete closure was 29.75 days for PRP-treated wounds. Presence or absence of statistical significance not reported. | |
| | Age range= 21-58 | Gender ratio= 4 M/4 F | | | | |
| | Inclusion= healthy volunteers > 21 years | Exclusion= history of diabetes, keloid/scar formation, collagen vascular disease, or bleeding disorder, anticoagulant or steroid use during past month | No drops out  
RESULTS APPEAR TO BE POOLED ACROSS GROUPS  
Day 21: 31% of control wounds had full closure  
Day 24: 44% of control wounds had full closure  
Day 28: 56% of control wounds had full closure | | | |
| | Wound type: iatrogenic punch wound (4-6 mm diameter) | | The average time to achieve complete closure was 35.38 days for control.  
The average time to achieve complete closure was 35.38 days for control.  
None of the above results achieved statistical significance. | | | |
| | Retrospective analysis design without benefit of randomization or blinding provides for less robust evidence to support net health outcome decisions. | Small sample size.  
Very difficult to determine which wounds received which intervention.  
Poor reporting of results. Results appeared to be pooled across groups despite the fact that each group received different treatment.  
Age range not representative of Medicare population.  
Healthy status not representative of Medicare population. | |
## Evidence Table: Chronic Wounds

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Design</th>
<th>Demographics</th>
<th>Intervention, outcome measures; instruments</th>
<th>Results</th>
<th>Methodological Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anitua, 2007</td>
<td>Randomized, open-label, controlled, prospective 7-day washout period then a baseline assessment then 8-week treatment period.</td>
<td>N= 15 (8 PRP; 7 control)  Mean age: 45 yrs PRP; 61 yrs control  Gender: 4 men PRP; 4 men control  Mean ulcer area: 5.5 cm² PRP; 8.9 cm² control</td>
<td>Initially: wound cleansing with normal saline/moist saline gauze dressings; debridement for ulcer bed infection  PRP group: received some PRP via injection into ulcer margins &amp; remainder as direct topical application to ulcer bed; PRP administered 1x/wk for 8 weeks.  Autologous PRP was produced using the PGRF System (BTI Biotechnology Institute, Vitoria-Gasteiz, Spain).  Control group: debridement &amp; saline cleansing 1x/wk for 8 weeks.  Sterile moist saline gauze dressings</td>
<td>3 drop-outs  Mean percentage of surface healed at eight weeks= 72.94% (p&lt;0.05).  1 ulcer bed infections  1 case of anemia but unclear from which group</td>
<td>Very small sample size (as acknowledged by the authors). The statistically significant result at 8 weeks appears to be based on a sample size of only 9 (the originally planned intent-to-treat analysis would be based on a sample size of 15).</td>
</tr>
</tbody>
</table>
vasculitis, anemia.

The primary outcome was percentage of ulcer surface area that healed. Intent-to-treat was the primary analysis. There was no mention of a power calculation.

Wound types: 64% venous; 29% pressure; 7% other.

Primary outcome was percentage of ulcer surface area that healed. Intent-to-treat was the primary analysis. There was no mention of a power calculation.

<p>| Barrett, 2003 | Uncontrolled, unblinded prospective | N= 16 (17 wounds) |
| | Inclusion= failed ≥ 4 weeks standard wound care |
| | Exclusion= infected wound |
| | Wound types: diabetic, decubitis, venous stasis, complicated surgical wound dehiscence |
| | PRP produced using SmartPReP (Harvest Technologies Corp) system |
| | Initial= Debridement + PRP + petrolatum impregnated gauze + gauze dressing |
| | Maintenance= daily topical hydrocolloid &amp; gauze dressing; PRP after 2 weeks as needed until complete closure |
| | Outcome= 100% re-epithelialization |
| | 16/17 (94%) wounds had complete wound closure |
| | 1 recurrence due to non-compliance |
| | #PRP applications per patient= 1-5 |
| | No adverse reactions reported. |
| | None |
| | Small sample size. Due to lack of randomization, blinding, and control, case reports do not provide robust evidence to support net health outcome decisions. |</p>
<table>
<thead>
<tr>
<th>N= 3/24 qualified for autologous PRP but only 2/3 were reported on in the article: Patient #2: 73 year old man with a traumatic wound Patient #11: 46 year old woman with a diabetic wound</th>
<th>PRP produced using MCS+ (Haemonetics Inc) system</th>
<th>Patient #</th>
<th>Result</th>
<th>#PRP applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>&gt;50% recovery</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Stopped treatment*</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*due to onset of osteomyelitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No adverse reactions reported.

