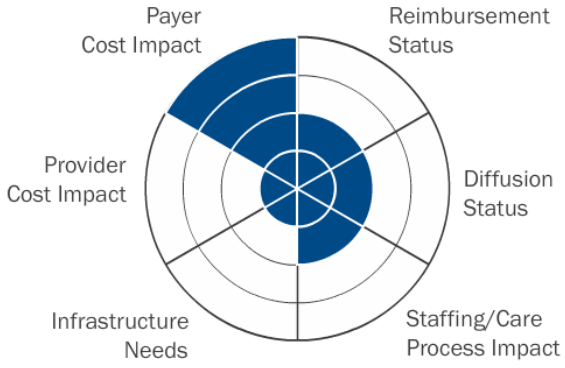
Tumor Treating Fields Therapy (Optune) for Recurrent Glioblastoma

HEALTH TECHNOLOGY ASSESSMENT INFORMATION SERVICE™

EMERGING TECHNOLOGY EVIDENCE REPORT

Executive Summary

Tumor treating fields (TTFs) therapy uses alternating electric fields to inhibit cell proliferation and lead to programmed cell death. TTF therapy targets dividing cells to stop tumor growth while sparing normal tissue. The Optune™ TTF system is intended to treat patients with glioblastoma by using transducer arrays placed on the patient's scalp according to the tumor's location. Patients use the device on an outpatient basis for at least 18 hours per day for 4 weeks to several months. Intended benefits include stabilizing the disease, having fewer treatment-related adverse events, and improving quality of life. A potential disadvantage is skin irritation.



Parameter Rating and Definition*	Rationale
Reimbursement Status: 2 Limited: Medicare has no national coverage determination; 1 to 3 private payers have issued positive payment policies.	Our searches of 11 representative, private, third-party payers that provide online medical coverage policies found 1 payer with a policy describing coverage with conditions, 7 payers denying coverage, and 3 payers without a specific policy.
Diffusion Status: 2 Early: Adopted by 10% to <25% of healthcare providers and facilities expected to use this technology.	In the United States, TTF therapy for recurrent glioblastoma is available at more than 170 cancer treatment centers. The Optune Treatment Kit is also commercially available in Austria, the Czech Republic, the United Kingdom, France, Germany, Greece, Israel, Ireland, Italy, Switzerland, Australia, and Japan.
Effects on Staffing and Care Processes: 2 Low: Limited staffing changes and/or care process changes needed.	Prescribers must participate in a 4-hour training program provided by Novocure, the manufacturer of Optune. Optune does not require regular maintenance, and Novocure provides patient technical support. Although physicians continue to monitor patients for disease management, treatment centers may experience a slight decrease in patient flow because of a shift of treatment from hospital chemoinfusion or radiation therapy clinics to treatment in a home setting.
Infrastructure Needs: 1 Negligible: No additional infrastructure needed to adopt the technology.	The home treatment setting obviates any need for additional hospital infrastructure.
Technology Cost Impact on Providers: 1 Negligible: Negligible: <$25,000 for acquisition and implementation.	Centers providing TTF therapy do not need to acquire the Optune Treatment Kit or other equipment because the patient procures the Optune once prescribed. Implementation costs are limited to staff training time and teaching patients how to use the device.
Technology Cost Impact on Payers: 4 Substantial: >$50,000 per patient and/or high utilization resulting in high aggregate cost.	Novocure leases Optune Treatment Kits to patients. The total monthly therapy cost is about $21,000, or about $86,000 when used an average of 4.1 months (median treatment duration) for the typical patient. Glioblastoma is diagnosed in about 7,000 U.S. patients annually; if 10% of these patients chose TTF therapy, the estimated aggregate cost to payers could be about $60.2 million, minus patient copays.

*Please see Appendix C for parameter definitions.

Evidence Summary of Selected Outcomes†

Key Outcomes Assessed	Evidence Base	Conclusions	GRADE-based Strength-of-evidence Rating*
Median overall survival	TTF vs. BSC: 1 RCT	No difference between TTF and BSC	Moderate
Quality of life	TTF vs. BSC: 1 RCT	Inconclusive: study reports insufficient information	Very low
Serious hematologic adverse events	TTF vs. BSC: 1 RCT	TTF causes fewer events than BSC	Moderate
Serious adverse events: metabolism and nutrition disorders, vascular disorders	TTF vs. BSC: 1 RCT	No difference between TTF and BSC	Low
Serious adverse events: gastrointestinal, nervous system disorders	TTF vs. BSC: 1 RCT	Inconclusive: study reports too few events	Very low
Adverse events: thrombocytopenia, leukopenia, diarrhea, infections	TTF vs. BSC: 1 RCT	TTF causes fewer events than BSC	Moderate
Adverse events: nausea, anorexia, muscle weakness, alopecia	TTF vs. BSC: 1 RCT	TTF causes fewer events than BSC	Low
Adverse events: skin site reactions, falls, rashes	TTF vs. BSC: 1 RCT	TTF causes more events than BSC	Low

BSC: Best standard of care
NA: Not applicable
RCT: Randomized controlled trial
TTF: Tumor treating fields

*Note: We grade strength of evidence based on the concepts and methods proposed by the GRADE working group. Please see Appendix A for details.
†: No studies compared tumor treating fields with palliative therapy

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Editor's Note

This Emerging Technology Evidence Report provides an analysis of full published studies in the clinical literature through October 15, 2015. ECRI Institute is anticipating a publication reporting the findings of the EF-14 (NCT00916409) clinical trial that tested the efficacy and safety of the Optune Treatment Kit as an adjuvant to temozolomide for treating patients with newly diagnosed glioblastoma. The findings of this trial may change the conclusions found in this report. ECRI Institute intends to publish an update to this report in 2016.

Overview

Related Names

Proprietary names: Optune™ Treatment Kit, Inovitro™ Lab Research System, NovoTAL™ System, NovoTTF-100A™ System, Tumor Treating Field Generator.

Generic names: TTFields therapy, TTF therapy.

Background/Disease

Glioblastomas (GBMs) (also known as glioblastoma multiforme) are central nervous system tumors "composed of a heterogeneous mixture of poorly differentiated neoplastic astrocytes."[1] GBM is the most common form of malignant primary brain tumor in adults, accounting for approximately 15% of all brain and central nervous system tumors and about 55% of all gliomas.[2] GBM is a grade IV astrocytoma, the most deadly type of glial cell tumor.[3] Risk factors include age, exposure to radiation, and a family history of brain tumors.

