



# Cigna Medical Coverage Policy

**Subject Autologous Cell Therapy for  
Cardiac and Peripheral Arterial  
Disease**

**Effective Date ..... 3/15/2014**  
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## Coverage Policy

**Cigna does not cover the transplantation of cells into the myocardium for any indication because it is considered experimental, investigational or unproven.**

**Cigna does not cover autologous intra-arterial or intra-muscular bone marrow cell transplantation for peripheral arterial disease and other occlusive conditions because it is considered experimental, investigational or unproven.**

## General Background

### Autologous Cell Therapy for Treatment of Damaged Myocardium

Autologous cell therapy has been proposed for the treatment of damaged myocardium associated with cardiovascular disease, including acute myocardial infarction (MI), cardiomyopathy, and heart failure. The use of several cell types, including skeletal myoblasts, mesenchymal stem cells (also referred to as bone marrow stromal cells), and hematopoietic stem cells, has been explored for myocardial repair. Skeletal myoblasts are tissue-specific stem cells. Immature myoblasts contained in skeletal muscle can fuse with surrounding myoblasts or with damaged muscle fibers to regenerate functional skeletal muscle. Mesenchymal stem cells and hematopoietic stem cells have the capacity to differentiate into any type of cell, depending on their microenvironment. As they mature, they can acquire all the characteristics of the target tissue, such as myocardium and cardiac vessels. Cells may be delivered systemically or locally, and must then proliferate to provide adequate new tissue prior to differentiating into functional cardiomyocytes that couple with the myocardium. Some cells may require significant manipulation prior to implantation. Stem cells may be delivered

via infusion into the coronary arteries or injection into the ventricular wall. The mechanism of action of cell therapy for damaged myocardium is not entirely clear and is likely multifactorial. Stem cells may improve cardiac function by increasing vascularity in the area of ischemia, and may also acquire phenotypic properties of the neighboring cardiac myocytes. In the case of acute MI, improved microvascular function may result in improved regional and global left ventricular function.

Although cell therapy for damaged myocardium is a promising treatment option, randomized controlled trials with long-term follow-up are necessary to establish the efficacy of these procedures and address a number of unresolved, technical issues, including optimum cell type, ideal number of cells, factors that promote engraftment, surgical delivery method and patient selection criteria.

### **U.S. Food and Drug Administration (FDA)**

The U.S. Food and Drug Administration (FDA) regulates cells that are processed in commercial laboratories, as well as the surgical devices used to inject the cells into the myocardium. The FDA has not yet issued approvals for any technology associated with the transplantation of autologous cells for the treatment of damaged myocardium. MyoCell™ and MyoCath™ (BioHeart, Fort Lauderdale, FL) are currently undergoing Phase I and II studies for investigation for FDA approval. MyoCell, which consists of expanded autologous skeletal myoblast, is delivered by the MyoCath, a transendocardial injection catheter. The system is being evaluated for feasibility as well as safety and efficacy in the treatment of post-infarct deterioration of cardiac function in subjects with congestive heart failure.

**Literature Review: Autologous Cell Therapy for Treatment of Damaged Myocardium** Traverse et al., for the Cardiovascular Cell Therapy Research Network (CCTRN) (2012) conducted a randomized, double-blind placebo controlled trial to determine the effect of intracoronary autologous bone marrow mononuclear cell (BMC) delivery after ST elevated myocardial infarction (STEMI). The primary end points were change in global (left ventricular ejection fraction [LVEF]) and regional (wall motion) LV function in infarct and border zones at six months, and change in LV function as affected by timing of treatment on day three vs. day seven. At six months, there was no significant increase in LVEF for the BMC group vs. the placebo group ( $p=.96$ ). There was no significant treatment effect on regional LV function observed in either infarct or border zones, and there were no significant differences in change in global LV function for patients treated at day three or day seven ( $p=.70$ ). Treatment timing had no significant effect on regional LV function recovery.

