Decision Memo for Dermal injections for the treatment of facial lipodystrophy syndrome (FLS) (CAG-00412N)

Decision Summary

On July 16, 2009, we initiated the national coverage determination (NCD) process by opening a tracking sheet for Dermal Injections for the Treatment of Facial Lipodystrophy Syndrome (CAG# 00412). After examining the available medical evidence, we are issuing the following decision.

Dermal injections for facial lipodystrophy syndrome (LDS) are only reasonable and necessary using dermal fillers approved by the Food and Drug Administration (FDA) for this purpose, and then only in HIV infected beneficiaries when facial LDS caused by antiretroviral HIV treatment is a significant contributor to their depression. All other indications are noncovered.

Back to Top

Decision Memo

To: Administrative File CAG-00412N
Reconstructive Treatments for Facial LDS

From:

Louis B. Jacques, MD
Director, Coverage and Analysis Group

Tamara Syrek Jensen, JD
Deputy Director, Coverage and Analysis Group

Marcel E. Salive, MD, MPH
Director, Division of Medical and Surgical Services

JoAnna Baldwin, MS
Lead Analyst, Division of Medical and Surgical Services

Madeline Ulrich, MD, MS
Medical Officer, Division of Operations and Information Management

Subject: National Coverage Decision Memorandum for Dermal Injections for Facial Lipodystrophy Syndrome

Date: March 23, 2010

I. Decision

On July 16, 2009, we initiated the national coverage determination (NCD) process by opening a tracking sheet for Dermal Injections for the Treatment of Facial Lipodystrophy Syndrome (CAG# 00412). After examining the available medical evidence, we are issuing the following decision.

Dermal injections for facial lipodystrophy syndrome (LDS) are only reasonable and necessary using dermal fillers approved by the Food and Drug Administration (FDA) for this purpose, and then only in HIV infected beneficiaries when facial LDS caused by antiretroviral HIV treatment is a significant contributor to their depression. All other indications are noncovered.

II. Background

In the United States, the majority of the population infected with HIV is generally younger and predominantly male whereas the Medicare beneficiary population is mostly aged >65 and 51% female. The CDC estimates that in 2006, 70% of those living with HIV were between the ages of 25 and 49 and 74% were male. In 2007, of the estimated 44,084 newly diagnosed HIV/AIDS cases only 1.8% (804 cases) were in the population aged >65[1]. These data tell us that while HIV is quite rare in the Medicare beneficiary population over age 65, HIV infected beneficiaries may have qualified for Medicare through disability.

In the late 1990s the introduction of protease inhibitors in combination with other anti-retroviral drugs such as reverse transcriptase inhibitors and antiviral nucleoside analogues resulted in increased CD4 cell counts and reduced viral load in patients being treated for human immunodeficiency virus (HIV) infection. These improvements, which lowered both the morbidity and mortality of HIV, came to be referred to as highly active antiretroviral therapy (HAART).[2] The use of these new treatments, however, was found to have complications that included: lipoatrophy (localized loss of subcutaneous fat); lipodystrophy (LD) (regionalized fat accumulation); and metabolic abnormalities (insulin resistance, hypercholesterolemia and hypertriglyceridemia). Collectively these complications are referred to as LDS.[3] When the treatment of HIV with HAART leads to facial lipoatrophy (FLA), it is the facial appearance caused by FLA that contributes to depression and related adverse psychological issues. FLA may occur by itself and should not be confused with HIV wasting, which may also occur in the face. HIV wasting affects muscle rather than subcutaneous fat and is not a part of LDS.

There is no agreement on either the precise mechanisms of LDS or its definition. There is no specific treatment to prevent its development following drug treatment for HIV, particularly with thymidine analogues. Some patients were initially so disturbed by changes in appearance resulting from drug therapy that they discontinued HAART, although at least one study concluded that there was no association between drug discontinuance and lipoatrophy[4]. Estimates of the number of HIV patients who have developed facial atrophy during treatment ranged as high as 80% in the late 1990s, but have declined in recent years as a result of modifications to HAART dosing. One recent review estimated the prevalence at 13%-38%[5].

Literature dealing with HIV induced FLA indicates that patients are particularly concerned with the adverse psychological effects of this condition relating to body image and how this negatively impacts quality of life through decreased self esteem, social isolation and depression. It is difficult to compare these adverse psychological effects across the literature as varying measures have been used. The LDS characteristically causes loss of facial fat from the cheeks giving the face a hollow appearance with thinning of the overlying skin. As the condition progresses, underlying musculature may appear more prominent with the overall impression of premature aging or illness. The fat lost from the face may redistribute to other parts of the body such as abdomen, neck and breasts. Atrophy of the arms and legs may also occur. Patients have reported feeling stigmatized by these changes, particularly if their HIV status has not been disclosed previously, and believe their relationships with others are adversely affected.

Implants or injectable soft-tissue materials such as bovine or human collagen, silicone or autologous fat have also been used to treat HIV FLA but are not addressed in this decision.This analysis focuses upon two recently approved synthetic injectable products for treatment of HIV FLA, poly-L-lactic acid and calcium hydroxylapatite.

III. History of Medicare Coverage

Current Request

CMS received an external request on behalf of a Medicare beneficiary for coverage of reconstructive treatments for facial LDS. This request was opened after the agency determined that dermal injections to treat this condition were not excluded as cosmetic surgery under §1862(a)(10) of the Social Security Act.

Benefit Category

On July 16, 2009, CMS posted a memorandum (http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=20) stating that the service is not excluded as cosmetic surgery and listing three Part B benefit categories that may apply. CMS did not have a national coverage determination regarding the use of dermal injections for the treatment of facial LDS. Absent national policy, coverage was at the discretion of local Medicare contractors.

Medicare is a defined benefit program. An item or service must fall within a benefit category under Part A or Part B as a prerequisite to Medicare coverage. Dermal injections for facial LDS may be included under the benefit categories set forth at section 1861(s)(1) of the Act when performed by a physician, section 1861(s)(2)(A) of the Act when performed incident to a physician's professional service in a physician's office, and section 1861(s)(2)(B) of the Act as a hospital service incident to physicians' services when rendered to hospital outpatients. This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

July 16, 2009	CMS opens a national coverage analysis for the use of dermal injections for the treatment of facial LDS in HIV infected persons.
August 15, 2009	CMS receives 43 comments by the closing date of the initial 30-day public comment period.
December 23, 2009	CMS posts the proposed decision memorandum.
January 22, 2010	Sixty-nine public comments are received on the proposed decision by the closing date of the 30-day comment period.

