I am submitting just one of several thousands of photos that we have taken of wounds treated with autologous platelet rich plasma. This patient is an elderly diabetic gentleman who had been treated by our group several times for various lower extremity non-healing ulcers. The attached photographs were taken three and a half weeks apart. As you will note, a single application of autologous platelet gel closed this wound on his great toe. Conventional prior treatments all failed to heal this ulcer. Please take this into consideration when making your decision for coverage of this product.

Respectfully,

Robert J. Brandt
Blood Recovery Systems of Florida, Inc.

Dear Sir or Madam,

The Association for the Advancement of Wound Care is pleased to have the opportunity to comment on "Autologous Blood Derived Products for Chronic Non-Healing Wounds (CAG-00190R2)."

On behalf of Dr. William Ennis, President Elect AAWC, and per your instructions, attached please find the document that could not accompany AAWC's comment submitted minutes ago at CMS page
https://www.cms.hhs.gov/mcd/public_comment.asp?nca_id=208&basketitem

If you have any questions, please do not hesitate to contact me.

Kind regards,

Tina Thomas
AAWC Executive Director
83 General Warren Blvd.
Suite 100
Malvern, PA 19355
Toll-free: 800-237-7285 ext. 223
Direct Line: 610-560-4158
Fax: 610-560-0501

To: Dr. Steve Phurroughs
Director, Coverage and Analysis group, CMS

From: William J. Ennis D.O.
President Elect AAWC

Cc: Executive Committee, AAWC
Tina Thomas, AAWC Executive Director

Re: NCD for Platelet rich plasma (PRP) for non healing wounds.

The AAWC is the largest, not for profit wound care organization in the United States with over 1,800 members. Our organization is represented by several healthcare disciplines as well as patients and lay caregivers. As part of our mission to facilitate optimal, evidence based wound care for patients, AAWC monitors and participates in legislative issues that have impact on our industry and membership.

AAWC does not support any company or product in particular, but AAWC does respond to process and legislative issues that impact optimal patient care. It has been well validated in the literature that growth factor therapy is a useful treatment for patients with non-healing wounds. Initially, this therapy was only available through the use of “procuren” solution, an autologous derived platelet therapy. Subsequently, bio engineered platelet derived growth factor (PDGF) became commercially available and FDA cleared, as a single agent. After the decision to eliminate payment for platelet gel in the early 1990’s, few patients were able to receive this therapy and research and development obviously was slowed by the lack of reimbursement. Recent modifications to the technique of obtaining, concentrating, activating and applying platelet derived gel has stimulated a resurgence in clinician use. In particular, there has been promising results in the treatment of acute surgical wounds where the majority of the current literature is focused.

A randomized, controlled trial reporting on the results of platelet gel therapy for diabetic foot ulcers has recently been published. Although the study failed to reach significance in the intent to treat population, sub-group analysis identified a population that seemed to achieve significantly more healing than control.

In summary, our organization has reviewed, as your group has, the current evidence surrounding the use of platelet gel in the treatment of both acute and chronic wounds. Although rigid criteria for statistically significant improvement in healing were not achieved, it is apparent that a large group of clinicians are currently using platelet gel with considerable success in the acute surgical setting. We respectfully request that a fair and complete review of the technology be conducted and that the absence of rigid scientific statistical outcomes for chronic, non healing diabetic wounds not cloud results obtained in surgical and acute wound settings, although surrogate endpoints other than healing were reported. While we are empathetic to the economic impact for CMS of these types of coverage decisions, the economic impact of non healing wounds is equally as important. If the data, in the eyes of CMS, is not compelling enough at this time for all wound types, we would suggest a consideration for studies of a sub-group of wound types. This should include a clear pathway for the necessary data to be collected and the study design. Direction from CMS as to which population would be of most potential importance from an economical and clinical basis would greatly improve the chances for companies pursuing this type of therapy in the future.

Thank you on behalf of our patients.

