



BlueCross BlueShield of Louisiana

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Charged-Particle (Proton or Helium Ion) Radiation Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 02/19/2014

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 May Be 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 charged-particle irradiation with proton or helium ion beams to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility for the use of charged-particle irradiation with proton or helium ion beams may be considered when any of the following criteria are met:

- Primary therapy for melanoma of the uveal tract (iris, choroid or ciliary body), with no evidence of metastasis or extrascleral extension, and with tumors up to 24 mm in largest diameter and 14 mm in height; or
- Postoperative therapy (with or without conventional high-energy x-rays) in patients who have undergone biopsy or partial resection of chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (skull-base chordoma or chondrosarcoma) or cervical spine. Patients eligible for this treatment have residual localized tumor without evidence of metastasis; or
- Treatment of prostate cancer,
- Treatment of pediatric central nervous system (CNS) tumors.

When Services Are Considered Investigational

Note: Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of charged-particle irradiation with proton or helium ion beams to be **investigational*** when patient selection criteria are not met.

Based on review of available data, the Company considers other applications of charged-particle irradiation with proton beams to be **investigational***, including but not limited to:

- Non-small-cell lung cancer (NSCLC) at any stage or for recurrence,
- Pediatric non-central nervous system (CNS) tumors,
- Tumors of the head and neck (other than skull-based chordoma or chondrosarcoma).

Background/Overview

Charged-particle beams consisting of protons or helium ions are a type of particulate radiation therapy (RT). They contrast with conventional electromagnetic (i.e., photon) RT due to several unique properties, including minimal scatter as particulate beams pass through tissue, and deposition of ionizing energy at

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precise depths (i.e., the Bragg peak). Thus, radiation exposure of surrounding normal tissues is minimized. The theoretical advantages of protons and other charged-particle beams may improve outcomes when the following conditions apply:

- Conventional treatment modalities do not provide adequate local tumor control;
- Evidence shows that local tumor response depends on the dose of radiation delivered; and
- Delivery of adequate radiation doses to the tumor is limited by the proximity of vital radiosensitive tissues or structures.

The use of proton or helium ion RT has been investigated in two general categories of tumors/abnormalities. However, advances in photon-based RT such as 3-D conformal RT, intensity-modulated RT (IMRT), and stereotactic body radiotherapy (SBRT) allow improved targeting of conventional therapy:

1. Tumors located near vital structures, such as intracranial lesions or lesions along the axial skeleton, such that complete surgical excision or adequate doses of conventional RT are impossible. These tumors/lesions include uveal melanomas, chordomas, and chondrosarcomas at the base of the skull and along the axial skeleton.
2. Tumors associated with a high rate of local recurrence despite maximal doses of conventional RT. One tumor in this group is locally advanced prostate cancer (i.e., Stages C or D1 [without distant metastases], also classified as T3 or T4).

Proton beam therapy (PBT) can be given with or without stereotactic techniques. Stereotactic approaches are frequently used for uveal tract and skull-based tumors. For stereotactic techniques, 3 to 5 fixed beams of protons or helium ions are used.

Rationale/Source

Uveal Melanomas and Skull-based Tumors

A systematic review of charged particle therapy found that local tumor control rate and 5-year overall survival (OS) for skull base chordomas treated with proton therapy were 63% and 81%, respectively, compared to post-surgical treatment with conventional photon therapy with reported local tumor control rates and 5-year OS of 25% and 44%, respectively, and surgery followed by fractionated stereotactic radiotherapy, which resulted in 5-year local tumor control of 50%. A summary of tumor control in published proton therapy studies of chondrosarcoma of the skull base was 95% 5-year local tumor control, similar to the results of conventional therapy.

Charged-particle beam RT has been most extensively studied in uveal melanomas, in which the focus has been to provide adequate local control while still preserving vision. Pooling data from 3 centers, Suit and Urie reported local control in 96% and a 5-year survival of 80%, results considered equivalent to enucleation. A 2005 summary of results from the United Kingdom reports 5-year actuarial rates of 3.5% for local tumor recurrence, 9.4% for enucleation, 61.1% for conservation of vision of 20/200 or better, and 10.0% death from metastasis. The available evidence also suggested that charged-particle beam irradiation is at least as effective as, and may be superior to, alternative therapies, including conventional radiation or resection to treat chordomas or chondrosarcoma of the skull base or cervical spine. A Technology Evaluation Centers (TEC) Assessment completed in 1996 reached the same conclusions.