V. FDA Status

Two dermal injectables have FDA approval for the indication reviewed in this memorandum. Both injectables have other approved indications.

RADIESSE© (http://www.accessdata.fda.gov/cdrh_docs/pdf5/P050037b.pdf, accessed 10/2/09)
Indications for use:
RADIESSE is indicated for subdermal implantation for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.
Device description:
RADIESSE is a sterile, non-pyrogenic, semi-solid, cohesive implant, whose principle component is synthetic calcium hydroxylapatite suspended in a gel carrier of sterile water for injection, glycerin and sodium carboxymethylcellulose. RADIESSE (1.3 cc and 0.3 cc) has a CaHA particle size range of 25-45 microns and should be injected with a 25 to 27 gauge needle.
Contraindications:
* RADIESSE is contraindicated for patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
* RADIESSE is not to be used in patients with known hypersensitivity to any of the components.
Warnings:
* Use of RADIESSE in any person with active skin inflammation or infection in or near the treatment area should be deferred until the inflammatory or infectious process has been controlled.
* Injection procedure reactions to RADIESSE have been observed consisting mainly of short-term (i.e., < 7 days) bruising, redness and swelling.
* Special care should be taken to avoid injection into the blood vessels. An introduction into the vasculature may occlude the vessels and could cause infarction or embolism...
* The safety and effectiveness of RADIESSE for use in the lips has not been established. There have been published reports of nodules associated with the use of RADIESSE injected into the lips.

SCULPTRA™ (http://www.accessdata.fda.gov/cdrh_docs/pdf3/P030050b.pdf, accessed 10/2/09)
Indications for use:
SCULPTRA is intended for restoration and/or correction of the signs of facial fat loss lipoatrophy) in people with human immunodeficiency virus.
Device description:
SCULPTRA is an injectable implant that contains microparticles of poly-L-lactic acid, a biocompatible, biodegradable, synthetic polymer from the alpha-hydroxy-acid family.
SCULPTRA is reconstituted prior to use by the addition of Sterile Water for Injection, USP (SWFI) to form a sterile non-pyrogenic suspension.

VI. General Methodological Principles

When making national coverage decisions under section 1862(a)(1)(A) of the Social Security Act, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will be either redacted or not be made available to the public. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

A patient, having been treated for HIV infection with HAART, may have developed LDS which can include changes in the physical appearance of the face such that they may contribute to psychological conditions (e.g., depression) or adversely impact a patient's adherence to antiretroviral regimens (therefore jeopardizing his or her health) and both of these are important health related outcomes of interest in this population. Therefore, improving the patient's facial appearance and resulting depression through the use of dermal injections could improve these health related outcomes.

We can examine depressive symptoms, social and work functioning, and quality of life as outcomes. Various scales are sometimes used to measure these outcomes. Analysis of a scaled outcome measure includes asking two questions: is the score meaningful and is the scale meaningful? It is important to use scales that are both reliable and valid. Reliability and validity determination is both an art and a science. Validity refers to the degree to which a test actually measures what it intends to measure. Reliability examines the consistency between two measures that evaluate the same thing, and is the ratio of the true variance to the total variance. There are several methods to assess reliability: examining internal consistency (how well do scale items measure a single characteristic); retest reliability (assesses to what degree multiple administrations of the scale produce the same results); and inter-rater reliability (the degree to which various raters produce the same result).

CMS focused its review on literature that reported psychological outcomes and outcomes related to medication adherence. While facial measurements and subjective measures of appearance are often reported, they do not necessarily correlate with psychological issues or medication adherence. Therefore, it is important that our review include publications that report other health related outcomes and not solely intermediate measures.

Adverse events are important medical outcomes. Patients and physicians use this information to make better-informed choices among treatment strategies. For instance, procedures such as facial dermal injections could include adverse events such as bruising, infection and scarring. Studies that provide an inclusive examination and explanation of adverse medical events are generally given more evidentiary weight.

Literature Search

CMS performed a literature search for review articles published within the last year (2008-2009) that provided a synthesis of the literature. A second search was then performed in Medline for articles that were published after the reviews (from August 2008 to present) using the search terms HIV and lipoatrophy and restricting to articles in English and reporting results of adult patients. Articles were excluded if they solely reported outcomes with re-treatments, provided a case report, used fillers not currently approved by the FDA or did not explicitly report the outcomes of interest.

B. Discussion of evidence reviewed

1. Question

Is the evidence sufficient to conclude that the use of dermal injections for the treatment of facial LDS in HIV infected persons improves any HIV-related health outcomes?

2. External Technology Assessment

CMS did not locate nor commission an external technology assessment for this decision.

3. Internal Technology Assessment

Review articles

Sturm LP et al. A Systematic Review of Permanent and Semipermanent Dermal Fillers for HIV-Associated Facial Lipoatrophy. 2009;23:699-714.
The results of a systematic review of permanent and semipermanent dermal fillers used for HIV induced lipoatrophy was published in 2009 by Sturm et al. Their review included human studies of facial injections of permanent or semipermanent dermal fillers, with sample sizes of at least 40 patients and a publication cut-off date of July 2008. Eleven studies were located including one randomized controlled trial (RCT), seven case series, two nonrandomized comparative studies and one pseudo-RCT. Substantial differences in study design prevented statistical pooling. Much of the article attempts to compare various fillers.

Efficacy outcomes included changes in skin thickness, subjective ratings of appearance (patient or physician reported opinions regarding improvement in appearance), patient satisfaction, and quality of life outcomes. Regarding skin thickness, the authors identified an RCT reporting, "…that linear measurements demonstrated significant increases of soft tissue depth at the maxilla…and base of nasal septum…in favor of the polylactic acid (PLA)-treated group, but there was no significant increase in facial soft tissue volume after treatment compared to patients who did not have treatment."Two comparative studies and evidence from case series point to improvements in skin thickness across all interventions included in this article.