Duckers et al. (2011) reported on a Phase II, randomized trial that evaluated the percutaneous intramyocardial transplantation of autologous skeletal myoblasts in congestive heart failure patients (SEISMIC trial). The patients were randomized 2:1 to autologous skeletal myoblast therapy vs. optimal medical treatment. The primary safety end-point was identified as the incidence of procedural and device related serious adverse events, whereas the efficacy endpoints were defined as the change in global left ventricular ejection fraction (LVEF) by multigated acquisition (MUGA) scan, change in New York Heart Association (NYHA) classification of heart failure and in the distance achieved during a six minute walk test (6MW) at 6-month follow-up. Forty subjects were randomized to the treatment arm ( $n=26$ ), or to the control arm ( $n=14$ ). There were 12 sustained arrhythmic events and one death after episodes of ventricular tachycardia (VT) in the treatment group and 14 events in the control group ( $P=ns$ ). At six month follow-up, 6MW distance improved by  $60.3\pm54.1$  meters in the treated group as compared to no improvement in the control group ( $0.4\pm185.7$  meters;  $P=ns$ ). In the control group, 28.6% experienced worsening of heart failure status (4/14), while 14.3% experienced an improvement in NYHA classification (2/14). In the myoblast-treatment arm, one patient experienced a deterioration in NYHA classification (8.0%), whereas five patients improved one or two classes (20.0%;  $P=0.06$ ). However, therapy did not improve the global LVEF as measured by MUGA at 6-month follow-up. This study is preliminary and further evaluation of efficacy and safety needs to be validated in future phase II/III studies.

Traverse et al. (2011) reported on results of a randomized, double-blind, placebo-controlled trial (LateTIME) of the National Heart, Lung, and Blood Institute-sponsored Cardiovascular Cell Therapy Research Network of 87 patients with significant LV dysfunction (LV ejection fraction [LVEF]  $\leq 45\%$ ) following successful primary percutaneous coronary intervention (PCI). The study examined if intracoronary delivery of autologous BMCs improves global and regional LV function when delivered 2 to 3 weeks following first MI. The authors noted that clinical trials suggest that intracoronary delivery of autologous bone marrow mononuclear cells (BMCs) may improve left ventricular (LV) function when administered within the first week following myocardial infarction (MI). Since a substantial number of patients may not present for early cell delivery, the efficacy of autologous BMC delivery two to three weeks post-MI warrants investigation. Intracoronary infusion of autologous BMCs (total

nucleated cells) or placebo (BMC: placebo, 2:1) was performed. The main outcomes were changes in global (LVEF) and regional (wall motion) LV function in the infarct and border zone between baseline and 6 months, measured by cardiac magnetic resonance imaging. Secondary end points included changes in LV volumes and infarct size. Change between baseline and six months in the BMC group vs. placebo for mean LVEF (48.7% to 49.2% vs. 45.3% to 48.8%; between-group mean difference,  $-3.00$ ; 95% CI,  $-7.05$  to  $0.95$ ), wall motion in the infarct zone (6.2 to 6.5 mm vs. 4.9 to 5.9 mm; between-group mean difference,  $-0.70$ ; 95% CI,  $-2.78$  to  $1.34$ ), and wall motion in the border zone (16.0 to 16.6 mm vs. 16.1 to 19.3 mm; between-group mean difference,  $-2.60$ ; 95% CI,  $-6.03$  to  $0.77$ ) were not statistically significant. No significant change in LV volumes and infarct volumes was observed; both groups decreased by a similar amount at 6 months vs. baseline. The authors concluded that among patients with MI and LV dysfunction following reperfusion with PCI, intracoronary infusion of autologous BMCs vs. intracoronary placebo infusion, two to three weeks after PCI, did not improve global or regional function at 6 months.