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Pediatric Central Nervous System Tumors

Radiation therapy is an integral component of the treatment of many pediatric CNS tumors including high-grade gliomas, primitive neuroectodermal tumors (PNETs), medulloblastomas, ependymomas, germ cell tumors, some craniopharyngiomas and subtotally resected low-grade astrocytomas. Children who are cured of their tumor experience long-term sequelae of radiation treatment, which may include developmental, neurocognitive, neuroendocrine, and hearing late effects. Radiation to the cochlea may lead to loss of hearing at doses greater than 35-45 Gy in the absence of chemotherapy, and the risk of ototoxicity is increased in children who receive ototoxic platinum-based chemotherapy regimens. Craniospinal irradiation, most commonly used in the treatment of medulloblastoma, has been reported to lead to thyroid dysfunction and damage to the lungs, heart and gastrointestinal tract. In addition, patients who receive radiation at a young age are at an increased risk of developing radiation-induced second tumors compared to their adult counterparts.

The development of more conformal radiation techniques has decreased inadvertent radiation to normal tissues; however, while IMRT decreases high doses to nearby normal tissues, it delivers a larger volume of low- and intermediate-dose radiation. Proton beam radiotherapy eliminates the exit dose to normal tissues and may eliminate ~50% of radiation to normal tissue.

A 2012 5-year update of a systematic review drew similar conclusions to the original review, that except for rare indications such as childhood cancer, the gain from proton RT in clinical practice remains controversial.

A 2012 review of the literature on the use of proton radiotherapy for solid tumors of childhood, the most common of which are CNS tumors, offered the following summaries of studies and conclusions.

Experience with the use of PBT for medulloblastoma, the most common malignant CNS tumor in the pediatric population, is relatively large. Although data on the late effects comparing proton to photon therapy are still maturing, dosimetric studies suggest that proton therapy in medulloblastoma should lead to decreased long-term toxicity.

Gliomas in locations where surgical resection can lead to unacceptable morbidity (e.g. optic nerves or chiasm, brainstem, diencephalon, cervical-medullary junction), are often treated with chemotherapy in young patients in order to delay radiation, with radiation to a dose of 54 Gy being reserved for unresectable lesions.

Loma Linda University Medical Center reported on proton radiation in the treatment of low-grade gliomas in 27 pediatric patients. Six patients experienced local failure; acute side effects were minimal. After a median follow-up of 3 years, all of the children with local control maintained performance status.

A dosimetric comparison of protons to photons for 7 optic pathway gliomas treated at Loma Linda showed a decrease in radiation dose to the contralateral optic nerve, temporal lobes, pituitary gland and optic chiasm with the use of protons.



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Massachusetts General Hospital reported on the use of protons in 17 children with ependymoma. Radiation doses ranged from 52.2 to 59.4 cobalt Gy equivalent. Median follow-up was 26 months, and local control, progression-free survival, and OS rates were 86%, 80%, and 89%, respectively. Local recurrences were seen in patients who had undergone subtotal resections. No deleterious acute effects were noted; the authors stated that longer follow-up was necessary to assess late effects. In the same study, 2 IMRT plans were generated to measure for dosimetric advantages with the use of protons for the treatment of infratentorial and supratentorial ependymomas. In both locations, the use of proton radiation provided significant decrease in dose to the whole brain, and specifically the temporal lobes. In addition, as compared to IMRT, proton radiation better spared the pituitary gland, hypothalamus, cochlea, and optic chiasm, while providing equivalent target coverage of the resection cavity.

Craniopharyngiomas are benign lesions, which occur most commonly in children in the late first and second decades of life. Massachusetts General Hospital reported on 5 children treated with combined photon/proton radiation or proton radiation alone with a median follow-up of 15.5 years. All 5 patients achieved local control without evidence of long-term deficits from radiation in endocrine or cognitive function. Loma Linda reported on the use of proton radiation in 16 patients with craniopharyngioma who were treated to doses of 50.4-59.4 cobalt Gy equivalent. Local control was achieved in 14 of the 15 patients with follow-up data. Follow-up was 5 years; 3 patients died, one of recurrent disease, one of sepsis, and one of a stroke. Among the survivors, one patient developed panhypopituitarism 36 months after debulking surgeries and radiation, a second patient had a cerebrovascular accident 34 months after combined primary treatment, and a third patient developed a meningioma 59 months after initial photon radiation, followed by salvage resection and proton radiation.