While studies reported a variety of subjective lipoatrophy ratings (some developed by the investigators, Global Aesthetic Improvement Scale and some not well-explained in the literature), an RCT, a comparative study and a case series all concluded improvements were demonstrated using semipermanent fillers. The authors report that patient satisfaction was high across interventions including the use of aesthetic scores and questions regarding satisfaction with the results of treatment which included a series of Yes or No questions related to attractiveness and emotional well-being. The authors report, "considerable variation in quality of life outcomes"; "…with many studies reporting improvements in some but not all of the measured health dimensions." The level of adverse event reporting varied. Among the safety outcomes reported, there were five unrelated deaths reported across 3 studies. Disease progression was reported in six studies with 5 studies reporting no disease progression or new AIDS defining events and one study reporting that 2 of 94 patients discontinued treatment because of disease progression. Three studies reported modification to antiretroviral dosing in 16% or less of patients and 2 studies reported no significant differences in adherence to anti-retroviral treatment. More than 40% of patients in 3 studies experienced subcutaneous lumps after poly-lactic acid (PLA) injections. One study reported an anaphylactic reaction and reports of infections were included in 3 studies.

The authors conclude, "The small number of well-designed studies limited the ability to draw firm conclusions. The products included for review appeared to increase skin thickness as measured by skin calipers, ultrasound, or subjective ratings of appearance, but long-term efficacy has not been established. Patient satisfaction was high in all of the studies. Short term safety appeared favourable, but long-term safety data were limited. More research is required to determine long-term safety and efficacy of these fillers for this population."

Doward LC et al. Impact of lipoatrophy on patient-reported outcomes in antiretroviral-experienced patients. AIDS Reader. 2008;18:242-246, 252-256, 262-265.
Doward et al. performed a literature review to include studies that focused on health related quality of life, particularly, focusing on patient reported outcomes. A systematic search was performed resulting in the inclusion of 30 studies in the review. Exclusion criteria included the absence of quality of life reporting, non-English and conference reports were also excluded. It does not appear that studies were excluded based on number of participants, study design or type of treatment. As the main purpose of the review was to assess the impact of lipoatrophy on HIV infected persons, much of the review described studies in which there was no intervention to treat the appearance of lipoatrophy rather than studies evaluating quality of life at baseline and some reevaluation quality of life at a later point. Doward found 16 studies that used a patient-reported outcome instrument, including 3 that used visual analog scales. The remaining studies employed psychological impact scales (the Beck Depression Inventory, the Hospital Anxiety and Depression Scale, Profile of Mood States-Adolescents, and Rosenberg Self-Esteem Scale), HIV-specific quality of life instruments (Medical Outcomes Study-HIV), generic instruments (SF-36, EuroQol) and one other instrument.

Doward et al. noted some major weaknesses across the literature including lack of long term studies, lack of well-controlled trials and lack of suitable patient reported outcome scales. A number of authors have proposed new reporting instruments or modifications to existing ones, but none has been widely adopted. This variation makes it difficult to compare results from different studies. There are no longer term studies looking at the durability of the effects from use of these dermal fillers nor are there studies of the potential for longer term adverse effects from the repeated courses of treatment usually needed to maintain facial improvements. Regarding the lack of well-controlled trials, Doward states, "All of the randomized studies identified were open-label and uncontrolled, which introduces concerns related to experimental bias and placebo effect and limits the robustness of the study's results."

Doward draws some conclusions regarding studies in which a corrective treatment was given to improve appearance (e.g., change in medications, autologous fat transfer and dermal fillers). "Switching the antiretroviral regimens (e.g., replacing stavudine or zidovudine with abacavir) produces only a modest effect." "The results from these studies appear to suggest that a proportion of participants were anxious and/or depressed and that these conditions improved following successful treatment of their lipoatrophy." Doward does not draw conclusions regarding success rates of the various treatments.

Studies used for product approval

Valantin M-A et al. Polylactic acid implants (New-Fill™) to correct facial lipoatrophy in HIV-infected patients: results of the open-label study VEGA. AIDS 2003; 17:2471–2477
This study was used as part of the FDA evaluation of Sculptra at the time of approval and is cited in the two external technology assessments and the Veterans Health Administration (VHA) guideline. The injectable filler used in this study was the poly-L-lactic acid (PLA) New-Fill™, which was the European name for Sculptra.

VEGA "was an open-label, single-arm, pilot study to evaluate the efficacy, safety, and the durability of PLA in the correction of facial lipoatrophy in HIV- infected patients over 96 weeks." Eligible study participants were HIV+, over 18 with "severe lipoatrophy defined as a thickness of fat tissue in the nasogenian area less than 2 mm as measured by ultrasonography" and must "have received antiretroviral therapy for more than 3 years, with stable plasma HIV-1 RNA levels <5000 copies/ml in the last 3 months." Patients with "any facial implant in the last 5 months, or current interferon or cytokine therapy were not eligible."

Over six weeks patients received "several" injections of PLA "into and around the deep dermis of the atrophied area of each cheek" at day 0 and weeks 2, 4, and 6. PLA is "a biocompatible and immunologically inert synthetic polymer" available as "0.15 g" of dry powder per vial which "was reconstituted with "3-4 ml of water for Injections BP." One cc of lidocaine for injection discomfort was injected locally. The quantity of PLA injected "depended on the severity of skin depression", with "a maximum of 4 ml into each cheek." Cheeks were massaged to "ensure better distribution." The "same trained dermatologist" performed all injections.

"Patients were evaluated by clinical examination, facial ultrasonography and photographs at screening, and at weeks 6, 24, 48, 72, and 96. Patient quality of life (QOL) was measured by visual analogue scale and collected at screening, week 12, 24, 48, 72, and 96. Following the ultrasound evaluation performed at week 6, a fifth set of injections of PLA could be performed if the facial total cutaneous thickness (TCT) was < 8 mm."

"The same trained radiologist" used ultrasound and color Doppler to "quantify the dermal, epidermal and fat thickness" noting the change in TCT between the skin and epidermis and any local reactions at the injection site. The primary end point was the number of patients achieving an arbitrarily selected mean increase in TCT < 10 mm at the nasogenian fold at week 24. Secondary endpoints included the change TCT and QOL from baseline at weeks 6, 12, 24, 48, 72, and 96; proportion of responders at weeks 6, 24, 48, 72, and 96; and patient tolerability.