Menasche et al. (2008) reported on results of a Phase II study of skeletal myoblast transplantation referred to as the myoblast autologous grafting in ischemic cardiomyopathy or MAGIC trial (Menasche, et al., 2004; Menasche, et al., 2008). The randomized, placebo-controlled, double-blind trial involved 97 patients in 30 clinical centers in several European countries and Canada. Patients received either cells grown from a skeletal muscle biopsy or a placebo solution injected in and around the scar. An implantable cardioverter-defibrillator was placed in all patients. The primary outcomes were the six-month changes in global and regional LV function as assessed by echocardiography. The safety end-points included a composite index of major cardiac adverse events and ventricular arrhythmias. Patients were randomized to receive myoblasts (400 [n=33] or 800 [n=34] million) or the placebo (n=30). The myoblast transfer did not improve regional or global LV function beyond that seen in the control group. The absolute change in ejection fraction (median [interquartile range]) between 6 months and baseline was 4.4% (0.2; 7.3), 3.4% ( $-0.3$ ; 12.4), and 5.2% ( $-4.4$ ; 11.0) in the placebo, low-dose, and high-dose groups, respectively (p=0.95). There were a higher number of arrhythmic events in the myoblast-treated patients, but six-month rates of major cardiac adverse events and of ventricular arrhythmias did not differ significantly between the groups.

The REPAIR-AMI trial (Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction), a double-blind, placebo-controlled, multicenter trial, included 204 patients and examined whether intracoronary infusion of enriched BMC is associated with improved global LV function in patients with MI treated with state-of-the-art methods (Schachinger, et al., 2006). At four months, it was noted that the absolute improvement in the global LVEF was significantly greater in the BMC group than in the placebo group. Patients with baseline LVEF at or below the median value of 48.9% appeared to derive the most benefit. At one year, intracoronary infusion of BMC was associated with a reduction in the prespecified combined clinical end point of death, recurrence of MI, and any revascularization procedure. Assmus, et al. (2010) reported on two-year outcomes from the REPAIR-AMI trial. At two years, the cumulative end point of death, myocardial infarction, or necessity for revascularization was noted to be reduced in the BMC group compared with placebo group (hazard ratio, 0.58; 95% CI, 0.36–0.94; p=0.025). In addition, the combined end point death and recurrence of myocardial infarction and rehospitalization for heart failure, reflecting progression toward heart failure, was reduced in the BMC group (hazard ratio, 0.26; 95% CI, 0.085–0.77; p=0.015). The authors note that larger studies focusing on clinical event rates are warranted to confirm the effects of BMC administration on mortality and progression of heart failure in patients with AMIs.

Clifford et al. (2012) conducted a Cochrane systematic review to evaluate the effectiveness of adult bone marrow-derived stem cells to treat acute myocardial infarction (AMI). The trial included 33 randomized controlled trials (1765 participants) that compared autologous stem/progenitor cells with no autologous stem/progenitor cells in patients with AMI. Stem/progenitor cells were not associated with statistically significant changes in the incidence of mortality or morbidity. In short term follow-up, stem cell treatment was observed to improve LVEF significantly (weighted mean difference [WMD] 2.87, 95% CI 2.00 to 3.73). The improvement in LVEF was maintained over long-term follow-up of 12–61 months (WMD 3.75, 95% CI 2.57–4.93). The authors concluded that the results of systematic review suggest that moderate improvement in global heart function is significant and sustained long-term. However, because mortality rates after successful revascularization of the culprit arteries are very low, larger number of participants would be required to assess the full clinical effect of this treatment. Standardization of methodology, cell dosing and cell product formulation, timing of cell transplantation and patient selection may also be required to reduce the substantial heterogeneity observed among the included studies.

Abdel-Latif et al. (2007) conducted a systematic review and meta-analysis of randomized controlled trials and cohort studies of bone marrow derived cells (BMCs) transplantation to treat ischemic heart disease. Eighteen studies (12 randomized controlled studies and six cohort studies) with 999 patients were included in the review. The main outcomes for the review were change from baseline in mean LV ejection fraction, infarct scar size, LV end-systolic volume and LV end-diastolic volume. The adult BMCs used in the studies included BM mononuclear cells, BM mesenchymal stem cells, and BM-derived circulating progenitor cells. When BMC transplantation was compared to controls, the results included: improved left ventricular ejection fraction (pooled difference, 3.66%; 95% confidence interval [CI], 1.93%–5.40%;  $p < 0.001$ ); reduced infarct scar size (–5.49%; 95% CI, –9.10% to –1.88%;  $p = 0.003$ ); and reduced left ventricular end-systolic volume (–4.80 ml; 95% CI, –8.20 to –1.41 ml;  $p = 0.006$ ). The authors note that the available evidence suggests that BMC transplantation is associated with modest improvements in physiologic and anatomic parameters in patients with both acute MI and chronic ischemic heart disease. The results support the conduction of large randomized trials to evaluate the long-term impact of BMC therapy as compared with standard of care on patient-important outcomes.