GBM symptoms depend on the tumor's location and may include weakness, numbness, language deficits, seizures, headaches, nausea, vomiting, and confusion.[4]

GBM is often resistant to standard chemotherapy. At the time of radiographic diagnosis, patients typically undergo a biopsy or a more extensive debulking surgery to remove as much of the tumor as possible.[3] Many factors influence clinician and patient decisions regarding surgical intervention. Depending on the patient's physical condition, adjuvant therapy may include radiation, systemic chemotherapy, or both, possibly followed by maintenance therapy with temozolomide.[3]

Virtually all GBMs recur after first-line treatment, and second-line options depend on prior treatments, the extent and location of recurrence, and the patient's condition.[5] Second-line treatments may include debulking surgery with or without local chemotherapy (i.e., nitrosourea wafers [Gliadel®]), focal radiation therapy (if a small tumor recurs in a single anatomic location), or salvage therapy with single-agent or combination systemic chemotherapy, including the following:[3,6]

- Bevacizumab (Avastin®)
- Bevacizumab plus irinotecan, BCNU/CCNU (1,3-bis(2-chloroethyl)1-nitrosourea / 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea)
- Alternative dose temozolomide
- PCV (procarbazine, CCNU, and vincristine)
- Cyclophosphamide
- Platinum-based agents

Treatment of recurrent diffuse disease may also include palliative care that focuses on "effective management of pain and other distressing symptoms, while incorporating psychosocial and spiritual care according to the patient / family needs, values, beliefs, and cultures."[7]

This report focuses on tumor treating fields (TTFs) therapy for recurrent GBM, which uses alternating electric fields to target proliferating cells.[8] TTF therapy is based on the concept that alternating electric fields may inhibit cell proliferation and lead to programmed cell death by disrupting charged proteins necessary for the formation of the mitotic spindle and interfering with cytokinesis (i.e., the end process by which two new cells are formed from a dividing cell).[9]

Incidence and Prevalence

United States

Gliomas account for 28% of primary brain tumors diagnosed annually in the United States, and GBM, the most common type of glioma, accounts for more than half of gliomas.[2] GBM's annual incidence is approximately 2 to 3 new cases per 100,000 people.[1] Gliomas may occur in individuals in every age group; however, they are more prevalent in people between 45 and 70 years of age.[1] GBM is more common in men than women (3:2 ratio) and Caucasians.[10]

GBM is the most deadly form of primary brain cancer. Survival expectancy of a patient with newly diagnosed GBM is 12 to 16 months.[11,12] The one-year survival rate for patients in whom GBM is diagnosed is 35%, and the five-year survival rate is <5%.[13] After GBM recurrence, the one-year survival rate is approximately 20%, and median survival ranges from three to nine months.[14] If left untreated, patients typically die within three months.[1]

Worldwide

GBM's overall incidence is consistent worldwide.[1] Internationally, GBM is the most common primary malignant brain tumor and accounts for 12% to 15% of all intracranial neoplasms and 50% to 60% of all astrocytic tumors.[1] The incidence of GBM in most European countries is about 2 to 3 new cases per 100,000 people per year.[1]

Technology Description

TTF therapy is a "locally or regionally delivered treatment that uses electric fields to target and disrupt cell division exhibited by cancer cells."[15] During the therapy, the device delivers low-intensity (i.e., 1 to 3 V/cm), intermediate-frequency (i.e., 200 kHz), alternating electric fields.[9]

This type of electric field may selectively inhibit tumor growth by "disrupting mitotic spindle microtubule assembly leading to dielectrophoretic dislocation of intracellular macromolecules and organelles during cytokinesis," thus interfering with completion of cell division.[15] Interference with these processes is thought to "lead to physical disruption of the cell membrane and to programmed cell death (i.e., apoptosis)."[9] This treatment may be selective for tumors because the electric fields are believed to affect only dividing cells that are found at high levels in tumors.[16] Because different cell types respond optimally to TTF therapy at different frequencies, the type of malignant cells targeted determines the frequency TTF uses for treatment.[17] Because normal adult brain cells proliferate very slowly, if at all, they are (in theory) minimally affected by the therapy.[9] Thus, TTF therapy targets dividing cells to stop tumor growth while sparing normal tissue.[9]

Figure 1. Optune Treatment Kit

Reprinted with permission from Novocure, Inc., Portsmouth, NH, USA.

The system used for TTF therapy is the Optune Treatment Kit (formerly NovoTTF-100A System, Novocure, Ltd.). The kit, shown in Figure 1, includes the electric field generator (Optune device), INE (insulated electrode) transducer arrays, power supply, portable battery, battery rack, battery charger, connection cable, and carrying case. The arrays are packaged with a gel layer, padding, medical tape, and overlapping liner.[18] Prescribers may lease the optional NovoTAL (transducer array layout) simulation software from the manufacturer.[19] The device is used continuously, so patients carry the six-pound portable generator in an over-the-shoulder bag or backpack during daily activities, with transducer arrays placed on their head and connected to the generator.[18]

To apply TTF therapy, four insulated transducer arrays are placed on the patient's shaved scalp according to the tumor's location. The optional NovoTAL simulation software may be used to determine optimal location for placement of the transducer arrays based on the patient's most recent magnetic resonance imaging (MRI) scan, head size, and tumor location.[19,20] The transducer arrays connect to the portable generator, which noninvasively delivers TTF therapy by generating 200 kHz electric fields within the brain in two perpendicular directions.[21] Optune's manufacturer, Novocure, presets the exact treatment parameters; no electrical output adjustments are available to the patient.[9] The patient or caregiver must reshave the scalp area and replace transducer arrays every four to seven days, learn how to change and recharge depleted batteries, and connect Optune to an external power supply.[18]

Patients can receive TTF therapy outside the hospital on a continuous basis (between 20 to 24 hours per day) for the treatment's duration, which is at least 4 weeks but can be several months.[18,22] To shower, patients must disconnect the transducer arrays from the generator.[22,23] The patient can place a shower cap over the existing transducer arrays on the scalp to keep them dry or remove them to shower and replace them with a new pair. A well-vented wig or hat can be worn over the transducer arrays.[22,23]

Intended Benefits and Potential Disadvantages

Intended benefits for using Optune as an alternative to chemotherapy for treating recurrent GBM include preventing tumor growth, fewer treatment-related adverse events (AEs), and better quality of life (QOL).[23]

Potential disadvantages include skin irritation under the transducer arrays and a higher rate of headaches compared with patients treated with chemotherapy.[23]

Care Setting

Cancer Center, Home Care, Outpatient

Manufacturers

Novocure, Ltd. (Jersey, United Kingdom) manufactures the Optune Treatment Kit at its Israeli subsidiary Novocure, Ltd. (Haifa, Israel) and distributes the product in the United States through its subsidiary Novocure, Inc. (Portsmouth, NH, USA).[24]