Forty-nine of 50 patients enrolled between June 2000 and February 2001 were male; median age 45.9 (33.1-58.0); 22 (46%) with AIDS; median years of antiretroviral treatment 8.6 (1.1-14.1); TCT both cheeks 2.9 (2.0-5.5); and visual analogue scale for well-being (44 patients reporting) 6.4 (0.0-10.0). Twenty-six patients received four sets of PLA injections, 20 received 5 sets and 4 were corrected with 3 sets. Ultrasound evaluation was not performed on two patients at week 6, one at week 24, one at week 48, two at week 72, three at week 96 and five patients had not reached week 96 at the date of write-up. TCT improvements were reported as the proportion of patients achieving $\geq$10 mm: 19% at week 6; 41% week 24; 6l% week 48; 52% week 72; and 43% at week 96. Median increases in TCT were significant ($P < 0.001$) at all points median increase of 5.1 mm at 6 weeks; 6.4 mm at week 24; 7.2 mm at week 72; and 6.8 at week 96.

QOL scales from 44 patients "progressively increased between baseline and week 48" with a median change of +0.3 at week 12; +0.8 at week 24; +0.8 at week 48; +0.4 at week 72 and +0.4 at week 96. No serious adverse events were observed during the study with localized injection site swelling and bruising spontaneously resolving. Twenty-two patients (44%) developed "palpable, but non-visible micronodules" which spontaneously resolved in six patients by week 96.

There were changes in concurrent antiretroviral therapy in 18 patients during the study, which could conceivably have affected study results. Three patients temporarily discontinued antiretroviral therapy (duration not stated). Thirteen patients switched from stavudine to other nucleoside reverse transcriptase inhibitors during the study: three because of lipoatrophy; four because of inefficacy; five because of other toxicities; and one for personal reasons. And two patients began stavudine. Authors noted that they believed it unlikely that these changes affected study results citing a Carr et al. (2003) study demonstrating "slow reversibility of the subcutaneous fat loss after replacing stavudine or zidovudine".

Authors note that "(I)n the context of this severe morphologic syndrome and with psychological consequences for most affected patients, use of a placebo or an untreated control group was not acceptable." And, "there are no substantial data on quantitative measurement available in the literature to evaluate similar interventions in the treatment of HIV-associated lipoatrophy."

In summary, the authors conclude that in the absence of a treatment for the underlying cause, "the use of biodegradable materials to improve physical appearance represents significant progress in therapeutic management of HIV-related lipoatrophy…. The efficacy, safety profile, and the simplicity of the injection schedule associated with the use of PLA make this filling material a potentially attractive treatment to alleviate the psychological and social consequences of facial lipoatrophy in affected HIV-infected patients."

Silvers SL, et al. Prospective, Open-Label, 18-Month Trial of Calcium Hydroxylapatite (Radiesse) for Facial Soft-Tissue Augmentation in Patients with Human Immunodeficiency Virus-Associate Lipoatrophy: One-Year Durability. Plast. Reconstr. Surg. 118 (Suppl.): 34S, 2006.
This study supported the FDA approval of Radiesse, reported by Silvers et al. (2006) and was cited in the Sturm external review. The study description, which follows, includes material from the peer-reviewed publication as well as from the more abbreviated description included in the Summary of Safety and Effectiveness on the FDA website.

Radiesse is a synthetic soft-tissue filler consisting of 30 percent calcium hydroxylapatite microspheres and 70 percent sodium carboxymethylcellulose gel carrier. The microspheres, measuring 25 to 40 µm, function as a scaffold for natural collagen growth as the gel carrier is replaced by connective tissue.

The study objective was to assess FLA changes and the incidence of adverse events in patients receiving Radiesse treatment, with follow-up evaluations at 3, 6, 12, and 18 months after initial treatment. The primary effectiveness endpoint was to evaluate correction of FLA at 3 months using the Global Aesthetic Improvement Scale (GAIS) score (Table 1). This is a non-validated scale as noted in the FDA review, with confirmation using standardized photographs. Secondary endpoints were evaluation using GAIS and photographs at 6 months and comparison of cheek skin thickness at baseline to 3 and 6 month values. GAIS scores at 12 and 18 months were also available. The safety endpoint was incidence, severity and duration of all local and systemic adverse events through 12 months. Eighteen month data are included from Journal publication.

Table 1: Global Aesthetic Improvement Scale (GAIS)

Rating	Description
Very much improved	Optimal cosmetic result for implant in this patient.
Much improved	Marked improvement in appearance from initial condition, but not completely optimal for this patient. A touch-up would slightly improve the result.
Improved	Obvious improvement in appearance from the initial condition, but a touch-up or retreatment is indicated.
No Change	The appearance is essentially the same as the original condition.
Worse	The appearance is worse than the original condition.

Three hundred fifty-four patients were screened for the study and 100 enrolled. Selection criteria which are not detailed "included, but were not limited to" age 18 or older, HIV+, CD4 count $\geq$ 250/mm^3, viral load $\leq$ 5000 copies/ml, HAART for at least three years, and grade of 2, 3, or 4 on the Facial Lipoatrophy Severity Scale (Table 2). We have not located information on validation of the scale. A detailed list of study exclusion criteria is included in the Summary of Safety and Effectiveness Data posted with the12/22/06 approval of Radiesse on the FDA website. They include hematologic and other conditions, which could impact study results.

Table 2: Facial Lipoatrophy Severity Scale

Grade	Description
1	Mild localized facial lipoatrophy
2	Deeper and longer atrophy, with facial muscles beginning to show through.
3	Atrophic area is even deeper and wider with muscles clearly showing through.
4	Lipoatrophy covers a wide area, extending up toward the eye sockets, and the facial skin lies directly on the muscles.

The Fitzpatrick Skin Type Matrix (Table 3) was developed by Dr. Thomas B. Fitzpatrick in 1975 and has been widely used in medical literature dealing with the skin.

Table 3: Fitzpatrick Skin Type Matrix

Fitzpatrick Skin Type	Description
I	Extremely fair skin, always burns, never tans
II	Fair skin, always burns, sometimes tans
III	Medium skin, sometimes burns, always tans
IV	Olive skin, rarely burns, always tans
V	Moderately pigmented brown skin, never burns, always tans
VI	Moderately pigmented black skin, never burns, always tans

The 100 patients (94 men and 6 women) enrolled in the study had a mean age of 48.2 years and 94% were non-smokers. Forty-four were Black, Hispanic or Asian, 56 were Caucasian, 51 had a Fitzpatrick Skin Score of IV, V or VI. The mean initial treatment volume was 4.8 mL with an additional 1.8 mL injected at 1 month "at the discretion of the treating physician" (85% of patients). At 6 months the mean touch-up volume in 89% patients was 2.4 mL. Four patients received only one treatment, 18 received two and 78 received three. "Lipoatrophy was treated until, in the judgment of the treating physician, the lipoatrophy was corrected." Silvers et al. state the "6-month touch-up was intended to allow for replacement of the resorbed gel carrier, which typically occurs over a 3-month period" and may also have been needed due to continued disease progression.