Lipinski et al. (2007) performed a meta-analysis of clinical trials on intracoronary cell therapy after acute MI to determine the impact of intracoronary cell therapy on post-infarction LV function. Ten controlled studies with 698 patients were included in the review, with a median follow-up of six months (range of 3 to 18 months). The primary end point in the studies was change in LVEF, with secondary end points including changes in infarct size, cardiac dimensions, and dichotomous clinical outcomes. Review of the studies indicated that subjects that received intracoronary cell therapy had a significant improvement in LVEF (3.0% increase; 95% CI 1.9 to 4.1;  $p < 0.001$ ), as well as a reduction in infarct size (–5.6%; 95% CI –8.7 to –2.5;  $p < 0.001$ ) and end-systolic volume (–7.4 ml; 95% CI –12.2 to –2.7;  $p = 0.002$ ), and a trend toward reduced end-diastolic volume (–4.6 ml; 95% CI –10.4 to 1.1;  $p = 0.11$ ). It was also noted that intracoronary cell therapy was associated with a minimally significant reduction in recurrent acute MI ( $p = 0.04$ ) and with trends toward reduced death, rehospitalization for heart failure and repeat revascularization. Meta-regression suggested the possibility of an existence of a dose-response association between injected cell volume and LVEF change ( $p = 0.066$ ). The authors concluded that the data confirms the beneficial impact of this therapy, and further multicenter randomized trials are supported.

### **Cell Therapy for Peripheral Arterial Disease**

Peripheral arterial (PAD) generally refers to a disorder that obstructs the blood supply to the lower or upper extremities. It is generally caused by atherosclerosis, but may result from thrombosis, embolism, vasculitis, fibromuscular dysplasia, or entrapment. PAD correlates strongly with risk of major cardiovascular events, and is frequently associated with coronary and cerebral atherosclerosis (Creager, et al., 2011). The main symptom of PAD is intermittent claudication. More severe symptoms include pain at rest, ulceration and gangrene. Worsening of the condition may lead to critical limb ischemia. The goal for treatment of PAD is reduction in cardiovascular morbidity and mortality, and improvement in quality of life by decreasing symptoms of claudication, eliminating rest pain, and preserving limb viability. Treatment may include risk factor modification by lifestyle measures and pharmacologic therapy to reduce the risk of adverse cardiovascular events, such as MI, stroke, and death. The symptoms of claudication may be treated with pharmacotherapy or exercise rehabilitation. Management of critical limb ischemia often includes endovascular interventions or surgical reconstruction to improve blood supply and to maintain limb viability. Revascularization may be performed in some patients with disabling symptoms of claudication that persist despite exercise therapy and pharmacotherapy (Creager, et al., 2011).

To treat the symptoms of severe forms of PAD where revascularization procedures are not possible, research has been focusing on the use of bone marrow (BM)-derived stem and progenitor cells, which have been utilized in a potential new therapeutic option to induce therapeutic angiogenesis. The goal with this treatment is to improve the vascularization of the ischemic leg so that perfusion increases sufficiently for wound healing to occur, and to resolve pain at rest. Intramuscular and intra-arterial injection or a combination of both has been investigated in treatment of PAD. The underlying principle of intramuscular injection is the creation of a cell depot with paracrine activity in the ischemic area, although the mechanisms by which transplanted cells improve the patients' clinical status are unclear (Lawall, et al., 2011). Intramuscular injection is generally administered into the gastrocnemius muscle along a symmetric grid with a fixed number of injections (between 20 and 60) in most trials. There is no apparent direct comparison between different intramuscular injection sites and numbers of injections. Issues to be resolved include selection of optimal cell type, isolation method, cell number, and the role of colony stimulating factors, route of administration, and paracrine stimulation mechanisms (Lawall, et al., 2011).