Regulatory Status

United States

In April 2011, Novocure received U.S. Food and Drug Administration (FDA) marketing approval through the premarket approval (PMA) application process for the NovoTTF-100A system (later renamed Optune Treatment Kit) as a monotherapy for recurrent GBM.[25]

As a condition of approval, Novocure must conduct a postapproval study to assess noninferiority in overall survival of patients with recurrent GBM treated with the Optune Treatment Kit compared with patients treated with best standard of care (BSC).[26] The study will enroll 486 patients with recurrent GBM and will be conducted in at least 30 sites, half of which will be in the United States.[26]

Since the original PMA, FDA approved 13 PMA supplements, 11 of which pertained to minor design changes, software modifications, and manufacturing process changes. In September 2014, FDA granted marketing approval through a PMA supplement for a trade-name change from NovoTTF-100A to Optune and for the transducer array, the electric field generator, and the device components to be named the Optune Treatment Kit.[27] In October 2015, FDA approved a PMA supplement expanding the clinical indication of the Optune Treatment kit to include Optune with temozolomide for treating newly diagnosed GBM.[28]

Europe

NovoTTF-100A (Optune) received a CE mark certification, permitting commercial distribution in Europe in 2009.[9]

Other Countries

The Australian Registrar of Therapeutic Goods lists NovoTTF-100A (Optune) and the INE transducer arrays for treating recurrent or newly diagnosed GBM.[29]

In September 2014, the Japanese Ministry of Health and Welfare granted NovoTTF-100A (Optune) the designation of "High Unmet Medical Need"[30] and in March 2015 approved the Optune Treatment Kit for treating patients with recurrent GBM.[31]

Reported Indications and Contraindications

United States

Labeled Indications

The Optune Treatment Kit is "intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed GBM, following histologically- or radiologically confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted."[9,18]

Optune with temozolomide "is indicated for the treatment of adult patients [22 years of age or older] with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy."[28]

Labeled Contraindications

The Optune Treatment Kit should not be used to treat patients with an active implanted medical device (e.g., deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, programmable shunts) because such combinations have not been tested and the Optune Treatment Kit could interfere with the implanted device's proper functioning.[18] Also, the Optune should not be used to treat patients with skull defects, a shunt, or bullet fragments or in patients with known sensitivity to conductive hydrogels used with the device transducer arrays.[18]

European Union and Switzerland

Labeled Indications

The Optune Treatment Kit is intended for treating patients with recurrent GBM who have progressed after surgery, radiotherapy, and temozolomide treatment for their primary disease. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after the latest surgery, radiation therapy, or chemotherapy.[24]

Also, in the European Union and Switzerland, the Optune Treatment Kit is intended for treating patients with newly diagnosed GBM, after surgery and radiotherapy with adjuvant temozolomide, concomitant to maintenance temozolomide. The treatment is intended for adult patients, 18 years of age or older, and should be started more than 4 weeks after surgery and radiation therapy with adjuvant temozolomide.

Labeled Contraindications

The Optune Treatment Kit should not be used in patients with the following:[24]

- Pregnancy
- Implanted pacemaker, defibrillator, or another implanted electric medical device
- Clinically significant hepatic, renal, or hematologic disease

- Significant additional neurologic disease (i.e., primary seizure disorder, dementia, progressive degenerative neurological disorder, meningitis or encephalitis, hydrocephalus with increased intracranial pressure)

Clinical Guidelines and Standards

ECRI Institute searches identified the following four relevant guidelines:

- National Comprehensive Cancer Network (NCCN): *Clinical Practice Guidelines in Oncology/Central Nervous System Cancers.* 2015. This guideline includes alternating electric field therapy (Optune Treatment Kit) as a treatment option for the recurrent disease pathway (GLIO-4), for local, multiple, or diffuse glioblastoma. According to this guideline, "patients with recurring glioblastoma may also consider alternating electric field therapy (category 2B)." This guideline defines a category 2B recommendation as "based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate."[32]
- American Association of Neuroscience Nurses: *Care of the Adult Patient with Brain Tumor.* 2014. This guideline includes alternating electric field therapy (Optune Treatment Kit) as a "novel therapy for primary malignant brain tumor" and recommends that "nurses should be aware that use of electrical tumor treatment fields may be considered a comparable treatment option to chemotherapy for patients with recurrent malignant glioma," as a level 1 recommendation (level 1 recommendation is based on Class 1 evidence defined in the guideline as "randomized control trials without significant limitations or meta-analysis").[33]
- European Association for Neuro-Oncology (EANO): *EANO Guideline on the Diagnosis and Treatment of Anaplastic Gliomas and Glioblastoma*. 2014. This guideline states: "new approaches of glioma therapy… device based therapies such as tumor-treating fields should only be administered in the context of clinical trials."[34]
- European Society for Medical Oncology (ESMO): *High-grade Glioma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up.* 2014. This guideline states: "Applying alternating electric fields—tumor-treating fields—using a battery powered device connected to electrodes placed on the patient's scalp—was compared with physicians' choice of chemotherapy in a randomized trial in recurrent disease. TTF failed to prolong survival compared with second-line chemotherapy [I, A]." This guideline defines Level of Evidence I as "evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity." This guideline defines Grade of Recommendation A as "strong evidence for efficacy with a substantial clinical benefit, strongly recommended."[35]

Other Evidence Reports

ECRI Institute searches identified the following relevant evidence report that addressed TTF therapy for GBM, published by the Australian Health Policy Advisory Committee on Technology in May 2012. This report concluded:[36]

> Based on data provided in the EF-11 pivotal study (FDA 2011a) TTF appears to be non-inferior to BSC [best standard chemotherapy] for the treatment of recurrent GBM. The treatment is associated with a higher rate of procedure-related AEs in the form of rashes due to electrodes; however, it is associated with a reduced rate of gastrointestinal AEs compared with BSC. In addition, TTF may confer a slight increase in overall survival, progression-free survival at six months, and time to progression. Importantly however, the mean duration of treatment was higher for the TTF group than the BSC group (4.2 months vs 2.6 months), and the study was sponsored by the manufacturer of the NovoTTF-100A [Optune] device (Novocure), thus caution should be taken when interpreting these results. As no data were presented comparing TTF to a no-treatment control group, it is difficult to ascertain what effect the toxicity of chemotherapy played with regards to outcomes of effectiveness. Additional comparative data is required before any definitive conclusions regarding the safety and effectiveness of TTF compared with BSC can be drawn.

