Hematopoietic Stem-Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

Policy # 00052
Original Effective Date: 01/28/2002
Current Effective Date: 09/17/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider allogeneic hematopoietic stem-cell transplantation (HSCT) to treat chronic lymphocytic leukemia (CLL) or small cell lymphocytic lymphoma in patients with markers of poor-risk disease to be eligible for coverage. (see Policy Guidelines and Rationale). Use of a myeloablative or reduced-intensity pretransplant conditioning regimen should be individualized based on factors that include patient age, the presence of comorbidities, and disease burden.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers allogeneic hematopoietic stem-cell transplantation (HSCT) to treat chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) except as noted above to be investigational.*

Based on review of available data, the Company considers autologous hematopoietic stem-cell transplantation (HSCT) to treat chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) to be investigational.*

Background/Overview
Hematopoietic Stem-Cell Transplantation
Hematopoietic stem cell transplantation refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte
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antigens (HLA) using cellular, serologic, or molecular techniques. Human leukocyte antigens refers to the tissue type expressed at the HLA A, B, and DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

Conventional Preparative Conditioning for Hematopoietic Stem-Cell Transplantation

The conventional (“classical”) practice of allogeneic SCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

The success of autologous HSCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

Reduced-Intensity Conditioning for Allogeneic Hematopoietic Stem-Cell Transplantation

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. Reduced-intensity conditioning regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HSCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of this Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.
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Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
Chronic lymphocytic leukemia and SLL are neoplasms of hematopoietic origin characterized by the accumulation of lymphocytes with a mature, generally well-differentiated morphology. In CLL, these cells accumulate in blood, bone marrow, lymph nodes, and spleen, while in SLL they are generally confined to lymph nodes. The Revised European-American/WHO Classification of Lymphoid Neoplasms considers B-cell CLL and SLL a single disease entity.

Chronic lymphocytic leukemia and SLL share many common features and are often referred to as blood and tissue counterparts of each other, respectively. Both tend to present as asymptomatic enlargement of the lymph nodes, tend to be indolent in nature, but can undergo transformation to a more aggressive form of disease (e.g., Richter’s transformation). The median age at diagnosis of CLL is approximately 72 years, but it may present in younger individuals, often as poor-risk disease with significantly reduced life expectancy.

Treatment regimens used for CLL are generally the same as those used for SLL, and outcomes of treatment are comparable for the two diseases. Both low- and intermediate-risk CLL and SLL demonstrate relatively good prognoses with median survivals of six to ten years, while the median survival of high-risk CLL or SLL may be only two years (see Policy Guidelines). Although typically responsive to initial therapy, CLL and SLL are rarely cured by conventional therapy, and nearly all patients ultimately die of their disease. This natural history prompted investigation of hematopoietic stem-cell transplantation as a possible curative regimen.

Blue Cross Blue Shield Policy Guidelines
Staging and Prognosis of Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
Two scoring systems are used to determine stage and prognosis of patients with CLL/SLL. As outlined in Table 1, the Rai and Binet staging systems classify patients into three risk groups with different prognoses, and are used to make therapeutic decisions.

Table 1. Rai and Binet Classification for CLL/SLL

<table>
<thead>
<tr>
<th>Rai Stage</th>
<th>Risk</th>
<th>Description</th>
<th>Median Survival (yr)</th>
<th>Binet Stage</th>
<th>Description</th>
<th>Median Survival (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Lymphocytosis</td>
<td>&gt; 10</td>
<td>A</td>
<td>3 or fewer lymphoid areas, normal hemoglobin and platelets</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>1</td>
<td>Intermediate</td>
<td>Lymphocytosis plus lymphadenopathy</td>
<td>7-9</td>
<td>B</td>
<td>3 or more lymphoid areas, normal hemoglobin and platelets</td>
<td>7</td>
</tr>
</tbody>
</table>
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II Intermediate
Lymphocytosis plus splenomegaly plus/minus lymphadenopathy 7-9

III High
Lymphocytosis plus anemia plus/minus lymphadenopathy or splenomegaly 1.5-5 C Any number of lymphoid areas, anemia, thrombocytopenia 5

IV High
Lymphocytosis plus thrombocytopenia plus/minus anemia, splenomegaly or lymphadenopathy 1.5-5

lymphocytosis = lymphocytes > 15 x 10^9/L for 4 wks; anemia = hemoglobin < 110 g/L; thrombocytopenia = platelets < 100 x 10^9/L

Because prognosis of patients varies within the different Rai and Binet classifications, other prognostic markers are used in conjunction with staging to determine clinical management. These are summarized in Table 2, according to availability in clinical centers.