Autologous intra-arterial or intra-muscular bone marrow cell transplantation for peripheral arterial disease and other occlusive conditions is an emerging technology. Studies evaluating this treatment approach are limited. Additional well designed randomized controlled trials are needed to evaluate the safety, efficacy, and long-term outcomes of this procedure..

### **Literature Review: Stem-Cell Transplantation for Peripheral Arterial Disease**

A Phase II double-blind placebo-controlled study was conducted by Poole et al. (2013) to investigate whether therapy with granulocyte-macrophage colony-stimulating factor (GM-CSF improves exercise capacity in patients with intermittent claudication (n=159). Patients were randomized to receive four weeks of subcutaneous injections of GM-CSF, 5000 ug/day three times per week (n=79), or placebo (n=80). There was no significant difference between groups in the primary outcome measure, peak treadmill walking time (PWT), at three months (mean difference in change in PWT, 53 seconds [95% CI, -6 to 112], p=.08).

Walter et al. (2011) reported on a Phase II, double-blind, randomized-start trial (PROVASA). Forty patients with critical limb ischemia received either intra-arterial administration of BM-MNC or placebo followed by active treatment with BM-MNC (open label) after three months. Intra-arterial administration of BM-MNC did not significantly increase ankle-brachial index and, therefore, the trial missed its primary end point. It was found that cell therapy was associated with significantly improved ulcer healing (ulcer area:  $3.2 \pm 4.7 \text{ cm}^2$  to  $1.89 \pm 3.5 \text{ cm}^2$  [P=0.014] versus placebo,  $2.92 \pm 3.5 \text{ cm}^2$  to  $2.89 \pm 4.1 \text{ cm}^2$  [P=0.5]) and reduced rest pain ( $5.2 \pm 1.8$  to  $2.2 \pm 1.3$  [P=0.009] versus placebo,  $4.5 \pm 2.4$  to  $3.9 \pm 2.6$  [P=0.3]) within three months. Limb salvage and amputation-free survival rates did not change between the groups. Repeated BM-MNC administration and higher BM-MNC numbers and functionality were found to be the only independent predictors of improved ulcer healing. Ulcer healing induced by repeated BM-MNC administration significantly correlated with limb salvage ( $r=0.8$ ;  $P<0.001$ ). The authors concluded that intra-arterial administration of BM-MNC is safe and feasible and accelerates wound healing in patients without extensive gangrene and impending amputation. They state that exploratory findings of this pilot trial need to be confirmed in a larger randomized trial in patients with critical limb ischemia and stable ulcers.

Prochazka et al. (2010) conducted a randomized study of 96 with critical limb ischemia (CLI). A total of 96 patients with CLI and foot ulcer (FU) were randomized into two groups. Patients in group I (n=42) underwent local treatment with autologous bone marrow stem cells (ABMSC) concentrate while those in group II (n=54) received standard medical care. The bone marrow concentrate was administered by 40 injections, into the ischemic limb along the posterior and anterior tibial artery. The frequency of major limb amputation in groups I and II was 21% and 44% within the 120 days of follow up, respectively ( $p<0.05$ ). In the salvaged limbs of group I both toe pressure and toe brachial index increased (from  $22.66 \pm 5.32$  to  $25.63 \pm 4.75 \text{ mmHg}$  and from  $0.14 \pm 0.03$  to  $0.17 \pm 0.03$ , respectively). The CD34+ cell counts in bone marrow concentrate (BMC) decreased (correlation:  $p=0.024$ ) with age, even though no correlation was found between age and healing. An unexpected finding in the study was made of relative, bone marrow lymphopenia in the initial bone marrow concentrates in patients who failed ABMSC therapy (21% of major limb amputation), with the difference noted to be statistically significant ( $p<0.040$ ). The authors concluded ABMSC therapy results in 79% limb salvage in patients suffering from CLI and FU. Lymphopenia and thrombocytopenia were identified as potential causative factors in the remaining 21% that suggest that at least a partial correction with platelet supplementation may be of use. Further studies are needed to validate these findings.