>This is in response to the open public comment period for the use of
>autologous blood derived products. I am a Family Nurse Practitioner
>and have been using this application for the past three years to treat
>acute and chronic non-healing wounds with GREAT success. Unfourtanely
>it has come as direct cost from the patients in which I have treated
>since it is not covered by Medicare. I honestly would have to say
that
>I have had an 80 plus percent success rate with complete closure and
>healing when using this product. It amazes me to think that this item
>it is not covered by Medicare from a cost containment standpoint
alone.
>When compared to what I would use traditionally, i.e. Negative
pressure
>wound vac, costly skin grafts, etc. My primary place of employment is
>Home Health and we see a large variety of wounds which get to be very
>costly, not only for the patient, agency, but also for the insurance
>provider. A lot of these wounds are having to be treated in the
>hospital setting for complications including but not limited to IV
>antibiotics and amputation. With the future direction of our country
>in regards to Medicare spending, the baby- boomers, and overall global
>spending, I feel it is crucial that we are wise in identifying those
>items that can save our system money. When you look at the benefits
>versus risk and cost it just makes good sense. A simple cost
>comparison of what is being done in lieu of Autologous Platelet
>Grafting such as skin grafts and surgery for dehischence, should make
>our head spin. I could go on for hours; however, I have made my
point.
>If I can be of any further assitance in regards to cost containment
and outcomes please do not hesitate to contact me at my numbers listed
below.
>
>In Kindest Regards,
>
>Todd Shaffett, RN, FNP-C
>985-630-5392 cell
>985-892-7722 office

American College of Surgeons

Washington Office: 1640 Wisconsin Avenue, NW • Washington, DC 20007 • 202/337-2701 • FAX 202/337-4271
e-mail: postmaster@facs.org ACS Web site: http://www.facs.org

July 25, 2007

Dr. Steve Phurrough
Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services
Office of Health Standards and Quality
Mail Stop C1-09-06
7500 Security Boulevard
Baltimore, MD 21244

Re: Request for reconsideration of autologous blood derivative products (CAG-00190R2)

Dear Dr. Phurrough:

I am commenting on behalf of the 71,000 Fellows of the American College of Surgeons (College) on the reconsideration of the non-coverage of autologous blood derivative products for chronic non-healing wounds. Cytomedix, the organization requesting the reconsideration, has requested coverage of platelet-rich plasma (PRP) for 1) wounds caused by an acute surgical incision or dehiscence and 2) full-thickness chronic wounds (such as Wagner grade II or higher, University of Texas Classification System Grade 2 or higher, or National Pressure Ulcer Advisory Panel Stage III and IV) that have failed an adequate course of standard therapy. I am restricting my comments to the coverage of PRP for wounds caused by an acute surgical incision or dehiscence.

Because of the large number of people who could receive the therapy, we believe CMS should insist on long-range randomized clinical trials enrolling a large number of people in several institutions. The current research does not meet those standards.

Only one article (the Englert article) reports on a randomly controlled trial; it covered only 30 patients in one institution and studied them for only 30 days postoperatively. It was a study of patients undergoing a coronary artery bypass graft (CABG) operation—an operation with a painful sternotomy incision. The authors found that chest and leg pain were reduced in patients getting PRP, but also reported on several limitations of their study and concluded by suggesting undertaking "further investigations including long-term/longitudinal follow up."

There are three articles reporting on non-randomized controlled trials. The Trowbridge article reported on a study involving postoperative infection in a large number of wounds at one institution; it relied on data submitted by physicians at the institution to the Society of Thoracic Surgeons (STS) database. However, the article concludes that:

> Future studies should include large samples and measures of product quality. Ideally, a consensus can be reached on three main issues: a uniform measure of infections, both superficial and sternal, and potentially wound dehiscence; applicable measures of platelet gel quality should be used; and a detailed report of any adverse events should be provided. If multiple teams report on sufficiently large samples, meaningful conclusions can be made concerning the use of platelet gel application as an anti-infective strategy.

The Mazzuco article reported on a trial with 53 wounds that included dehisced sternal wounds and necrotic skin ulcers of various types. That is the only study that involved dehisced wounds. The Hom article involved healthy people—not aged or disabled beneficiaries requiring surgery.

The request is for coverage of all acute wounds. Virtually all of them heal satisfactorily with currently available techniques. If coverage is extended to acute wounds, we urge that restrictions be placed on the coverage because of the lack of good evidence that treatment with PRP is effective for all wounds. Restricting coverage to certain wounds and/or coverage with evidence development would both be appropriate.

The results are encouraging and the College is supportive of PRP therapy. However, the long term effects of PRP therapy need to be considered. In addition, the costs need to be considered in light of the satisfactory healing of most wounds without PRP therapy.

If you have any questions about this letter, please contact Cindy Brown in the College's Washington Office. She may be reached on 202-337-2701 or at cbrown@facs.org.

Sincerely,

John T. Preskitt, M.D.

John Preskitt, MD FACS

WO:JP:jh/td

TERUMO

TERUMO CARDIOVASCULAR SYSTEMS CORPORATION
6200 Jackson Road, Ann Arbor, Michigan 48103-9300

July 23, 2007

Centers for Medicare and Medicaid Services
Department of Health & Human Services
Baltimore, MD 21244

Re: Public Comment Period: Autologous Blood Derived Products for Chronic Non-Healing Wounds (CAG-00190N)

Dear Dr. Phurrough,

This letter is in regards to the public comment period for a formal coverage reconsideration of the Autologous Blood Derived Product PRP Gel (CAG-00190N). We are writing in support for a National Coverage Determination (NCD) for the use of PRP Gel to treat wounds.