---

<table>
<thead>
<tr>
<th>N= 53 Dehiscent Sternal Wounds</th>
<th>PRP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>64 (8)</td>
<td>66 (5)</td>
</tr>
<tr>
<td>Gender ratio-M/F</td>
<td>6/4</td>
<td>8/4</td>
</tr>
</tbody>
</table>

**Dehiscent Sternal Wounds**

<table>
<thead>
<tr>
<th>Treatment= PRP 2x/wk Control= daily washing and cleaning of wound; 1 patient received hyperbaric therapy</th>
<th>Time to complete healing (median, weeks)</th>
<th>3.5*</th>
</tr>
</thead>
<tbody>
<tr>
<td>total hospital length of stay (median, days)</td>
<td>31.5#</td>
<td></td>
</tr>
</tbody>
</table>

* p= 0.0002  
# p< 0.0001

**Dehiscent Sternal Wounds**

<table>
<thead>
<tr>
<th>Time to complete healing (median, weeks)</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>total hospital length of stay (median, days)</td>
<td>52.5</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>N= 17 Necrotic Skin Ulcers</th>
<th>PRP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>61 (18)</td>
<td>63 (16)</td>
</tr>
</tbody>
</table>

**Necrotic Skin Ulcers**

<table>
<thead>
<tr>
<th>Treatment= saline washings, PRP</th>
<th>PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to complete healing (median, weeks)</td>
<td>3.5*</td>
</tr>
<tr>
<td>total hospital length of stay (median, days)</td>
<td>31.5#</td>
</tr>
</tbody>
</table>

* p= 0.0002  
# p< 0.0001

---

None

**Small sample size. Due to lack of randomization, blinding, and control, study design does not provide robust evidence to support net health outcome decisions.**

---

**Lack of randomization and blinding weakens the study design. Relatively small sample sizes. The absolute number and frequency of complete healing not reported.**

**Strongly statistically significant results for both wound types.**
<table>
<thead>
<tr>
<th>Gender ratio- M/F</th>
<th>8/9</th>
<th>5/9</th>
<th>1x/wk Control= daily washing/cleaning with hyaluronic acid; 1 patient received autologous cultured fibroblasts</th>
<th>PRP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time to need for surgery (median, weeks)</td>
<td>15*</td>
<td>35.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*p&lt;0.0001</td>
<td>Data from patients who received hyperbaric therapy or autologous cultured fibroblasts were censored during statistical analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Complete closure by week 4 of treatment</td>
<td>No adverse reactions reported.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No adverse reactions reported.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No adverse reactions reported.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No adverse reactions reported.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No adverse reactions reported.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dehiscent Sternal Wounds**

Outcomes = time to complete healing; total hospital length of stay

**Necrotic Skin Ulcers**

Outcomes = time to need for surgery

---

**McAleer, 2006**

Case report

Wound type: diabetic

- N= 1
- Age= 57
- Gender= male

A Biomet system was used to produce PRP

Debridement + PRP + compressive dressing 1x/week

Complete closure by week 4 of treatment

No adverse reactions reported.

None

Small sample size. Due to lack of randomization, blinding, and control, case reports do not provide robust evidence to support net health outcome decisions.

---

**Klayman, 2006**

Case report

Wound type: chronic incision wound post total knee

- N= 1
- Age= 51
- Gender= male

PRP produced using SmartPReP (Harvest Technologies Corp) system

Wound size decreased from 15x15 cm to 8x6 cm with sufficient granulation tissue to proceed to skin grafting.

No adverse reactions reported.

None

Due to lack of randomization, blinding, and control, case reports do not provide robust...
<table>
<thead>
<tr>
<th>Wound types:</th>
<th>N= 24 (33 wounds)</th>
<th>A Biomet system was used to produce PRP</th>
<th>20/33 (61%) wounds had complete wound closure</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>arthroplasty in a patient with diabetes</td>
<td>PRP applied about once per week for 4 weeks; a continuous vacuum-assisted wound closure device was applied after each PRP treatment</td>
<td>Mean time to complete closure: 11 weeks</td>
<td>Small sample size. Due to lack of randomization, blinding, and control, study design does not provide robust evidence to support net health outcome decisions.</td>
<td>evidence to support net health outcome decisions</td>
</tr>
<tr>
<td>Venous stasis: 3</td>
<td>Vascular-assisted wound closure device was applied after each PRP treatment</td>
<td>5/33 wounds had no improvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcer: 2</td>
<td>Debridement + PRP + sterile gauze + and compressive dressing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic ulcers in patients with diabetes: 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcers due to diabetes-induced neuropathic patholgy: 6</td>
<td>Maintenance = debridement + PRP every 2 weeks until complete closure; limited weight-bearing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age range= 25-91 (median: 62)</td>
<td>Outcome = complete wound closure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender ratio= 13 F/11 M</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McAleer, 2006</td>
<td>Initial = Debridement + PRP + sterile gauze + and compressive dressing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncontrolled, unblinded prospective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion= presence of chronic nonhealing lower extremity wound treated unsuccessfully for ≥ 6 mos with traditional methods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion= ankle-arm indices &lt;0.60, signs of systemic or lower extremity soft tissue infection; radiographic evidence of osteomyelitis; gangrenous changes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
venous stasis, 
decubitis ulcer, arterial insufficiency, traumatic ulcers in patients with diabetes, ulcers due to diabetes-induced neuropathic pathology