Considerations for Hospitals

Staffing Requirements

Clinicians, nurses, and select medical personnel who have completed Novocure's training or Novocure's device specialists may teach patients how to connect the device to an external power supply, charge depleted batteries, and replace the batteries. Treatment settings are preset so that clinicians and patients do not have to adjust the device's electrical outputs.[18,23] Use of the Optune Treatment Kit is not anticipated to create a shift in staffing requirements.

Infrastructure Requirements

The Optune Treatment Kit provides TTF therapy on a continuous basis, and patients receive treatment outside the hospital.[18,23] Existing infrastructure is probably sufficient for treatment centers using the Optune Treatment Kit and the optional NovoTAL software system.

Impact on Patient Scheduling/Flow

Cancer treatment centers will probably experience a slight decrease in patient flow. Patients receiving TTF therapy for recurrent GBM can receive treatment outside the hospital setting, unlike the most commonly used alternative, bevacizumab, which requires intravenous administration. Trained medical providers or Novocure's device specialists may initially assist with fitting the Optune Treatment Kit to the patient's scalp.[23] Optune does not require regular maintenance, and Novocure provides a troubleshooting guide with each device and 24-hour technical telephone support.[18,19,23]

Safety

Potential Complications

TTF therapy is delivered locally through a nonchemical pathway, does not deliver electric current to the tissue, and does not stimulate nerves or muscles;[17,37] thus, treatment with Optune is not expected to cause serious AEs.[9] However, treatment may cause any of the following:[9,23]

- Local warmth and tingling sensation beneath transducer arrays
- Allergic reaction to the plaster or gel
- Skin breakdown or ulcer
- Infection at electrode skin contact site
- Pain and/or local skin bums (caused by overheated transducer array)
- Headache
- Fatigue/malaise
- Muscle twitching
- Seizures
- Falls
- Cognitive changes

Labeled Warnings

The Optune Treatment Kit instructions for use list the following warnings:[18]

- Using the device without receiving appropriate training can result in breaks in treatment and may cause increased scalp rash, open sores on the head, allergic reactions, or electric shock.

- To use an over-the-counter topical steroid (i.e., 0.1% hydrocortisone) cream when replacing transducer arrays if skin irritation occurs. Not treating skin irritation can lead to skin breakdown, infections, pain, and/or blisters that could require an interruption of TTF therapy.
- Trained personnel should perform all servicing of the Optune Treatment Kit to avoid causing damage to the system.

Labeled Cautions

The Optune Treatment Kit instructions for use list the following cautions that may damage the device or cause a break in treatment:[18]

- Do not use components that do not come with the Optune Treatment Kit.
- Ensure that screws or plates used under the skin are between the round discs that make up the transducer arrays.
- Inform the treating clinician of any inactive implanted medical device in the brain.
- Do not use components that look damaged.
- Do not wet the device or the transducer arrays.
- Do not connect or disconnect the transducer arrays if Optune is in the "on" position.

Labeled Notices

Labeled notices include the following:[18]

- Optune and the transducer arrays will activate metal detectors.
- Using the system for fewer than 18 hours a day or stopping treatment before 4 weeks lowers the chances of treatment response.
- Patients should stop using Optune only after instruction by a clinician.
- Patients planning to be away from home for >2 hours should carry an extra battery and/or the power supply.
- Patients should have at least 12 extra transducer arrays at all times.
- Blocking the vents located on the front or sides of the device and the vents of the battery chargers may cause overheating.
- Transducer arrays are for single use and should not be reused.
- Batteries may weaken over time.
- Patients should carry the troubleshooting guide with them at all times.

FDA Manufacturer and User Facility Device Experience Database Reports

FDA's Manufacturer and User Facility Device Experience (MAUDE) database contains medical device reports (MDRs) of suspected device-associated deaths, serious injuries, and malfunctions submitted to FDA by mandatory reporters (i.e., manufacturers, importers, and device user facilities) and voluntary reporters (i.e., healthcare professionals, patients consumers). According to the FDA website:[38]

- This passive surveillance system "has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data."
- The incidence or prevalence of an event "cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use."

- MDR data alone "cannot be used to establish rates of events, evaluate a change in event rates over time or compare event rates between devices."
- Although FDA updates MAUDE monthly and "seeks to include all reports received before the update, the inclusion of some reports may be delayed."

The MAUDE database also contains duplicate reports in some cases (same event reported by different entities) and reports of events not related to the device or surgery (e.g., death due to a medical condition). These weaknesses should be taken into consideration when viewing the following, which contains the results of our June 7, 2015, search of the MAUDE database on NovoTTF-100A (Optune).

Our search between January 2011 and June 2015 yielded 53 reports involving the Optune Treatment Kit (NovoTTF-100A): 25 reports of death, 14 reports of injury, and 14 reports labelled as "other." Determining the cause of events from MAUDE is not possible; therefore, these events may not be related to the Optune system.

Training and Credentialing

Manufacturer-sponsored Training

Optune Treatment Kit prescribers must be trained and receive a training certificate before prescribing the system. To become a certified prescriber, clinical and select support staff participate in a four-hour training program provided by Novocure, which includes the following topics:[24]

- Physics and mechanism of action
- Preclinical data
- Clinical data in recurrent GBM
- Transducer array layout
- Optune system parts
- Treatment initiation
- Treatment follow-up
- Patient home use

Training culminates in a medical personnel training test, a hands-on demonstration, and practice of system assembly and transducer array application.[24] Physicians may also complete additional training for using the optional NovoTAL simulation software. According to one clinical reviewer who provided comments to ECRI Institute on this technology, "many physicians who prescribe the Optune treatment kit are not certified in NovoTAL."[19]

General Training

The Optune Treatment Kit product labeling lists the following warning for patients:[18]

> Use Optune only after receiving training from qualified personnel, such as a doctor, a nurse, or other medical personnel who have completed a training course given by the device manufacturer (Novocure). Ask to see a certificate signed by Novocure that says they completed a training course. Your training will include a detailed review of this manual and practice in the use of the system. In addition, you will be trained in what to do if there are problems with treatment.

Also, patients need training in the maintenance of the electrical field generator (e.g., battery charging and replacement) and the maintenance of transducer array contacts.[18]

Competing and Complementary Technologies

Competing

After exhausting surgical and radiotherapy options, some practitioners may choose the following alternative treatments for recurrent GBM, depending on prior treatment, extent of the disease, and the patient's medical condition:[1,3,9,39]

- Bevacizumab (Avastin)
- Bevacizumab plus systemic chemotherapy (i.e., irinotecan, BCNU/CCNU, temozolomide)
- Single-agent or combination systemic chemotherapy (i.e., temozolomide, nitrosourea, combination PCV, cyclophosphamide, platinum-based).

The Optune Treatment Kit competes with and complements temozolomide for treating newly diagnosed GBM.[39]

Although listed as a potential competing technology to systemic chemotherapy, TTF therapy may ultimately complement the therapy for treating recurrent GBM. (See *Future Trends* section below.)