The use of Platelet Rich Plasma (PRP) or Autologous Platelet Gel (APG) dates back to the mid 1970's as a therapy to improve the wound healing process and improve hemostasis. In the past several years this treatment has become a standard of care at many institutions across the country. PRP has been used to significantly contain costs by accelerating wound healing and reducing the incidence of infection; many clinicians as well as patients have attested to the positive benefits of this therapy (*see reference list attachment*). Additionally, new clinical evidence has been published that fully supports the standard of practice and medically necessary use of PRP, demonstrating a clinically significant impact on outcomes, as well as showing a potentially significant economic impact by reducing infection and improving the overall healing rate in patients with chronic wounds.

PRP gel may also be medically necessary to treat acute surgical wounds. Newly published evidence specific to cardiovascular procedures clearly reports reduced pain, bruising and infection rates associated with these surgical wounds. Recent publications by Trowbridge, Mazzucco and Englert all demonstrate significant findings. Trowbridge, et al evaluated over 2,200 patients and demonstrated a significant decrease in surgical deep and superficial sternal wound infections. With the cost implications of a sternal wound infection projected at $20,012 per incidence, a significant cost impact at a national level could be realized with the further use of PRP gel.

TERUMO

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6200 Jackson Road, Ann Arbor, Michigan 48103-9300

Terumo Cardiovascular Systems Corporation is a global medical device company and a licensed distributor of the Harvest SmartPReP®2 Platelet Concentrate system. The SmartPReP®2 system utilizes a process to generate an autologous platelet graft from a small volume of blood at the point-of-care. The system has been used in thousands of procedures and has a full regulatory 510k clearance (K991430, K000456, K011032, BK000037, K020252.)

Enclosed, you will find a comprehensive list of clinical studies and evidence that support the use of PRP. We strongly feel that CMS should issue coverage for the use of PRP and that all patients should be granted the right to receive this therapy.

Sincerely,

Peter Wojcik
Senior Product Manager – Platelet Therapy

Platelet Rich Plasma - Related Articles

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2.

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Dr.Steve Phurrough
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Department of Health and Human Services
Baltimore, MD 21244

Dear Dr. Phurrough

I am writing this letter to provide you more information regarding coverage for clinical treatments with blood products in wound care. I have been using autologous platelet grafting with the Harvest Technology Smart Prep system for more than 4 years, and in fact have been using this technology in other areas of treatment for musculoskeletal pathology such as plantar fasciosis and Achilles tendonopathy. The clinical results have been astounding, and I have the case studies documented with digital photography in wounds, as well as power Doppler high resolution ultrasound imaging in musculoskeletal areas to corroborate this statement. Additionally, in wound care, I was referred several "train wreck" cases from hospital based wound care centers, which they could not heal. One patient brought me his bill for nearly $70,000 for wound care which included approximately 40 HBO treatments. We closed his wound in 35 days with two treatments of autologous platelet application.

Sadly, there is some confusion with payers who believe that this technology is the same, or nearly similar with platelet derived wound healing formulas such as Procuren, and therefore should be classified the same. As you know, Procuren is only a growth factor releasate with no platelets, white cells, fibrinogen, or other proteins other than already released growth factors. They are absolutely different products!

This technology is well documented in the scientific literature, and has assumed a large role in our management of delayed osseous unions, and acceleration of difficult osteotomies.

Thank you for your consideration in this matter. Please do not hesitate to contact me if I can provide you with any further information.

Stephen L. Barrett, D.P.M.,MBA,FACFAS
Associate Professor, Midwestern
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3

SmartPReP® Platelet Concentrate System

for the preparation of
Autologous Platelet Rich Plasma
(Platelet Graft)

Harvest Technologies Corp
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Tim Mueller
Marketing Director

Autologous Platelet Rich Plasma (Platelet Grafting)

The use of autologous biologic products such as Platelet Rich Plasma (PRP) or Platelet Concentrate (PC) or Autologous Platelet Grafting (APG) to augment and accelerate the wound healing process, especially with healing impaired patients, has become standard of practice over the last several years. This cover letter and documentation package sets out to provide 1) evidence supporting the use of PRP to improve healing of open cutaneous wounds including chronic wounds, acute surgical incisions, and dehisced wounds and 2) PRP produced from the SmartPReP Platelet Concentrate System is significantly different than platelet releasate type products (e.g. Procuren).