Table 2. Markers of Poor Prognosis in CLL/SLL

<table>
<thead>
<tr>
<th>Community Center</th>
<th>Specialized Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced Rai or Binet stage</td>
<td>IgVh wild type</td>
</tr>
<tr>
<td>Male sex</td>
<td>Expression of ZAP-70 protein</td>
</tr>
<tr>
<td>Atypical morphology or CLL/PLL</td>
<td>del 11q22-q23 (loss of ATM gene)</td>
</tr>
<tr>
<td>Peripheral lymphocyte doubling time &lt; 12 months</td>
<td>del 17p13 (loss of p53)</td>
</tr>
<tr>
<td>CD38^</td>
<td>trisomy 12</td>
</tr>
<tr>
<td>Elevated beta2-microglobulin level</td>
<td>Elevated serum CD23</td>
</tr>
<tr>
<td>Diffuse marrow histology</td>
<td>Elevated serum tumor necrosis factor-a</td>
</tr>
<tr>
<td></td>
<td>Elevated serum thymidine kinase</td>
</tr>
</tbody>
</table>
Elevated serum lactate dehydrogenase level

Fludarabine resistance

**Reduced-Intensity Conditioning for Allogeneic Hematopoietic Stem-Cell Transplantation**

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for RIC allogeneic HSCT. These include those whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen. A patient who relapses following a conventional myeloablative allogeneic HSCT could undergo a second myeloablative procedure if a suitable donor is available and his or her medical status would permit it. However, this type of patient would likely undergo RIC prior to a second allogeneic HSCT if a complete remission could be re-induced with chemotherapy.

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (6 of 6). Related donors mismatched at one locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, where usually there is sharing of only three of the six major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

**Rationale/Source**

The original Policy was based on 2 TEC Assessments. One from 1999 examined autologous hematopoietic stem-cell transplantation (autologous HSCT) for CLL or SLL; the other from 2002 was on allogeneic hematopoietic stem-cell transplantation (allogeneic HSCT) to treat CLL or SLL. Both documents indicated that existing data were insufficient to permit scientific conclusions regarding the use of either procedure, limited by interstudy heterogeneity in patient’s baseline characteristics, procedural differences, sample size, and short follow-up. A direct comparative analysis from the International Bone Marrow Transplant Registry (IBMTR) commissioned by TEC in 2002 to analyze allogeneic HSCT results was insufficient to permit scientific conclusions on the net health outcome of this procedure for relapsed or refractory CLL or SLL.

Literature searches conducted between 2002 and July 2008 found no randomized trials of HSCT compared with conventional-dose therapy for CLL or SLL. Recent reviews discuss uncertainties with respect to the type of transplant (autologous vs allogeneic), the intensity of pretransplant conditioning, the optimal timing of transplantation in the disease course, the baseline patient characteristics that best predict likelihood of clinical benefit from transplant, and the long-term risks of adverse outcomes. The conclusions reached in these reviews suggest that although autologous HSCT may prolong survival in selected patients with CLL or SLL, for example, those with chemotherapy-sensitive malignancy who had a good response to front-line therapy and transplanted early in the course of disease, it has not yet been shown to be curative.
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Autologous HSCT
A systematic review of autologous HSCT for CLL or SLL included 9 studies (total n=361, 292 of which were transplanted) identified from a search of MEDLINE databases from 1966 to September 2006. Studies were included if they were full-publication English language reports of prospective randomized, nonrandomized, or single-arm design. The analysis suggested that autologous HSCT may achieve significant clinical response rates (74%-100%) with relatively low treatment-related mortality (TRM) (0%–9%). However, molecular remissions are typically short-lived, with subsequent relapse. Overall survival (OS) ranged from 68% at 3-year follow-up to 58% at 6-year. Secondary myelodysplasia and myelodysplastic syndrome that may progress to frank acute myelogenous leukemia has been reported in 5% to 12% of patients in some studies of autologous HSCT, which suggests caution in considering this approach, especially given the indolent nature of CLL or SLL. The authors of the review concluded that in the absence of randomized, comparative studies, it is uncertain whether autologous HSCT is superior to conventional chemotherapy (or current chemo-immunotherapy) combinations as first-line consolidation treatment in CLL or SLL patients, regardless of disease risk, or as salvage therapy in those with relapsed disease.