Complementary

Complementary technologies include pain medication and corticosteroids for symptom relief and anticonvulsants to help prevent seizures, which are commonly associated with brain tumors.

Researchers may study TTF effects on cancer cells in a laboratory setting. In November 2013, Novocure launched the Inovitro™ Lab Research System, comprising a TTF generator controlled by proprietary software and up to five base plates, each with eight ultra-high dielectric constant ceramic petri dishes. The Inovitro "allows researchers to set target TTF intensity and frequency in each ceramic dish, and observe real time values of those parameters during an experiment."[40]

Phase of Diffusion

TTF therapy is in an early state of diffusion. Worldwide, as of January 2015, approximately 2,220 patients have received TTF therapy using the Optune Treatment Kit.[24]

United States

In the United States, TTF therapy for recurrent GBM is available at more than 190 cancer treatment centers where clinicians have undergone training in use of the Optune Treatment Kit.[41]

Other Countries

TTF therapy has been available in the United Kingdom, Ireland, France, Germany, Italy, Greece, and Switzerland since 2009 for newly diagnosed and recurrent GBM. In July 2014, Novocure announced the commercial launch of the Optune Treatment Kit in Austria, the Czech Republic, England, France, Germany, Greece, Israel, and Switzerland.[42] The commercial launch will allow trained clinicians in these countries to prescribe the Optune system outside the clinical trial setting.[42] As of August 2015, Optune is also available in Australia and Japan.[41]

Future Trends

Other Indications

Some clinical researchers assert that TTF "could be further evaluated in combination with chemotherapy, as a maintenance treatment, or as a salvage therapy if radiotherapy or surgery is not possible."[43] Clinical studies are ongoing to determine the safety and efficacy of TTF therapy as part of combination therapy for treating recurrent GBM. TTF therapy is under investigation as a combination therapy with chemotherapy plus bevacizumab and as a combination therapy with chemotherapy after irradiation therapy for treating recurrent GBM.[44,45]

Technology in Development

TTF therapy is also being evaluated for treating brain metastases in patients with non-small cell lung cancer,[46] advanced pancreatic adenocarcinoma (together with gemcitabine),[47] recurrent ovarian cancer,[48] recurrent atypical anaplastic meningioma, and malignant mesothelioma.[49]

Costs

Novocure leases the Optune Treatment Kit to patients. The total monthly cost of TTF therapy is approximately $21,000.[50]

Reimbursement

ECRI Institute provides the following as reference and for information purposes only. Coding, coverage, and reimbursement information provided does not constitute legal advice and does not guarantee payment.

Coverage

The U.S. Centers for Medicare & Medicaid Services (CMS) has no national coverage determination for TTF therapy (Optune) for recurrent GBM. Thus, coverage decisions are left to the discretion of local Medicare carriers.

Our searches of 11 representative, private, third-party payers that provide online medical coverage policies (Aetna, Anthem, Blue Cross/Blue Shield [BC/BS] of Alabama, BC/BS of Massachusetts, CIGNA, HealthPartners, Humana, Medica, Regence, United Healthcare, Wellmark) found 1 payer with a policy describing coverage with conditions, 7 payers that deny coverage, and 3 payers with no specific policy. See Table 1 for details. According to Novocure, several payers, including CIGNA, Emblem Health, United Healthcare, Harvard Pilgrim Health Care, HealthLink, Tricare, and several BC/BS (MN, TX, IL, FL, OH, CA, NJ), have provided coverage for the Optune Treatment Kit on a case-by-case basis through medical necessity review.[24,51]

Table 1. Third-party Payer Policies for Tumor-treating Fields for Recurrent Glioblastoma

Payer	Policy Name	Date of Last Review	Coverage Policy
Aetna[52]	Electric Tumor Treatment Fields	7/17/2015	Aetna "considers devices to generate electric tumor treatment fields (ETTF) medically necessary as monotherapy for persons with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma), after histologically or radiologically confirmed recurrence in the supratentorial region of the brain after receiving chemotherapy."
Anthem[53]	Electric Tumor Treatment Field	11/13/2014	Anthem considers "the use of devices to generate electric tumor treating fields as a treatment for malignant tumors investigational and not medically necessary."
BC/BS of Alabama[54]	Tumor-Treating Fields Therapy for Glioblastoma	8/2014	"Tumor-treating fields therapy for glioblastoma does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered investigational."
BC/BS of Massachusetts[55]	Tumor-Treatment	5/2015	BC/BS of Massachusetts considers "tumor treatment fields to treat glioblastoma investigational."
HealthPartners[56]	Electric Tumor Treatment Fields to Treat Glioblastoma	8/2014	"Electric tumor treatment fields therapy is covered per the National Comprehensive Cancer Network Guidelines as follows: 1. For patients with glioblastoma that recurs or progresses after initial treatment; and 2. When Avastin as second line treatment has also failed."

Payer	Policy Name	Date of Last Review	Coverage Policy
Humana[57]	Electric Tumor Treatment Fields	4/23/2015	"Humana members may not be eligible under the plan for electric tumor treatment fields. This technology is considered experimental / investigational as it is not identified as widely used and generally accepted for the proposed use as reported in the nationally recognized peer-reviewed medical literature published in the English language."
Regence[58]	Tumor-Treatment Fields Therapy for Glioblastoma	2/2015	"Tumor treatment fields therapy to treat glioblastoma is considered investigational."
Wellmark[59]	Tumor Treatment Fields	11/2014	"The use of electrical tumor treatment fields is considered investigational for all indications including, but not limited to, treatment of glioblastoma multiforme, due to a lack of evidence demonstrating an impact on improved health outcomes."

Coding

The American Medical Association has not assigned Current Procedural Terminology (CPT) codes to describe TTF for recurrent GBM. In January 2014, CMS assigned a specific Healthcare Common Procedure Coding System (HCPCS) code to describe TTF therapy (i.e., E0766). Designation of the single HCPCS code E0766 represents the device, all device accessories, and necessary monthly supplies.[60]

Payment

For outpatient procedures performed in the United States, the technical component is reimbursed under an Ambulatory Payment Classification as part of Medicare's Hospital Outpatient Prospective Payment System, and the professional component is reimbursed according to Medicare's Physician Fee Schedule.