We believe that a therapeutic dose (protein load - platelets increased to a level of 4x or greater in an end volume of 10cc of PRP) applied to the wound site provides the physician and patient with a valuable adjunctive wound healing therapy. This wound healing treatment option should be available to all individuals in need, not only the ones that can financially afford to pay for this treatment option out-of-pocket.

Because it works, you will also find that this therapy saves the program money when compared to less effective presently covered therapies, such as whirlpool and endless dressing changes. We feel PRP therapy should be covered by CMS for the benefit of patients, providers, and tax payers. Consequently, we respectfully ask for your consideration in this matter.

Harvest Technologies Corp., Plymouth, MA

Harvest Technologies Corp. (Plymouth, MA) is a small, private manufacturer of autologous blood devices designed to help the body accelerate the natural healing process. The SmartPReP® Platelet Concentrate System for preparing autologous PRP has been used as medically necessary and policy compliant in hundreds of thousands of procedures including chronic non-healing wounds such as diabetic foot ulcers, diabetic leg wounds, venous stasis ulcers, and dehisced wounds from the foot to the sternum.

SmartPReP® Platelet Concentrate System Product Differentiation and Charactierization

It is critical to differentiate the SmartPReP® Platelet Concentrate System from platelet derived/releasate wound healing formulas (e.g. Procuren).

1. The SmartPReP® Platelet Concentrate System utilizes a process to generate an autologous platelet graft from a small (<60 cc) volume of blood at the point-of-care.
2. The SmartPReP® Platelet Concentrate System does not destroy platelets and does not manufacture or derive anything from them.
3. Since platelet releasates are not blood clots or grafts, the do not replace the body's natural response to tissue injury.
4. The PRP prepared by the SmartPReP® Platelet Concentrate System contains all the living cellular elements present in the patient's circulatory system.
5. The SmartPReP® Platelet Concentrate System uses the patient's own blood to derive an autologous clot or graft.
6. The SmartPReP® Platelet Concentrate System enhances the patient's natural response to tissue injury.

In short, there is no similarity between the Harvest Technologies SmartPReP® Platelet Concentrate System and platelet derived wound healing formulas/releasates.

Basic Biology

- All surgery results in tissue and cellular damage/injury.
- In order to optimize the natural tissue regeneration process, three biological components are required
  - Scaffold (dirt) – which can simply be the matrix of the clot or in cases of defects a tissue graft
  - Undifferentiated Cells (seeds) – which come from nearby healthy tissue
  - Signal Proteins and Adhesion Molecules (fertilizer) – which actively draw cells into the scaffold and trigger cell division
- The body's natural response to this injury is a well documented series of steps called the healing cascade.
  - In the first stage, the body forms a clot to seal the wound and achieve hemostasis. The formation of the clot includes a coagulation process of activated platelets and fibrin. The blood clot also contains many types of living cells that inhabit the circulatory system and modulate the healing cascade.
  - During the second stage (inflammatory), the macrophages and white blood cells from both the clot and surrounding tissues cleanse the wound.
  - During the third stage (regeneration), the proteins in the clot and drawn to the injury site initiate cell division for growing tissue.
  - Finally, these immature tissues are remodeled into mature tissue during the final remodeling stage
- While the primary purpose of the blood clot is to seal the wound, the proteins found in blood initiate and modulate the first three phases of the healing cascade. Consequently, increasing the protein load at the wound site up-regulates or accelerates the early phases of wound healing.
- Practitioners now have the technology to cost effectively use this healing physiology to the patient's advantage. These wound sealants use the patient's own blood and are natural, living, autologous platelet rich coagulums commonly referred to as platelet grafts. While platelets are an important constituent of the graft, the graft also includes all the living cellular elements noted above.
- As a result, the process of harvesting autologous platelet rich plasma and grafting these cellular elements from the patient's circulatory system to their integumentary system is a true grafting of tissues from one location to another. In addition, autologous platelet grafting practitioners may also choose to incorporate additional therapies and materials such as:
  - Scaffold – Allograft, autograft, synthetic materials
  - Undifferentiated Cells – bone marrow aspirate, surrounding tissue cells
  - Signal Proteins and Adhesion Molecules – plasma, white blood cells, platelets

Theory

- Much research has focused on the body's natural process of healing as it relates to the grafting or placement of these cells and proteins at the surgical site and in higher than native concentrations. Clinical opinion is that such concentrations may be likely to enhance cell migration and proliferation, thereby accelerating the healing rate.
- Regardless of the final results of research supporting this theory, the process of grafting the patient's autologous platelet coagulum to the wound sit is the most perfect copy of nature's wound sealant available to the patient and the practitioner. For this reason alone, the patient will likely experience clinical benefits.