Massachusetts General Hospital reported on the use of protons in the treatment of germ cell tumors in 22 patients, 13 with germinoma and 9 with non-germinomatous germ cell tumors (NGGCTs). Radiation doses ranged from 30.6 to 57.6 cobalt Gray equivalents. All of the NGGCT patients received chemotherapy prior to RT. Twenty-one patients were treated with cranial spinal irradiation, whole ventricular RT, or whole brain radiation followed by an involved field boost; one patient received involved field alone. Median follow-up was 28 months. There were no CNS recurrences and no deaths. Following RT, 2 patients developed growth hormone deficiency, and 2 patients developed central hypothyroidism. The authors stated that longer follow-up was necessary to assess the neurocognitive effects of therapy. In the same study, a dosimetric comparison of photons and protons for representative treatments with whole ventricular and involved field boost was done. Proton radiotherapy provided substantial sparing to the whole brain and temporal lobes, and reduced doses to the optic nerves.

Moeller and colleagues reported on 23 children who were enrolled in a prospective observational study and treated with PBT for medulloblastoma between the years 2006-2009. As hearing loss is common following chemoradiotherapy for children with medulloblastoma, the authors sought to compare whether proton radiotherapy led to a clinical benefit in audiometric outcomes (since, compared to photons, protons reduce radiation dose to the cochlea for these patients). The children underwent pre- and 1-year post-radiotherapy pure-tone audiometric testing. Ears with moderate-to-severe hearing loss prior to therapy were censored, leaving 35 ears in 19 patients available for analysis. The predicted mean cochlear radiation dose was 30 ^{60}Co -Gy Equivalents (range 19-43). Hearing sensitivity significantly declined following radiotherapy across

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all frequencies analyzed ($p < 0.05$). There was partial sparing of mean post-radiation hearing thresholds at low-to-midrange frequencies; the rate of high-grade (grade 3 or 4) ototoxicity at 1 year was 5%. The authors compared this to a rate of grade 3-4 toxicity following IMRT of 18% in a separate case series. The authors concluded that preservation of hearing in the audible speech range, as observed in their study, may improve both quality of life and cognitive functioning for these patients.

Merchant and colleagues sought to determine whether proton radiotherapy has clinical advantages over photon radiotherapy in childhood brain tumors. Three-dimensional imaging and treatment-planning data, which included targeted tumor and normal tissues contours, were acquired for 40 patients. Histologic subtypes in the 40 patients were 10 each with optic pathway glioma, craniopharyngioma, infratentorial ependymoma, or medulloblastoma. Dose-volume data were collected for the entire brain, temporal lobes, cochlea, and hypothalamus, and the data were averaged and compared based on treatment modality (protons vs. photons) using dose-cognitive effects models. Clinical outcomes were estimated over 5 years. With protons (compared to photons), relatively small critical normal tissue volumes (e.g. cochlea and hypothalamus) were spared from radiation exposure when not adjacent to the primary tumor volume. Larger normal tissue volumes (e.g. supratentorial brain or temporal lobes) received less of the intermediate and low doses. When these results were applied to longitudinal models of radiation dose-cognitive effects, the differences resulted in clinically significant higher intelligence quotient (IQ) scores for patients with medulloblastoma and craniopharyngioma and academic reading scores in patients with optic pathway glioma. There were extreme differences between proton and photon dose distributions for the patients with ependymoma, which precluded meaningful comparison of the effects of protons versus photons. The authors concluded that the differences in the overall dose distributions, as evidenced by modeling changes in cognitive function, showed that these reductions in the lower-dose volumes or mean dose would result in long-term, improved clinical outcomes for children with medulloblastoma, craniopharyngioma, and glioma of the optic pathway.

Pediatric Non-Central Nervous System Tumors

There is scant data on the use of PBT in pediatric non-CNS tumors and includes dosimetric planning studies in a small number of pediatric patients with parameningeal rhabdomyosarcoma and late toxicity outcomes in other solid tumors of childhood.