CMS has not established any specific payments for this technology in its published fee schedules. Patients will be responsible for cost-sharing according to their durable medical equipment benefit. The Musella Foundation for Brain Tumor Research and Information has established a copayment assistance program for patients receiving TTF for recurrent GBM. Patients living in the United States and meeting certain income requirements may receive up to $5,000 per year for the treatment.[61] According to a *New York Times* article, Novocure provides Optune to patients without insurance coverage free of charge.[50] According to one clinical expert who provided comments to ECRI Institute on this technology, although the reimbursement for planning array positioning is not determined, physicians who use the NovoTAL software to develop treatment plans may bill for each treatment plan they develop."[19]

Cost-effectiveness and Considerations

ECRI Institute searches did not identify any cost-effectiveness studies on TTF therapy for recurrent GBM.

Evidence Review

We reviewed evidence to address the following four key questions:

Key Question 1: How does the effectiveness of TTF therapy compare with that of other treatment options for patients with recurrent GBM?

Key Question 2: How does the effectiveness of TTF therapy compare with that of palliative therapy alone for treating recurrent GBM?

Key Question 3: How do AEs reported for TTF therapy compare with AEs reported for other treatments for recurrent GBM?

Key Question 4: What AEs are reported in studies of TTF therapy?

For Key Questions 1 and 3, we compared TTF therapy with BSC, which may include debulking surgery with or without local chemotherapy, focal radiation therapy, bevacizumab, bevacizumab plus systemic chemotherapy, and single-agent or combination systemic chemotherapy for patients with recurrent GBM. For Key Question 2, we compared TTF therapy with palliative therapy alone for patients with recurrent GBM. For Key Question 4, we report device-related AEs for patients with recurrent GBM. Our evidence review focuses on the following patient-oriented outcomes:

- Overall survival
- One-year survival
- Time to disease progression
- Progression-free survival at six-months
- QOL
- AEs

Methods

In June 2015, we searched MEDLINE, EMBASE, the Cochrane Library, CINAHL, and PubMed to identify relevant studies. See the *Search Strategy* section below for keywords and subject headings used in this search. We further retrieved relevant information via review of bibliographies/reference lists from peer-reviewed and gray literature. Gray literature consists of reports, studies, articles, and monographs produced by government agencies, private organizations, educational facilities, consulting firms, and corporations.

Study Selection Criteria

ECRI Institute applied the following study-selection criteria to identify appropriate studies that could address the key questions:

- Study must be published in English.
- Study must be reported as a full-length article. We excluded abstracts and meeting presentations because they do not give complete results and sufficient detail about methodology to assess the risk of bias, and final results may differ from preliminary results.
- To avoid double counting of patient outcomes, if more than one article has been published to describe the same study, the article must be the latest published report or have the most complete report of an outcome.
- Comparative studies must assess at least 10 patients in each arm. Smaller studies are at greater risk of patient-selection bias and often are not statistically reliable.
- The study must have assessed TTF therapy using the NovoTTF-100A or Optune Treatment Kit.
- To address Key Question 1, we include randomized controlled trials (RCTs) and comparative studies that compare TTF therapy with other treatments for recurrent GBM.

- To address Key Question 2, we include RCTs and comparative studies that compare TTF therapy plus palliative care with patients receiving palliative care only.
- To address Key Question 3, we include RCTs and comparative studies that compare TTF therapy with other treatments for recurrent GBM.
- To address Key Question 4, we include studies that report on AEs in patients with recurrent GBM that received TTF therapy.

Included Studies

We identified three studies that addressed at least one of our key questions: a multicenter RCT (Stupp et al.[21]), a patient registry (Patient Registry Dataset [PRiDe], Mrugala et al.[62]), and a single-arm pilot trial (Kirson et al.[16]). See Table 2 below for study details.

Table 2. Included Studies

Author/Year	Study Design/Objective Patient Population (n Per Group)	Key Outcomes and Follow-up Times	Addresses Key Question #
Stupp et al.* 2012[21]	Multicenter RCT to evaluate superiority of TTF therapy over BSC. The study's hypothesis was that TTF therapy "would increase the overall survival of recurrent glioblastoma patients compared to patients treated with BSC." Enrolled patients were over 18 years of age with radiologically confirmed recurrent glioblastoma. Patients with similar baseline characteristics were randomly assigned at a 1:1 ratio to receive TTF therapy (n = 120) with the Optune Treatment Kit or BSC (active control; n = 117). Patients received BSC "according to local practice and depending on prior treatment exposure." BSC included the following treatments alone or in combination: bevacizumab (31%), irinotecan (31%), nitrosoureas (25%), carboplatin (13%), temozolomide (11%), PCV (9%), etoposide (3%), imatinib (2%), procarbazine (1%), and hydroxyurea (1%).	Overall survival, 1-year survival; time to disease progression; progression-free, 6-month survival; QOL; and AEs Follow-up was for at least 6 months. The trial provided continued medical follow-up for 2 months after disease progression.	1,3,4
Mrugala et al. 2014[62]	Postmarketing registry (Patient Registry [PRiDe]) to determine the safety and efficacy of the Optune Treatment Kit. All patients with recurrent glioblastoma who received TTF therapy in USA (n = 457). Patients in this registry may have received treatments (e.g., chemotherapy, bevacizumab) in addition to TTF therapy.	AEs October 2011 to November 2013.	4
Kirson et al.* 2007[16]	Single-arm pilot study to determine the safety and efficacy of the Optune[a] Treatment Kit. Patients with recurrent glioblastoma over 18 years of age, who received adjuvant temozolomide for primary treatment, with a Karnofsky score ≥70 (i.e., performance status score ranging between 100% [perfect health] and 0 [death]), and who did not have brain surgery in the previous 4 weeks and radiotherapy in the previous 8 weeks (n = 10).	AEs Patients received TTF therapy until disease progression or a maximum of 18 months	4

*Sponsored by manufacturer

[a] Former name was NovoTTF-100A

AEs: Adverse events
BSC: Best standard of care
PCV: Procarbazine, CCNU, and vincristine
PRiDe: Patient Registry Dataset
QOL: Quality of life
RCT: Randomized controlled trial
TTF: Tumor treating fields

Strength-of-evidence Assessment

We graded strength of evidence (SOE) for selected patient outcomes that potentially matter the most to decision makers. Our grading approach is based on the concepts and methods proposed by the GRADE working group. We also incorporated the evidence assessment methods used by the Agency for Healthcare Research and Quality's Evidence-based Practice Centers. Our grading approach addressed risk of bias, consistency, directness, precision, magnitude of effect, dose-response gradient, and plausible confounders that would reduce a demonstrated effect. We assigned an evidence grade of "high," "moderate," "low," or "very low" for each selected outcome. The definitions of these evidence grades and more detailed description of the grading methods are provided in Appendix A.

Findings

Key Question 1: How does the effectiveness of TTF therapy compare with that of other treatment options for patients with recurrent GBM?