The authors also state that the primary efficacy endpoint of a GAIS rating of "Improved" or better ($\geq$ 3) at 3 months was met by all patients and continued to be met at 6 and 12 months. At 18 months (1 year after the last injection) of 94 assessable patients, the ratings for 9 patients had changed to "No change" from baseline.

Cheek thickness measurements of left and right cheeks performed at baseline, 3 months and 6 months are included in the chart from the FDA decision, below. The journal article states that at 12 months the left cheek thickness was 6.9 mm (decrease of 0.2 mm from 6 months or an increase from baseline of 2.4 mm) and right cheek was 7.0 mm (decrease of 0.5 mm from 6 months or an increase from baseline of 2.2 mm). Eighteen month data was unavailable at publication.

Table 4: Cheek Thickness Measurements [Summary of Safety and Effectiveness Data Table 13]

	BASELINE	3 MONTH			6 MONTH		
	Mean (N=100)	Mean (N=100)	Δ From Baseline	p-Value	Mean (N=97)	Δ From Baseline	p-Value
Left Cheek	4.7 mm	7.3 mm	2.6 mm	<0.0001	7.1 mm	2.4 mm	<0.0001
Right Cheek	4.9 mm	8.0 mm	2.1 mm	<0.001	7.5 mm	2.7 mm	<0.0001

	BASELINE	3 MONTH			6 MONTH		

Patient satisfaction was assessed using questions "modeled after the Freiburg Questionnaire on Aesthetic Dermatology and Cosmetic Surgery" administered at 3, 6, 12 and 18 months and including:

- Has the Radiesse treatment been beneficial to you?
- Is your emotional wellbeing better since receiving Radiesse?
- Do you have more confidence in your appearance since receiving Radiesse?

At 3 months, 91 of 100 patients answered "yes" to the wellbeing question with the number rising to 96 at 6 months. Positive responses to other questions at 3 and 6 months ranged from 98%-100%. Details of the 12 and 18 month replies to these questions are not available.

The FDA's conclusions included:

- There were no serious adverse events noted during the study. The most common adverse events were ecchymosis, edema, erythema, pain and pruritis.
- Radiesse is seen on both x-ray and CT scan; it is unlikely that presence of Radiesse will mask underlying structures or abnormal growths in the areas in which it is injected.
- There is no evidence of Radiesse migration.

The following note is also added: "An important consideration for injectable materials is the effect of the device on various skin types. In this study, the sponsor enrolled a representative sampling of the demographic variables in the US. A larger number of males were enrolled"

Studies published after the review articles

Carruthers A, Carruthers J. Evaluation of injectable calcium hydroxylapatite for the treatment of facial lipoatrophy associated with human immunodeficiency virus. Dermatol Surg. 2008;34(11):1486-99.
The authors studied soft tissue augmentation with calcium hydroxylapatite microspheres in 30 patients (29 men and 1 woman) with FLA due to HIV infection. In an open-label study with 12 month follow-up, the average initial treatment volume was 9.5 mL per patient (both sides); total volumes per patient after 12 months averaged 16.1 mL. At all time points, all patients were rated as improved or better and responded affirmatively to satisfaction questions. Most commonly reported adverse events were edema (93%), ecchymosis (83%), and erythema (77%). The authors conclude that this is a "well-tolerated treatment for patients with HIV-associated FLA."

Levy RM, Redbord KP, Hanke CW. Treatment of HIV lipoatrophy and lipoatrophy of aging with poly-L-lactic acid: a prospective 3-year follow-up study. J Am Acad Dermatol. 2008;59(6):923-33.
The authors evaluated the long-term efficacy and safety of Poly-L-lactic acid (PLLA), during 3 years of follow-up of a prospective cohort study of 65 patients including 27 HIV-infected and 38 uninfected patients with lipoatrophy. Of those patients, 12 were lost to follow-up. Both HIV-positive and HIV-negative patients demonstrated statistically significant improvement in FLA score at the end of 3 years. Subgroup analyses revealed no statistically significant difference in FLA score between years 2 and 3 among patients who did not receive treatment during the third year. Few adverse events were reported, and included subcutaneous papule formation, which improved spontaneously and partially responded to subcision in one patient. The authors concluded that, "Results appear to be long lasting and correction can be maintained for up to 3 years with additional treatment sessions."

Mest DR, Humble GM. Retreatment with injectable poly-l-lactic acid for HIV-associated facial lipoatrophy: 24-month extension of the Blue Pacific study. Dermatol Surg. 2009;35 Suppl 1:350-9.
The authors evaluated the safety, duration of effect, and satisfaction with serial injections of poly-l-lactic acid (PLLA) for HIV-associated FLA in a single-site, open-label, retreatment study of 65 patients. Almost 10% of patients had persistent correction > 36 months, based on patient report. Approximately 50% required three or fewer retreatments to maintain satisfactory correction (determined by patient and physician). Milder lipoatrophy on initial presentation required fewer retreatments and had more sustained correction. The mean patient satisfaction score was 4.9 (1 = dissatisfied, 5 = very satisfied) at study end. No serious adverse events were reported.

Peterson S, Martins CR, Cofrancesco Jr J. Lipodystrophy in the Patient with HIV: Social, Psychological, and Treatment Considerations. Aesthetic Surg J 2008;28:443–451.
Peterson et al. note that patients "see themselves as disfigured, isolated and stigmatized" by the apparent physical changes in their bodies resulting from lipoatrophy and that " (L)ow self-esteem, poor body image and depression are common sequelae of lipoatrophy". Modifying HAART regimens has been tried with limited success as a method of preventing manifestations of lipoatrophy, however, "after lipodystrophy has progressed (this) offers only limited benefit." Discontinuation of HAART leads to failure of disease treatment. In the absence of effective treatments to prevent lipoatrophy the use of approved fillers has become popular.