The conclusions of the systematic review of autologous HSCT outlined above are congruent with results of the Phase III European Intergroup randomized trial that compared autologous HSCT (n=112) or postinduction observation (n=111) for consolidation in patients with CLL who were in complete remission (59% of total) or very good partial remission (27% of total) following fludarabine-containing induction therapy. Patient age ranged from 31 to 65 years, with Binet stage A progressive (14%), B (66%), and C (20%) disease. None were known to have 17p deletion; 45% were known to not carry 17p deletion, but that status was unknown in 54% of all patients. The primary outcome, median event-free survival (EFS), was 51 months (range, 40-62) in the autograft group, compared with 24 months (range, 17-32) in the observed group; the 5-year EFS was 42% and 24%, respectively (p<0.001). The relapse rate at 5-year follow-up was 54% in the autograft group versus 76% in the observational group (p<0.001); median time to relapse requiring therapy or to death (whichever came first) was 65 months (range, 59-71) and 40 months (range, 25-56), respectively (p=0.002). Overall survival probability at 5-year follow-up was 86% (95% confidence interval [CI], 77% to 94%) in the autograft arm, versus 84% (95% CI, 75% to 93%) in the observation arm (p=0.77), with no evidence of a plateau in the curves. There was no significant difference in nonrelapse mortality (NRM) between groups, 4% in the autologous HSCT group and 0% in the observation group (p=0.33). Myelodysplastic syndrome was observed at follow-up in 3 patients receiving an autograft and in 1 patient in the observational group.

In a subsequent report published in 2013, the authors of the European Intergroup randomized controlled trial (RCT) presented quality-of-life (QOL) findings from this trial. Two secondary analyses were performed to further investigate the impact of HSCT and relapse on QOL. In the primary analysis, the authors demonstrate an adverse impact of HSCT on QOL, which was largest at 4 months and continued throughout the first year after randomization. Further, a sustained adverse impact of relapse on QOL was observed, which worsened over time. Thus, despite better disease control by autologous HSCT, the side effects turned the net effect toward inferior QOL in the first year and comparable QOL in the following 2 years after randomization.
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A subsequent prospective, RCT assessed the efficacy of autologous HSCT in previously untreated CLL patients. A total of 244 patients (181 men) of median age 56 years (range, 31-66) had Binet stage B (n=185) or C (n=56) disease. Among enrollees, 237 started planned therapy, 6 of whom discontinued. All 231 patients underwent induction chemotherapy; 103 (45%) entered complete remission and were randomly allocated to autologous HSCT (n=52) or observation (n=53). The 3-year estimated OS rates were 98% (95% CI, 94% to 100%) in the observation arm, and 96% (95% CI, 90% to 100%) in the HSCT arm (p=0.73). The estimated hazard ratio for death was 1.2 (95% CI, 0.3 to 3.8) in the HSCT arm relative to the observation arm (p=0.82). During the 36 months after randomization, HSCT was associated, on average, with an extra 9 months without clinical symptoms or blood signs of CLL progression (32±1 month) compared with observation (23±2 months). An editorial that accompanied this report suggests using autologous HSCT in this setting may prolong time to progression compared with observation, but that because OS is not improved, autologous HSCT remains investigational for CLL/SLL patients.

The results of the GOELAMS LLC 98 randomized trial were published in final form in 2012. This trial aimed to compare 2 strategies in previously untreated high-risk CLL patients 60 years-old or younger. Arm A comprised conventional chemotherapy of 6 monthly courses of CHOP (vincristine, doxorubicin, and oral prednisone) followed by 6 additional CHOP courses every 3 months in patients who achieved a partial response (PR) or complete response (CR). Arm B consisted of 3 monthly CHOP courses; patients who achieved a very good partial response (VGPR) or CR received consolidation therapy consisting of high-dose cyclophosphamide plus total-body irradiation followed by autologous HSCT; rituximab was not used in this study. Among 86 total patients, 39 and 43 were evaluable in arms A and B, respectively. The primary outcome was progression-free survival (PFS); on an intention-to-treat basis, the median PFS reached 22 months in arm A and 53 months in arm B at median follow-up of 77 months (p<0.001). Median OS time, however, was 104.7 months (95% CI, 99.9 to 109.5) in arm A and 107.4 months (95% CI, 58.2 to 156.6) in arm B, a nonsignificant difference. This trial shows that front-line high-dose therapy with autologous HSCT prolongs PFS but does not significantly improve the duration of OS.

Allogeneic HSCT

Allogeneic HSCT has been under investigation for the past 2 decades based on a potent graft-versus-leukemia (GVL) effect expressed as a permanently active cellular immune therapy in the recipient, independent of chemotherapy-related cytotoxicity. As indicated in the Description section of this policy, allogeneic HSCT may include use of myeloablative or reduced-intensity pretransplant conditioning regimens.

Data compiled in numerous review articles suggest that myeloablative allogeneic HSCT has curative potential for CLL or SLL. Long-term disease control (33%-65% OS at 3-6 years) due to a low rate of late recurrences has been observed in all published series, regardless of donor source or conditioning regimen. However, high rates (24%-47%) of TRM discourage this approach in early or lower-risk disease, particularly among older patients whose health status typically precludes the use of myeloablative conditioning.