Moazzami et al. (2011) reported on a Cochrane review of local intramuscular transplantation of autologous mononuclear cells for critical lower limb ischemia. Two small, randomized studies, with a combined total of 57 patients, met the inclusion criteria. In one study the effects of intramuscular injections of bone marrow derived mononuclear cells (BMMNCs) in the ischemic lower limbs of patients with critical limb ischemia (CLI) were compared with control (standard conservative treatment). No significant difference was observed between the two groups for either pain ( $P=0.37$ ) or the ankle brachial pressure index (ABI) parameter. However, the treatment group showed a significantly smaller proportion of participants undergoing amputation compared with the control group ( $P=0.026$ ). In the other study, following subcutaneous injections of granulocyte colony-stimulating factor (G-CSF) for five days peripheral blood derived mononuclear cells were collected and then transplanted by intramuscular injections into ischemic lower limbs. The effects were compared with daily intravenous prostaglandin E1 injections (control group). Pain reduction was greater in the treatment group than in the control group ( $P<0.001$ ) as was an increase in ABI (mean increase 0.13 vs. 0.02;  $P<0.01$ ). The treatment group experienced a statistically significant increase in pain-free walking distance compared with the control group (mean increase 306.4m vs. 78.6m,  $P=0.007$ ). A smaller proportion of participants underwent amputation

in the treatment group as compared with the control group (0% versus 36%,  $P=0.007$ ). The author concluded that the data from the published trials suggest that there is insufficient evidence to support this treatment. These results were based on only two trials which had a very small number of participants. Therefore evidence from larger, randomized, controlled trials is needed in order to provide adequate statistical power to assess the role of intramuscular mononuclear cell implantation in patients with critical limb ischemia.

Fadini et al. (2010) conducted a meta-analysis and systematic review of the literature regarding autologous stem cell therapy for PAD. Most were pilot studies that assessed the safety and feasibility of cell therapy. There were six controlled trials (four randomized and two non-randomized), plus four trials in which the non-treated limbs served as internal controls. The route of cell administration was intramuscular in 33 studies, intra-arterial in 4 trials and combined intra-arterial plus intramuscular in 1 trial. The median follow-up was six months. A meta-analysis of 37 trials indicated that autologous cell therapy was effective in improving surrogate indexes of ischemia, subjective symptoms and hard endpoints (i.e., ulcer healing and amputation). However, G-CSF monotherapy was not associated with significant improvement in the same endpoints. Patients with thromboangiitis obliterans demonstrated some larger benefits than those with atherosclerotic PAD. The intra-muscular route of administration and the use of bone marrow cells appeared to be more effective than the intra-arterial administration and the use of mobilized peripheral blood cells. The procedures appeared to be well-tolerated and generally safe. The authors concluded that the meta-analysis indicates that intramuscular autologous bone marrow cell therapy is a feasible, relatively safe and potentially effective therapeutic strategy for PAD patients, who are not candidates for traditional revascularization. Larger, placebo-controlled, randomized multicenter trials need to be planned and conducted to confirm these findings.

### **Professional Societies/Organizations**

The use of cell therapy is not mentioned in the 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Guidelines for the Management of Heart Failure or the 2011 Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease.

The 2011 ACCF/AHA/Society for Angiography and Intervention (SCAI) Guideline for Percutaneous Coronary Intervention includes intracoronary stem cell infusions for chronic and acute ischemic heart disease as one of numerous potential advances in the field of PCI that were considered for formal evaluation by the writing committee, but it was thought that there were insufficient data at present to formulate any formal recommendations.