Non-Small Cell Lung Cancer

A 2010 TEC Assessment assessed the use of PBT for NSCLC. This TEC Assessment addressed the key question of how health outcomes (OS, disease-specific survival, local control, disease-free survival, and adverse events) with PBT compare with outcomes observed for SBRT, which is an accepted approach for using RT to treat NSCLC.

Eight PBT case series were identified in the Assessment that included a total of 340 patients. No comparative studies, randomized or nonrandomized, were found. For these studies, stage I comprised 88.5% of all patients, and only 39 patients were in other stages or had recurrent disease. Among 7 studies reporting 2-year OS, probabilities ranged between 39% and 98%. At 5 years, the range across 5 studies was 25% to 78%. It is unclear if the heterogeneity of results can be explained by differences in patient and treatment characteristics.

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The report concluded that the evidence is insufficient to permit conclusions about the results of PBT for any stage of NSCLC. All PBT studies are case series; there are no studies directly comparing PBT and SBRT. Among study quality concerns, no study mentioned using an independent assessor of patient-reported adverse events; adverse events were generally poorly reported, and details were lacking on several aspects of PBT treatment regimens. The PBT studies were similar in patient age, but there was great variability in percent within stage IA, sex ratio, and percent medically inoperable. There is a high degree of treatment heterogeneity among the PBT studies, particularly with respect to planning volume, total dose, number of fractions, and number of beams. Survival results are highly variable. It is unclear whether the heterogeneity of results can be explained by differences in patient and treatment characteristics. In addition, indirect comparisons between PBT and SBRT, comparing separate sets of single-arm studies on PBT and SBRT may be distorted by confounding. In the absence of randomized controlled trials, the comparative effectiveness of PBT and SBRT is uncertain.

The 2010 TEC Assessment noted that adverse events reported after PBT generally fell into the following categories: rib fracture, cardiac, esophageal, pulmonary, skin, and soft tissue. Adverse events data in PBT studies are difficult to interpret due to lack of consistent reporting across studies, lack of detail about observation periods and lack of information about rating criteria and grades.

Pijls-Johannesma and colleagues conducted a 2010 systematic literature review through November 2009 examining the evidence on the use of particle therapy in lung cancer. Study inclusion criteria included that the series had at least 20 patients and a follow-up period \geq 24 months. Eleven studies, all dealing with NSCLC, mainly stage I, were included in the review, 5 investigating protons (n = 214) and 6, C-ions (n = 210). The proton studies included one Phase 2 study, 2 prospective studies, and 2 retrospective studies. The C-ion studies were all prospective and conducted at the same institution in Japan. No Phase 3 studies were identified. Most patients had stage 1 disease, however, a wide variety of radiation schedules were used, making comparisons of results difficult, and local control rates were defined differently across studies. For proton therapy, 2- to 5-year local tumor control rates varied in the range of 57–87%. The 2- and 5-year OS and 2- and 5-year cause-specific survival (CSS) rates were 31–74% and 23% and 58–86% and 46%, respectively. These local control and survival rates are equivalent to or inferior to those achieved with stereotactic RT. Radiation-induced pneumonitis was observed in about 10% of patients. For C-ion therapy, the overall local tumor control rate was 77%, but it was 95% when using a hypofractionated radiation schedule. The 5-year OS and CSS rates were 42% and 60%, respectively. Slightly better results were reported when using hypofractionation, 50% and 76%, respectively. The authors concluded that the results with protons and heavier charged particles are promising but that, because of the lack of evidence, there is a need for further investigation in an adequate manner with well-designed trials.

A 2010 systematic review of charged-particle RT for cancer concluded “evidence on the comparative effectiveness and safety of charged-particle RT in NSCLC cancer is needed to assess the benefits, risks, and costs of treatment alternatives.”

A 2010 indirect meta-analysis reviewed in the 2010 TEC Assessment found a nonsignificant difference of 9 percentage points between pooled 2-year OS estimates favoring SBRT over PBT. The nonsignificant difference of 2.4 percentage points at 5 years also favored SBRT over PBT. Based on separate groups of



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single-arm studies on SBRT and PBT, it is unclear if this indirect meta-analysis adequately addressed the possible influence of confounding on the comparison of SBRT and PBT.