Driver, 2006

Prospective, randomized, double-blinded, controlled, multi-center with a 7-day screening period (which included baseline wound assessment and debridement and application of control saline gel), a 12-week treatment period, and a 12-week follow-up period.

Inclusion= age 18-95, wound area between 0.5 and 20 cm² inclusive, full-thickness without exposure of tendon, muscle, ligaments or bone; wound ≥ 4

For the intention-to-treat analysis group:

- N= 72 (40 PRP; 32 control)
- Mean (SD) age= 56 (10) PRP; 57 (9) control
- Gender ratio= 80% M PRP; 84%M control
- Mean (SD) wound area (cm²)= 4 (5) PRP; 3 (3) control
- Mean (SD) wound volume (cm³)= 1.7 (4) PRP; 0.9 (1.2) control

PRP produced using Autologel (Cytomedix Inc) system

PRP group:
- Debridement + PRP + contact layer dressing + foam dressing
- Control group:
- Debridement + normal saline gel + contact layer dressing + foam dressing

Treatment was applied 2x per week til the wound completely healed, the 12-week treatment phase ended, or the patient withdrew or was withdrawn from the study.

All patients used

INTENT-TO-TREAT EFFICACY ANALYSIS

Wide variability in baseline wound area and volume seen in the PRP group and in the control group (with volume variability significantly greater in PRP group compared to control; p<0.0001)

There were no other statistically significant differences between groups.

<table>
<thead>
<tr>
<th># patients with complete wound closure (%)</th>
<th>PRP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>13/40 (32.5)</td>
<td>9/32 (28)</td>
</tr>
</tbody>
</table>

p= 0.79

Results from analysis of secondary outcomes not reported.

A subsequent independent audit of the study showed a 44% rate of protocol violations (32/72) that prompted a revised sample size and analysis.

Randomized controlled trial design was compromised by the large number of protocol violations.

The lack of statistical significance in the primary efficacy analysis was most likely due to the variability inserted by the large number of protocol violations and by the wide variability in wound size.

The results of this trial can serve to generate hypotheses for future randomized controlled trials but not to
fixed ankle-foot orthoses and crutches or a walker
During the 12-week treatment phase, re-initiation of treatment was prompted by re-opening of a complete closed wound.
Primary outcome= complete wound closure
Secondary outcomes= %change in wound area from baseline; %change in wound volume from baseline; area closure rate /day; volume closure rate /day
Inter-site enrollment variability led to grouping of sites during statistical analysis; 5 groups formed: teaching facilities, army facility, physicians in private practice (2 distinct sites), ambulatory care

**ANALYSIS**

No statistically significant differences between groups except %Caucasians in PRP was greater (P=0.02).

<table>
<thead>
<tr>
<th></th>
<th>PRP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td># patients with</td>
<td>13/19* (68)</td>
<td>9/21 (43)</td>
</tr>
<tr>
<td>complete wound</td>
<td></td>
<td></td>
</tr>
<tr>
<td>closure (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaplan-Meier median</td>
<td>45#</td>
<td>85</td>
</tr>
<tr>
<td>time to complete</td>
<td></td>
<td></td>
</tr>
<tr>
<td>closure (days)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p= 0.125  #p= 0.126

Size frequency distributions showed 35/40 (88%) of wounds had an area of ≤ 7.0 cm² and a volume of ≤ 2.0 cm³. An efficacy analysis of the non-outlier group (called the majority wounds group) was performed.

**SUBSET EFFICACY ANALYSIS**

<table>
<thead>
<tr>
<th></th>
<th>PRP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td># patients with</td>
<td>13/16 (81)</td>
<td>8/19 (42)</td>
</tr>
<tr>
<td>complete wound</td>
<td></td>
<td></td>
</tr>
<tr>
<td>closure (%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P= 0.036

Wide variation in healing outcomes between the 4 remaining investigational site groups (1 of the original 5 groups was eliminated during the audit) was found: 50-100% variability in PRP group and 25-67% variability in control group.
|   |   | clinics. | No statistically significant differences in the rate of adverse events were seen between PRP and control groups. |   |   |