### **Use Outside the U.S.**

The European Society of Cardiology (ESC) published a consensus statement concerning the clinical investigation of the autologous adult stem cells for repair of the heart. The statement noted the following regarding this treatment (Bartunek, et al., 2006):

- The use of autologous stem/progenitor cell therapy is not at a stage to be used in routine clinical practice.
- It is timely to perform the following studies that should be designed on the basis of the published data:
  - Further large, double-blind, randomized controlled trials for the use of autologous bone marrow cells in the treatment of AMI. The patient population should be all those presenting within 12 hours of AMI and treated with immediate revascularization, be it primary angioplasty or fibrinolysis.
  - A double-blind, randomized controlled trial for the use of autologous bone marrow cells in the treatment of MI in those patients presenting late (>12 h) or who fail to respond to therapy (candidates for 'rescue' angioplasty). Although, these groups may represent a small proportion of all patients with AMI, their prognosis remains poor.
  - Double-blind, randomized controlled trials for the use of autologous bone marrow cells or skeletal myoblasts in the treatment of heart failure secondary to ischemic heart disease. At some stage, the role of autologous stem/progenitor cells in the treatment of cardiomyopathies (in particular, dilated cardiomyopathy) will need to be examined.
  - A series of well-designed small studies to address safety or mechanism to test specific hypotheses (e.g., studies with labeled cells or to investigate paracrine or autocrine mechanisms). Such hypotheses would have arisen from basic science experiments.
  - Studies to confirm the risk/benefit ratio of the use of cytokines alone (e.g., granulocyte colony stimulating factor) or in conjunction with stem/progenitor cell therapy.

- The studies should include the following:
  - The end points should focus on robust clinical outcomes, as well as MACE (major adverse cardiac events), subjective benefit, and economic gain.
  - Outcome measures for future trials should be standardized so that comparisons can be made.
  - Questions concerning optimal timing of delivery, number of cells delivered, and the route of delivery (e.g., at the time of bypass surgery or by percutaneous techniques) will need to be addressed.
  - Studies in this field will need to recruit approximately 1000 patients to provide enough statistical power to be meaningful. The studies should be multicenter and ideally pan-European.
- It is not until the results of these studies are available that the role of autologous cells as a treatment could be considered.

## Summary

Autologous cell therapy using several cell types, including skeletal myoblasts, mesenchymal stem cells and hematopoietic stem cells, has been proposed as a method to treat myocardial damage. Although this is a promising emerging technology, large-scale randomized controlled clinical trials with long-term follow-up are necessary to establish the efficacy of these procedures. A number of technical issues remain unresolved, including optimum cell type, ideal number of cells, factors that promote engraftment, surgical delivery method and patient selection criteria. The long-term viability of the transplanted cells has not been proven.

Autologous intra-arterial or intra-muscular bone marrow cell transplantation has been explored for the treatment of peripheral arterial disease and other occlusive conditions. Studies published to date are limited. Additional well designed trials with long-term follow-up are needed to determine the safety, efficacy and long term outcomes of this treatment.

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## Coding/Billing Information

**Note:** 1) This list of codes may not be all-inclusive.

2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

**Experimental/Investigational/Unproven/Not Covered when used to report the transplantation of cells into the myocardium:**

CPT* Codes	Description
33999	Unlisted procedure, cardiac surgery
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38232	Bone marrow harvesting for transplantation; autologous
93799	Unlisted cardiovascular service or procedure
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post transplant care in the global definition

**Experimental/Investigational/Unproven/Not Covered when used to report autologous intra-arterial or intra-muscular bone marrow cell transplantation for peripheral arterial disease and other occlusive conditions:**

CPT* Codes	Description
37799	Unlisted vascular surgery
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38232	Bone marrow harvesting for transplantation; autologous

93799	Unlisted cardiovascular services or procedure
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post transplant care in the global definition

#### Experimental/Investigational/Unproven/Not Covered

CPT* Codes	Description
0263T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, 1 leg, including ultrasound guidance, if performed; complete procedure including unilateral or bilateral bone marrow harvest
0264T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, 1 leg, including ultrasound guidance, if performed; complete procedure excluding bone marrow harvest
0265T	Intramuscular autologous bone marrow cell therapy, with preparation of harvested cells, multiple injections, 1 leg, including ultrasound guidance, if performed; unilateral or bilateral bone marrow harvest only for intramuscular autologous bone marrow cell therapy

\*Current Procedural Terminology (CPT®) © 2013 American Medical Association: Chicago, IL.

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