The combination of proton beam radiotherapy with transpupillary thermotherapy in the treatment of ocular melanoma was being studied in a 2006 randomized-controlled trial.

Head and Neck Tumors, other than Skull-based

The literature on the use of PBT for head and neck tumors (other than skull-based) is scant and consists of dosimetric planning studies for nasopharyngeal carcinoma, and a case series of 91 patients who received combined proton and photon radiotherapy for advanced paranasal sinus tumors.

National Cancer Institute Clinical Trials

Two Phase III trials are comparing photon versus carbon ion RT in patients with low and intermediate grade chondrosarcoma of the skull base (NCT01182753) and chordoma of the skull base (CT01182779).

A Phase III trial is comparing hypofractionated proton radiation versus standard dose for prostate cancer (NCT01230866).

Clinical Input Received through Physician Specialty Society and Academic Medical Center

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 2 physician specialty societies (4 responses) and 4 academic medical centers. There was uniform support for the use of PBT in pediatric CNS tumors. Two reviewers expressed support for the use of PBT in pediatric non-CNS tumors; data for this use are scant. Input on head and neck tumors (non-skull based) was mixed.

Summary

- Studies on the use of charged-particle beam RT to treat uveal melanomas have shown local control and survival rates considered equivalent to enucleation. Therefore, it is considered medically necessary for this indication.
- Available evidence suggests that charged-particle beam irradiation is at least as effective as, and may be superior to, alternative therapies, including conventional radiation or resection to treat chordomas or chondrosarcoma of the skull base or cervical spine. Therefore, it is considered medically necessary for this indication.
- For pediatric CNS tumors, there is a small body of literature on long-term outcomes with the use of PBT. This modality of treatment of pediatric CNS tumors has the potential to reduce long-term side effects, as dosimetric studies of proton therapy compared with best available photon-based treatment have shown significant dose-sparing to developing normal tissues. Clinical input uniformly supported this use of PBT. Therefore, PBT may be considered medically necessary in the treatment of pediatric CNS tumors.

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- For pediatric non-CNS tumors, scant data exists and consists of dosimetric planning studies and a few case series in a small number of patients. Therefore, this indication is considered investigational.
- Results of proton beam studies for clinically localized prostate cancer have shown similar results and outcomes when compared to other radiation treatment modalities. Given these conclusions, along with information that PBT is generally more costly than alternative treatments, PBT is considered not medically necessary for treating prostate cancer.
- In treating lung cancer, definite evidence showing superior outcomes with proton beam RT versus SBRT (an accepted approach for treating lung cancer with radiation), is lacking. Therefore, this indication is considered investigational.
- In treating head and neck cancer (other than skull-based tumors), the data are scant and support from clinical input was mixed. Therefore, this indication is considered investigational.

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HCPCS	S8030
ICD-9 Diagnosis	All related diagnosis
ICD-9 Procedure	92.26

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01/26/2006 Quality 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.
09/20/2006 Medical Policy Committee approval. Coverage eligibility changed for the treatment of prostate cancer from not medically necessary to "eligible for coverage".
12/06/2006 Medical Director review
12/20/2006 Medical Policy Committee approval. Coverage eligibility unchanged.
02/13/2008 Medical Director review
02/20/2008 Medical Policy Committee approval
02/04/2009 Medical Director review
02/19/2009 Medical Policy Committee approval. No change to coverage eligibility.
02/04/2010 Medical Policy Committee review
02/17/2010 Medical Policy Implementation Committee approval. No change to coverage eligibility. Rationale replaced.
02/03/2011 Medical Policy Committee review
02/16/2011 Medical Policy Implementation Committee approval. New investigational statement added.
02/02/2012 Medical Policy Committee review
02/15/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/07/2013 Medical Policy Committee review
02/20/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/06/2014 Medical Policy Committee review
02/19/2014 Medical Policy Implementation Committee approval. Added that proton radiotherapy may be considered eligible for coverage with criteria for the treatment of pediatric central nervous system tumors. Investigational statements added for pediatric non-central nervous system tumors and head and neck tumors (non-skull based).

Next Scheduled Review Date: 02/2015

*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:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- 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

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Charged-Particle (Proton or Helium Ion) Radiation Therapy

Policy # 00187

Original Effective Date: 01/26/2006

Current Effective Date: 02/19/2014

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.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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