Sadick NS. The impact of cosmetic interventions on quality of life. Dermatology online J. 2008;14(8):2.
Dr. Neil Sadick, in writing about the impact of cosmetic interventions on the quality of life, noted the growing concern about the impact of HIV lipoatrophy on patients' psychological health and social well-being, particularly, "depression, problems with self-esteem and interpersonal relationships, in addition to nonadherence to the treatment. Recent data indicate that cosmetic nonsurgical treatment of HIV lipoatrophy with injectable facial rejuvenators can improve quality of life in these patients."

Observational studies of lipoatrophy and QOL

Guaraldi G, Murri R, Orlando G, et al. Severity of Lipodystrophy Is Associated with Decreased Health-Related Quality of Life. AIDS Patient Care and STDs. 2008;22:577-585.
Guaraldi et al. state that while it seems intuitive that LD has a negative effect on quality of life that assessment has not been well corroborated in the literature. Previous attempts to correlate LD with quality of life were hampered by lack of specificity in study instruments and small sample size. This paper found that "in 13% of cases physician(s) found moderate to severe LD when the patient did not perceive it" and "6% of moderate to severe LD was not captured by physician". The lack of consensus on a definition on LD hampers development of the body of literature. In conclusion, the authors state: "the importance of lipodystrophy lies not in actual changes in body shape and in the association with lipid abnormalities, but also on the impact of changes on the patient's quality of life. Negative impact on quality of life may also decrease motivation and adherence to therapy and even lead to discontinuation of treatment. The best overall assessment of the impact of LD may require both patient- and physician-based measures. Better measurement will help us to be most effective in implementing strategies to reduce the burden of LD."

4. MEDCAC

A meeting of the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) was not convened for this analysis.

5. Evidence-based guidelines

Alam A, Gladstone H, Kramer E, et al. ASDA Guidelines of Care: Injectable Fillers Dermatologic Surgery. 2008;34:S115-S148.
The American Society for Dermatologic Surgery consensus-based guidelines produced by a committee of experts separate the recommendations by type of filler. Of particular interest are sections of the guideline dealing with the appropriate technique and physician qualifications for injecting either poly-L-lactic acid (Sculptra) or calcium hydroxylapatite (Radiesse).

Regarding the use of calcium hydroxylapatite, the guidelines note that, "In general, this viscous filler is most successfully used in the deep dermis or subcutis, where it is less likely to be visible or to extrude. Superficial fine lines and very fine depressions should not routinely be injected with this material." Physician training or qualifications are addressed for this filler and recommendations include residency training in a specialized field and hands-on training courses or preceptorship with an experienced injector. Also included are specific recommendations regarding the location of the injection within the layers of skin tissue, specifically, dermal-subcutaneous border injections is recommended. An effect lasting 12-15 months is expected. If a booster is given 2-3 months after injection, 15-18 months of last effect is possible. Under the subheading of "Evidence-Based Medicine", the guidelines state, "To date, clinical studies have been extended case series without controls. Long-term follow-up studies are not available."

Poly-L-lactic acid (PLLA) is said in the guidelines to be intended for volume correction. The physician training and qualification recommendations are similar to calcium hydroxylapatite however the delivery of the injectable is quite different. PLLA is delivered as, "A series of injections, usually two to four, is required for optimal correction. Injections should be given at least 4 weeks apart." It further states that depth of injection varies by facial location. Regarding side effects, "Particular to PLLA is the appearance of nodules. Palpable nodules may arise within a few weeks of injection or many months later. These may represent mechanical clumping of material or, less commonly, a foreign body granuloma. If visible, these may be dispersed with sterile saline delivered by a 26-gauge needle." The document notes "a lack of long-term studies documenting longevity. However, available studies indicate correction lasts 18 to 24 months, at which time additional correction may be delivered."

Lundgren JD, Battegay M, Behrens G, et al. European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV . HIV Medicine. 2008;9:72-81.
While the European AIDS Clinical Society guidelines deal with the whole spectrum of metabolic abnormalities related to combined antiretroviral therapy, a summary dealing with prevention and management of LD contains the following: "The preferred strategy to prevent lipoatrophy is avoiding exposure to the two thymidine analogues (stavudine and zidovudine). Alternatively, pre-emptive switch away from these drugs should be considered. In many cases where lipoatrophy has developed, reversal is slow and gradual. Other interventions have either not been sufficiently studied or are known to induce other complications and are hence not generally recommended." The summary table for management of lipoatrophy notes under "Surgical intervention" that it is:

- Offered for cosmetic relief of FLA only (fillers may be absorbable (limited effect) or permanent (durability of the desired cosmetic effect is unknown)
- Limited randomized trials and no comparative studies of different approaches.

Veterans Health Administration (VHA) Treatment of Antiretroviral-Induced Facial Lipoatrophy in Human Immunodeficiency Virus (HIV)-Infected Patients. January 22, 2008. Available at http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=1640 [accessed 11/5/09]
This literature-based directive includes a discussion of the mental health complications of what the VHA calls antiretroviral-induced facial lipoatrophy (AIFL). The VHA highlights that the purpose of treating patients with AIFL is to improve the patient's mental health and not for cosmetic reasons. The directive states that the HIV treating physician is responsible for "determining whether the patient has facial lipoatrophy of sufficient severity that the patient's mental health is substantially impaired due to depression, stigmatization or social isolation and is willing to undergo Sculptra or Radiesse treatment."

The directive issues the following VHA policy:

It is VHA policy that eligible veterans with AIFL may undergo treatment for this disorder at VHA facilities, or be referred by VHA on a cost basis to outside facilities for such treatment, if it would improve the patient's mental health.

The directive also restricts the types of providers that are allowed to administer the injectables. Administration is explicitly limited to dermatologists, plastic surgeons and otolaryngologists that have appropriate training and experience in the use of the products administered. Only the two FDA approved injectables are allowed and restrictions regarding their interval of administration and total use are included in the directive.

6. Professional Society Position Statements

Position statements were not located.

7. Expert Opinion

We did not solicit outside expert opinion on this topic.