We identified one RCT, Stupp et al.,[21] that provides data to address this question. The RCT compares TTF therapy with BSC and reports on overall survival, progression-free six-month survival, one-year survival, time to disease progression, and QOL. We also examined the FDA Summary of Safety and Effectiveness Data (SSED) document,[9] which provides additional data on this RCT. According to the FDA SSED document, 4 patients in the TTF group never received treatment due to withdraw of consent (n = 3) or pretreatment AE (n = 1), and 26 patients in the BSC group never received treatment due to withdraw of consent (n = 15), nonadherence (n = 5), pretreatment AE (n = 3), or other unspecified reasons (n = 3).[9]

Overall Survival

In the intent-to-treat population, after 24 months of follow-up, the median overall survival duration in the TTF therapy group was not statistically different from that of the BSC group (6.3 months versus 6.4 months, p = 0.98).[9] After 39 months of follow-up, Stupp et al. reported 6.6-months median overall survival duration in the TTF therapy group compared with 6.0-months median overall survival duration in the BSC group.[21] However, according to the FDA SSED, "after 24 months, the number of subjects remaining may be too small to reliably estimate the long term survival outcome."

One-year Survival

Based on evidence described in the FDA SSED, the percentage of patients alive at 1-year follow-up in the TTF therapy group "was very similar to that in the BSC chemotherapy group" (25/114 evaluable patients [21.9%] versus 23/104 evaluable patients [22.1%]).[9]

Time to Disease Progression

Tumor progression was assessed using MRI and clinical information based on "neurological status, steroid dosing, AEs, and investigator assessment of progression."[21] Based on evidence described in the FDA SSED adjudicated by an FDA clinical events committee, the median time-to-disease progression in the TTF therapy group was not statistically different from that in the BSC group (9.3 weeks versus 9.6 weeks, p = not significant).[9]

Progression-free Survival at Six Months

Based on evidence described in the FDA SSED adjudicated by an FDA clinical events committee, progression-free survival at 6 months in the TTF therapy group was 21.4% (22/103 evaluable patients) and in the BSC group 15.2% (14/92 evaluable patients).[9] The difference in progression-free survival in the TTF therapy group was not statistically different from that in the BSC group.[9]

Quality of Life

To assess QOL, investigators used QOL questionnaires (i.e., EORTC QLQ-C30 [European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30], EORTC QLQ-BN20) at baseline and every three months until progression. EORTC QLQ-C30 is a validated cancer-specific QOL measure that includes 30 questions regarding symptoms, health, and competency to perform various daily life tasks. The QLQ-C30 comprises five functional scales, three symptom

scales, a global health status/QOL scale, and six single items. The EORTC QLQ-BN20 is a validated brain-cancer-specific module intended for patients undergoing chemotherapy or radiotherapy. It includes 20 items that assess future uncertainty, visual disorder, motor dysfunction, communication deficit, other disease symptoms, and treatment toxicities.[63]

Stupp et al.[21] reported limited QOL findings obtained from patients who remained in the study ≥3 months and for whom data were available (TTF therapy group [36/120 patients; 30%], BSC group [27/117 patients; 23%]).[21] This limited data were presented in bar graphs without specific scores or analysis of statistical significance. The study authors reported the following:[21]

- No meaningful differences between the study groups in the domains of global health and social functioning
- Higher scores for cognitive and emotional functioning in the TTF therapy group
- Slightly higher scores for physical functioning in the BSC group
- Slightly higher scores for role functioning in the TTF therapy group
- Increased pain and fatigue in the BSC group
- Higher symptom scores for treatment-associated toxicities (i.e., gastrointestinal AEs) in the BSC group

The FDA SSED and the sponsor executive summary document *NovoTTF-100A System for the Treatment of Recurrent GBM*, 2011, report QOL findings as percent change from baseline at three-month follow-up.[9,64] The FDA SSED, which did not include specific QOL scores, stated, "QOL ratings based on QLQ C-30 and BN-20 questionnaires were consistently higher in the TTF therapy group for 5 out of 6 general scales and 7 out of 9 symptom scales than in the BSC group."[9]

Key Question 2: How does the effectiveness of TTF therapy compare with that of palliative therapy alone for treating recurrent GBM?

Our searches did not identify any studies that provide data to address this question.

Key Question 3: How do AEs reported for TTF therapy compare with AEs reported for other treatments for recurrent GBM?

Stupp et al.[21] provides data to address this question. We report here AEs described in the RCT that compared the safety and effectiveness of TTF therapy with those of BSC for treating recurrent GBM. We also examined the FDA SSED,[9] which provides additional data on this RCT. The safety analysis included 116 patients who had received at least 1 day of TTF therapy and 91 patients who received at least 1 dose of chemotherapy.[9,21]

In the RCT,[21] the percentage of patients reporting at least 1 AE was not statistically different between the study groups (64/116 [55%] in the TTF group and 54/91 [59%] in the BSC group; p = 0.55, calculated by ECRI Institute).[9] Also, the percentage of patients reporting at least 1 serious AE was not statistically different between groups (18/116 [16%] in the TTF group and 17/91 [19%] in the BSC group; p = 0.55, calculated by ECRI Institute).[9] We further analyzed data from the FDA SSED that details AEs in ≥2% of patients in either study group. AEs reported in the FDA SSED are those occurring during treatment but before disease progression to avoid confounding AEs that may result from the disease condition.[9] In AEs occurring in ≥10% of patients, BSC treatment caused more hematologic disorders, diarrhea, nausea, and infections (AEs typically associated with chemotherapy) than TTF. Patients treated with TTF experienced more skin site reactions than those treated with BSC. Table 3 includes AEs in ≥2% of patients in either study group with a statistically significant difference between groups.

Table 3. Adverse Events in Comparative Trials: Tumor-treating Fields Therapy versus Best Standard of Care

Adverse Event	Tumor-treating fields Therapy [# Events/# Patients Assessed (%)]	Best Standard of Care [# Events/# Patients Assessed (%)]	Between-group p-Value[a]
Thrombocytopenia	3/116 (3%)	11/91 (12%)	p = 0.006
Leukopenia	1/116 (1%)	6/91 (7%)	p = 0.02
Abdominal pain	0/116 (0%)	6/91 (7%)	p = 0.005
Diarrhea	0/116 (0%)	11/91 (12%)	p = 0.0001
Nausea	3/116 (3%)	15/91 (16%)	p = 0.0004
Infections	5/116 (4%)	11/91 (12%)	p = 0.037
Fall	5/116 (4%)	0/91 (0%)	p = 0.045
Skin site reaction	18/116 (16%)	0/91(0%)	p = 0.00008
Anorexia	0/116 (0%)	4/91 (4%)	p = 0.023
Muscle weakness	0/116 (0%)	3/91(3%)	p = 0.049
Alopecia	0/116 (0%)	3/91 (3%)	p = 0.049
Rash	5/116 (4%)	0/91(0%)	p = 0.045