- Practitioners will also help avoid complications and treatment failures associated with other non-autologous wound care therapies. In fact, patients who have been refractory to other therapies often respond well to autologous platelet grafting (reference enclosed Dr. Stephen Barrett letter and the Drs Britton and Dellinger white papers).

Brief Summary of the Basic Research of Clinical and Physiologic Benefits

- Platelets can affect mitogenic activity of osteoblasts (Slater, 1995).
- Platelets at baseline levels act on human mesenchymal stem cells with respect to cell recruitment and cell division (Haynesworth, 2002).
- There is a dose dependent relationship between protein load and cell migration and cell proliferation which increases as the load of proteins increases (Haynesworth, 2002).
- Several studies relate the increase in cell proliferation to increase in platelet count above baseline (Marx, 1997; Bruder, 2002; Sclafani, 2005).
- Platelet concentration can result in enhance cell proliferation and thereby allow for a reduction in autograft requirements (Patel, 2001).
- Platelet concentration can enhance healing in soft tissue (Marx, 2000; Carter, 2003)

Clearly, an established place in the medical literature describes the natural wisdom and standard of practice of platelet grafts and the biological action of platelet growth factors in cell proliferation. Sherwin Kevy, MD, of the Center for Blood Research Laboratories has documented that the platelet concentrate prepared with the Harvest Technologies SmartPReP® Platelet Concentrate System has the same functional characteristics as platelets in circulatory system.

This point is very critical and important – The concentrated platelets are functional, viable, and able to release their reservoir of growth factors once activated. Once again, there is no similarity between the product produced by the Harvest Technologies SmartPReP® Platelet Concentrate System and platelet releasate type products.

PRP Product Documentation

We believe that for a company to market a system for platelet rich plasma, the system must have documentation regarding the following:

- Evidence that the concentration process does not affect cell viability and functionality. The platelets in PRP should be equivalent to transfusable platelets using the AABB viability parameters for pH, P-Selectin (%) which measures activation, Platelet Aggregation (%) which measures functionality, and Hypotonic Stress (O.D.).
    - The Harvest Technologies SmartPReP® Platelet Concentrate System concentrates platelets in a manner that are equivalent to the AABB requirements for transfusable platelets (Kevy and Jacobson).
- The system recovers a high percentage of cells from a small sample of blood with a high level of reproducibility
    - The Harvest Technologies SmartPReP® Platelet Concentrate System consistently concentrates platelets to a 4x or greater above baseline (Kevy, 2001; Kevy, 2004; Stammers, 2004).

- The system consistently and reliably concentrates platelets to a level 4x or greater above baseline in 10 cc of end product from 60 cc of whole blood processed (Haynesworth – 5x; Fennis – 4x; Marx – 3.4x; Stammers – 4.5x)
    - The Harvest Technologies SmartPReP® Platelet Concentrate System consistently concentrates platelets to a 4x or greater above baseline (Kevy, 2001; Kevy, 2004; Stammers, 2004).
- Documentation of the protein load or total number of platelets being delivered to the wound site
    - Growth factor levels (e.g. PDGF, TGF-β, etc.) increase linearly with the concentration of platelets from the Harvest Technologies SmartPReP® Platelet Concentrate System (Kevy and Jacobson, 2001).
- Evidence of the clinical effect in a biologic model
    - The platelet concentrate produced using Harvest Technologies SmartPReP® Platelet Concentrate System was shown to up-regulate cell proliferation (Haynesworth, 2002; Sclafani, 2005).
- The system has a robust regulatory profile
    - Unlike most of the general purpose centrifuges that have no such FDA clearance, the Harvest Technologies SmartPReP® Platelet Concentrate System has several 510k clearances (K991430, K000456, K011032, BK000037, K020252)

Autologous Platelet Graft Applications

The Autologous Platelet Graft has been used and documented by several physicians around the country to be effective in a number of surgical procedures including but not limited to

- Chronic non-healing wounds
- Diabetic foot ulcers
- Diabetic leg wounds
- Venous stasis ulcers
- Pressure ulcers
- Split thickness skin grafts
- Rhytidectomy
- Blephoroplasties
- Brow lifts
- Breast reconstruction
- Abdominalplasties
- Laser resurfacing
- Dehisced sternal wounds
- Vein harvesting

It is our purpose to provide you with scientific and clinical evidence that has been either published or presented over the last few years to help demonstrate the effectiveness and need for autologous biomaterials such as Autologous Platelet Grafting

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