8. Public Comments

CMS uses the initial public comments to inform its proposed decision. Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

Initial 30-day comment period

CMS received 43 comments in favor of coverage with five of those comments citing published evidence. While CMS generally posts comments to the website after redacting protected health information (PHI), comments that include extensive PHI are not posted, if after redaction, no substantive comment remains. The majority of commenters stated that due to the appearance and the stigma of having HIV, patients with facial LDS suffer from decreased quality of life, decreased self esteem, social withdrawal, are less likely to work and lead less productive lives. Commenters noted that if CMS provides coverage for other reconstructive procedures then dermal injections for facial LDS should also be covered. Other commenters stated that in an attempt to slow the progression of facial LDS, at a detriment to their health, patients do not adhere to their antiretroviral therapies. One commenter was against coverage stating that the procedure is cosmetic and therefore should not be covered.

Comments on Proposed Decision

Sixty-nine comments were received during the comment period. It should be noted that a substantial number of comments contained extensive protected health information and were not posted to the CMS website. Fifty-five commenters supported the proposed decision. While all commenters supported Medicare coverage of dermal injections for HIV positive patients with facial LDS, 14 commenters disagreed with the clinical indications detailed in the proposed decision. Thirteen commenters specifically addressed the proposed requirement that beneficiaries manifest depression secondary to facial LDS.

Comment
Some commenters provided testimony regarding the effectiveness of dermal injections and said either they or their friends were able to resume activities and going out in public after receiving a series of injections.

Response
The evidence reviewed demonstrates that certain patients benefit from receiving dermal injections for facial LDS and that their depressive symptoms can improve, allowing them to resume a more normal life. The article by Peterson et al. (2008) indicates that "(L)ow self-esteem, poor body image and depression are common sequelae of lipatrophy." Doward et al. (2008) further state that patients "…were anxious and/or depressed and that these conditions improved following successful treatment of their facial lipoatrophy."

Comment
One commenter said that depression should be diagnosed by a qualified mental health provider.

Response
While some of these patients may be under the care of a qualified mental health provider for their depression, a written diagnosis by a mental health professional is not a prerequisite for Medicare coverage of dermal injections.

Comment
Several commenters said that requiring the diagnosis of depression is too restrictive. Some disagreed with including depression as a requirement for coverage and said that injections should be covered regardless of the presence of depression. Other commenters stated that injections should be used to prevent the onset of depression, as treatments for depression (e.g., medications) can have their own side effects that could be avoided.

Response

CMS disagrees that depression should not be a component of the clinical indications for coverage of dermal injections. We do not believe that the diagnosis of depression is overly restrictive as we recognize that depression varies greatly in terms of severity and type and may vary over time and the term depression as used in this policy encompasses these variations. In addition the policy is not requiring patients be treated separately for depression (e.g., seeing a psychiatrist or on an anti-depressant medication) in order to have the diagnosis.

Still, depression is an essential aspect of the patient's medical condition that is being treated by dermal injections and the evidence demonstrates that depression improves in patients post-procedure. We have modified the language of our decision to reflect the limitation that dermal injections for facial LDS are covered "only in HIV infected beneficiaries when facial LDS caused by antiretroviral HIV treatment is a significant contributor to their depression."

Comment
Other commenters questioned how facial LDS can be proven as the cause of the patient's depression. One commenter was concerned that once depression improves the patient would not be eligible for the necessary continued maintenance injections.

Response
We believe the treating clinician will be able to discuss depression with the patient and determine the extent to which their treatment related facial LDS contributes to the depression. We have revised the decision language to say that the LDS caused by antiretroviral treatment for HIV must be a significant contributor to the patient's depression.

Comment
Instead of using depression as the coverage criteria, one commenter suggested using cheek thickness as an assumption of the level of depression and self-esteem.

Response
We are not adopting the recommendation contained in the comment. In clinical studies, cheek thickness was used primarily to measure changes in appearance in a single patient and would be taken prior to dermal injections and sometime after dermal injections. Improvements in cheek thickness or other measures, while objective, do not necessarily translate equally to an improvement in the way patients perceive or feel about themselves or their adherence to medications. We do not have a validated scale to know if improvements in cheek thickness or other objective measure translates to improvements in a patient's feelings of depression.

Comment
Commenters stated that with requiring a diagnosis of depression, the agency was being biased and discriminatory and further stated that the same requirements were not put on the National Coverage Determination (140.2) for Breast Reconstruction Following Mastectomy.

Response
CMS disagrees that the decision is biased or discriminatory. Indeed, most public commenters favored expanded Medicare coverage for this service. As noted above, the policy is based on the published evidence which demonstrates that the patient's medical condition, including depression, improves after receiving dermal injections. Each NCD developed by CMS is based on a separate evidentiary record consistent with §1869(f) of the Social Security Act.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act §1862(l). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." See §1862(a)(1)(A)of the Act. This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment.

We found no current estimates of the prevalence of HIV-associated lipoatrophy. It is unknown if the disorder varies across subpopulations or in different groups. Therefore, we do not precisely know its incidence or prevalence in the Medicare population.

The psychological effects of HIV-associated lipoatrophy are significant, thus it would seem that a treatment that can improve this situation is important. Another critical concern is that patients on long-term antiretroviral therapy may consider medication non-compliance in an effort to avoid this stigmatizing condition, which would be a devastating result. Dermal injections do not treat the underlying condition of HIV infection nor do they treat other components of the HAART induced lipodystrophy syndrome. However, the injections do treat health related patient outcomes by improving depression through improvements in facial appearance in patients with stigmatizing facial lipoatrophy, allowing them to maintain normally functioning lives and continue medication regimens.

The strongest evidence for treatment with dermal fillers for those affected with HIV lipoatrophy comes from the two systematic reviews. Studies are generally small with variable methodologic quality, variable subjective outcomes and unclear endpoints. Authors acknowledge that a better understanding of the association between LD and quality of life is needed, to better recognize long-term toxicities of antiretrovirals and to identify patient-related endpoints useful in assessing the efficacy of strategies for treating LD (Guaraldi 2008). Sorting the noise from the signal in these studies is difficult; however, in the studies patients appear to genuinely benefit despite the inability to control for other important variables such as other medical treatments. Reported adverse events are minimal.

A majority of studies on the use of dermal fillers report results primarily for young to middle-aged male Caucasian patients. The relative paucity of data for women, minorities and the elderly makes it difficult to determine the value or possible harms of these treatments for those populations. Importantly however, HIV infected beneficiaries are more likely to be younger than the usual age range of Medicare beneficiaries. Men are more common than women among beneficiaries younger than age 65. Thus, these data may be reflective of the affected Medicare beneficiary population. We specifically invited but did not receive any public comment on this point.