The development of RIC regimens has extended the use of allogeneic HSCT to older or less fit patients who account for the larger proportion of this disease than younger patients, as outlined in several recent...
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Six review articles. Six published nonrandomized studies involved a total of 328 patients with advanced CLL who underwent RIC allogeneic HSCT using conditioning regimens that included fludarabine in various combinations that included cyclophosphamide, busulfan, rituximab, alemtuzumab, and total-body irradiation. The majority of patients in these series were heavily pretreated, with a median of 3 to 5 courses of prior regimens. Among individual studies, 27%-57% of patients had chemotherapy-refractory disease, genetic abnormalities including del 17p13, del 11q22, and VH unmutated, or a combination of those characteristics. A substantial proportion in each study (18%-67%) received stem cells from a donor other than a human leukocyte antigen (HLA)-identical sibling. Reported NRM, associated primarily with GVHD and its complications, ranged from 2% at 100 days to 26% overall at median follow-up that ranged from 1.7 to 5 years. Overall survival rates ranged from 48% to 70% at follow-up that ranged from 2 to 5 years. Similar results were reported for PFS, 34% to 58% at 2-5 year follow-up. Very similar results were reported from a Phase II study published in 2010 of RIC allogeneic HSCT in patients (n=90; median age, 53 years; range, 27-65) with poor-risk CLL, defined as having one of the following: refractoriness or early relapse (ie, <12 months) after purine-analog therapy; relapse after autologous HSCT; or, progressive disease in the presence of an unfavorable genetic marker (11q or 17p deletion, and/or unmutated IgVh status and/or usage of the VH3-21 gene). With a median follow-up of 46 months, 4-year NRM, EFS, and OS were 23%, 42%, and 65%, respectively. EFS was similar for all genetic subsets, including those with a 17p deletion mutation.

Summary
The body of evidence from single-arm prospective and registry-based studies suggests allogeneic HSCT can provide long-term disease control and overall survival in patients with poor-risk CLL/SLL. This conclusion is supported by clinical input from transplant specialists as noted below. Until recently, it has been unclear what patient- and disease-specific characteristics can be used to select patients who could benefit from allogeneic HSCT compared with those for whom less-intensive or no therapy may be indicated. This question has been addressed by investigations of cytogenetic and molecular abnormalities that can be associated with differential response to various therapies. Some of these are outlined in Table 2 in the Policy Guidelines section above.

Autologous HSCT is feasible in younger patients but is not curative, particularly in those with poor-risk CLL. None of the studies of autologous HSCT published to date has shown a plateau in overall survival at 4 to 6 years posttransplant. It may result in prolongation of overall survival, compared with conventional therapy, but this must be considered in the context of improved outcomes using conventional chemoimmunotherapy. Furthermore, evidence from the European Intergroup randomized controlled trial suggests quality-of-life issues are important in selecting patients for autologous HSCT and may dictate the management course for individuals who are otherwise candidates for this approach.

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3. Blue Cross and Blue Shield Association (TEC). High-dose chemotherapy plus autologous stem cells to treat chronic lymphocytic leukemia or small lymphocytic lymphoma. TEC Assessments 2002, Volume 17, Tab 4.

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<th>Code Type</th>
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12/06/2001 Medical Policy Committee review
01/28/2002 Managed Care Advisory Council approval
03/31/2004 Medical Director review
04/20/2004 Medical Policy Committee review. Format revision.
04/26/2004 Managed Care Advisory Council approval
06/03/2005 Medical Director review
06/21/2005 Medical Policy Committee review. Format revision. Rationale and Source added.
07/15/2005 Managed Care Advisory Council approval
07/07/2006 Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
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08/01/2007 Medical Director review
08/06/2009 Medical Policy Committee approval.
07/01/2010 Medical Policy Committee approval.
07/21/2010 Medical Policy Implementation Committee approval. Policy statement regarding allogeneic transplant in patients with markers of poor-risk disease changed; now may be considered medically necessary.
07/07/2011 Medical Policy Committee approval.
07/20/2011 Medical Policy Implementation Committee approval. No change to coverage.
06/28/2012 Medical Policy Committee review
07/27/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013 Coding updated
08/01/2013 Medical Policy Committee review
08/21/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/04/2014 Medical Policy Committee review
Next Scheduled Review Date: 09/2015

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:
  A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
  B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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     2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
     3. Reference to federal regulations.

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  A. In accordance with nationally accepted standards of medical practice;
  B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
  C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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