The published studies tend to be small, lack control groups and present minimal descriptions on patient selection, exclusion and other factors which might affect study results. Most authors agree that there is a need for improvement in study methodology including development of a validated measurement tool to determine severity of the condition, inclusion of more women and non-Caucasian patients in trials and longer term studies of health outcomes.

Nearly all studies rely on patient self-assessment of the severity of symptoms to determine both the need for treatment of facial atrophy and the success of treatment. Many attempts have been made to develop a generally accepted method of assessing the severity of the condition as well as how it has responded to treatment, including direct measurement of skin thickness or facial volume with calipers; various rating scales; and use of various imaging techniques such as DEXA, CT and MRI. Many studies also use photographs of the patient during therapy to document results, but there appears to be no general agreement on an objective methodology. The physician and patient may disagree and either/both may be subject to a positive bias from study participation alone. Most authors point to the lack of objective measures and uniform definitions as limitations on validity of study results. However, it's important to note that while there is significant variation in patient selection and reporting of results, the totality of the evidence (including Peterson (2008) and Doward (2008) who directly address this issue) points to improvements in psychological outcomes of patients treated with dermal fillers.

There are no studies dealing with the long-term psychological outcomes of treatment of manifestations of HIV antiretroviral treatment-related FLA with dermal fillers. Available data report short-term results for patients who report improvements in health-related quality of life and body image while or shortly after receiving a course of dermal injections. It's expected that patients will require repeat injections to maintain the desired outcome.

The aspect of treatment of HIV antiretroviral treatment-related facial LDS being reviewed in this decision is whether the use of the two dermal fillers, approved by the FDA for this purpose, improves the quality of life of affected patients by restoring a more normal appearance thus improving body image and reducing the psychosocial effects of HIV disease. In summary, we believe that there is adequate evidence only that the use of dermal injections in HIV infected persons for the treatment of antiretroviral treatment related facial LDS improves the psychological outcomes of patients with depression. Thus this service is not reasonable and necessary for beneficiaries whose depression is not significantly contributed to by their HIV antiretroviral treatment related LDS. We did not find evidence of improvement in any other health outcomes.

IX. Conclusion

On July 16, 2009, we initiated the NCD process by opening a tracking sheet for Dermal Injections for the Treatment of Facial Lipodystrophy Syndrome (CAG# 00412). After examining the available medical evidence, we are issuing the following decision.

Dermal injections for facial lipodystrophy syndrome (LDS) are only reasonable and necessary using dermal fillers approved by the Food and Drug Administration (FDA) for this purpose, and then only in HIV infected beneficiaries when facial LDS caused by antiretroviral HIV treatment is a significant contributor to their depression.All other indications are noncovered.

XI. References

Alam A, Gladstone H, Kramer E, et al. ASDA Guidelines of Care: Injectable Fillers. Dermatologic Surgery. 2008;34:S115 -S148.

Carruthers A, Carruthers J. Evaluation of injectable calcium hydroxylapatite for the treatment of facial lipoatrophy associated with human immunodeficiency virus. Dermatol Surg. 2008;34(11):1486-99.

Collins EJ, Burgoyne RW, Wagner CA, et al. Lipodystrophy Severity Does Not Contribute to HAART Non-adherence. AIDS and Behavior. 2006;10(3):273-277.

Doward LC et al. Impact of lipoatrophy on patient-reported outcomes in antiretroviral-experienced patients. AIDS Reader.2008;18:242-246, 252-256, 262-265.

Eschavez M Horstman W. Relationship between lipoatrophy and quality of life. AIDS Reader. 2005;15:369-75.

Guaraldi G, Murri R, Orlando G, et al. Lipodystrophy and Quality of Life of HIV-Infected persons. AIDS Rev 2008; 10:152 -61.

Guaraldi G,Murri R, Orlando G, et al. Severity of Lipodystrophy Is Associated with Decreased Health-Related Quality of Life. AIDS Patient Care and STDs. 2008;22:577-585.

James J, Carruthers A, Carruthers J. HIV-Associated Facial Lipoatrophy. Dermatol Surg 2002;28:979–986.

Levy RM, Redbord KP, Hanke CW. Treatment of HIV lipoatrophy and lipoatrophy of aging with poly-L-lactic acid: a prospective 3-year follow-up study. J Am Acad Dermatol. 2008;59(6):923-33.

Lundgren JD, Battegay M, Behrens G, et al. European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. HIV Medicine. 2008;9:72-81.

Mest DR, Humble GM. Retreatment with injectable poly-l-lactic acid for HIV-associated facial lipoatrophy: 24-month extension of the Blue Pacific study. Dermatol Surg. 2009;35 Suppl 1:350-9.

Peterson S, Martins CR, Cofrancesco Jr J. Lipodystrophy in the Patient with HIV: Social, Psychological, and Treatment Considerations. Aesthetic Surg J 2008;28:443–451.

Sadick NS. The impact of cosmetic interventions on quality of life. Dermatology online J. 2008;14(8):2.

Silvers SL, et al. Prospective, Open-Label, 18-Month Trial of Calcium Hydroxylapatite (Radiesse) for Facial Soft-Tissue Augmentation in Patients with Human Immunodeficiency Virus-Associate Lipoatrophy: One- Year Durability. Plast. Reconstr. Surg. 118 (Suppl.): 34S, 2006.

Sturm LP et al. A Systematic Review of Permanent and Semipermanent Dermal Fillers for HIV-Associated Facial Lipoatrophy. AIDS Patient Care and STDs. 2009;23:699-714.

Valantin M-A et al. Polylactic acid implants (New-Fill™) to correct facial lipoatrophy in HIV-infected patients: results of the open-label study VEGA. AIDS. 2003;17:2471–2477.

Veterans Health Administration (VHA) Treatment of Antiretroviral-Induced Facial Lipoatrophy in Human Immunodeficiency Virus (HIV)-Infected Patients. January 22, 2008. Available at http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=1640 [accessed 11/5/09]

Waters L, Nelson M. Long-term complications of anti-retroviral therapy: lipoatrophy. Int J Clin Pract. 2007;61(6):999-1014.

Appendix A

General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

-
- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

---

[1] http://www.cdc.gov/hiv/topics/surveillance/basic.htm#incidence

[2] James et al., 2002

[3] Waters & Nelson. 2007

[4] Collins et al., 2006

[5] Waters & Nelson, 2007

Back to Top