[a] Calculated by ECRI Institute

The proportion of patients who experienced treatment-emergent serious AEs was not statistically different between groups (15/116 [12.9%] in the TTF group versus 10/91 [10.9%] in the BSC group; relative risk = 1.18 95% confidence interval [CI]: 0.55 to 2.50, p = 0.67, calculated by ECRI Institute).[9] Patients treated with TTF experienced fewer hematologic treatment-emergent serious AEs 0/116 (0%) than patients treated with BSC 4/91 (4%), and the difference was statistically significant (p = 0.02, calculated by ECRI Institute). Patients treated with TTF and patients treated with BSC experienced similar rates of treatment-emergent serious AEs (gastrointestinal disorders, metabolism and nutrition disorders, nervous system disorders, vascular disorders) occurring in ≥2% of patients, and the differences between groups were not statistically significant. Table 4 includes treatment-emergent AEs occurring in ≥2% of patients in either study group listed as Grade 3 (severe or medically significant) or Grade 4 (life-threatening) by AE system or term.[21,64]

Table 4. Treatment-emergent Serious Adverse Events: Tumor-treating Fields Therapy versus Best Standard of Care

Adverse Event System(Adverse Event Term)	Tumor-treating Fields Therapy[a] Grades 3 and 4 n = 116	Best Standard of Care[a] Grades 3 and 4 n = 91	Between-group p-Value[b]
Hematologic	0/116 (0%)	4/91 (4%)	p = 0.02
Hematologic (thrombocytopenia)	1/116 (1%)	2/91 (2%)	p = 0.43
Gastrointestinal	1/116 (1%)	3/91 (3%)	p = 0.38
Gastrointestinal (diarrhea)	0/116 (0%)	2/91 (2%)	p = 0.11
Metabolism and nutrition disorders	1/116 (1%)	3/91 (3%)	p = 0.21
Nervous system disorders	8/116 (7%)	6/91 (7%)	p = 0.93
Nervous system disorders (convulsion)	2/116 (2%)	2/91 (2%)	p = 0.81
Vascular disorders	1/116 (1%)	3/91 (3%)	p = 0.21
Vascular disorders (pulmonary embolism)	1/116 (1%)	2/91 (2%)	p = 0.43

[a] Number of patients calculated by ECRI Institute

[b] Calculated by ECRI Institute

The between-group difference in the number of study patients discontinuing treatment due to AEs was not statistically significant (13/116 [11%] versus 7/91[8%]; p = 0.4, calculated by ECRI Institute).

Key Question 4: What AEs are reported in studies of TTF therapy?

Three studies provided data to address this question. Stupp et al.,[21] Mrugala et al.,[62] and Kirson et al.[16] report AEs associated with TTF therapy. The FDA SSED[9] also reports AEs possibly or definitely related to TTF therapy in the RCT.

Mrugala et al.[62] reported "no new AEs were detected in PRiDe compared to those found in EF11 [Stupp et al.]."[62] Mrugala et al.[62] report heat sensation and electric sensation in the context of AEs; however, these are not associated with patient injuries and were not reported in Stupp et al., the SSED, or Kirson et al. Reported AEs for patients treated with TTF therapy are presented in Table 5.

Table 5. Adverse Events Reported for Patients Using Optune TTF Therapy

Adverse Event	Author/Year	Tumor-treating Fields Therapy [# Events/# Patients Assessed (%)]
Skin reaction	SSED[9] 2012	18/116 (16%)
	Mrugala et al.[62] 2014	111/457 (24.3%) [a]
Contact dermatitis	Kirson et al.[16] 2007	9/10 (90%) [b]
Fall	SSED[9] 2012	1/116 (1%)
	Mrugala et al. 2014	18/457 (3.9%) [a]
Heat sensation	Mrugala et al. 2014	52/457(11.3 %) [a]
Neurologic disorder	Mrugala et al. 2014	48/457 (10.4 %) [a]
Seizure	Mrugala et al. 2014	41/457 (8.9 %) [a]
Electric sensation	Mrugala et al. 2014	35/457 (7.7 %) [a]
Headache	Mrugala et al. 2014	26/457 (5.7 %) [a]
	SSED[9] 2012	4/116 (3%)
Pain/discomfort	Mrugala et al. 2014	21/457 (4.7 %) [a]
Psychiatric disorder	Mrugala et al. 2014	13/457 (2.9%) [a]
Gastrointestinal disorder	Mrugala et al. 2014	13/457 (2.9 %) [a]
Fatigue	Mrugala et al. 2014	11/457 (2.5 %) [a]
Malaise	SSED[9] 2012	2/116 (2%)

[a] Number of patients calculated by ECRI Institute

[b] Percentage calculated by ECRI Institute

SSED: Summary of Safety and Effectiveness Data

Published results of the RCT reported that "27 patients in the TTF therapy group discontinued treatment early (often within a few days) due to noncompliance or inability to handle the device."[21]

Ongoing Clinical Trials

ECRI Institute searches identified 6 relevant ongoing trials with a planned enrollment of at least 30 patients. See Table 6 for details.

Table 6. Ongoing Clinical Trials for Tumor Treating Fields Therapy

Study Name/Clinical Site NCT Identifier	Planned Enrollment	Study Design and Objective Primary Endpoints	Estimated Completion Date
Recurrent Glioblastoma			
A Prospective Phase II Trial of NovoTTF-100A[a] With Bevacizumab (Avastin) in Patients With Recurrent Glioblastoma Cleveland Clinic Taussig Cancer Institute, Case Comprehensive Cancer Center (Cleveland, OH, USA), Case Medical Center, University Hospitals Seidman Cancer Center NCT01894061	n = 40 patients at least 22 years of age with histologically confirmed GBM or other grade IV malignant glioma recurrent after external-beam fractionated radiotherapy and temozolomide chemotherapy	Single-group assignment study assessing "the efficacy of the combination of bevacizumab and NovoTTF-100A[a] in bevacizumab-naive patients with recurrent glioblastoma." Primary endpoint: Progression-free 6-month survival	10/2016
A Prospective, Non-randomized, Concurrent Control, Open Label, Post-approval Study of NovoTTF-100A[a] in Recurrent GBM Patients 8 U.S. sites NCT01756729	n = 486 patients at least 22 years of age with radiologic or histologic evidence of recurrent GBM	Nonrandomized, concurrent control study assessing whether the efficacy of using the NovoTTF-100A[a] system to treat patients with recurrent GBM in real-life settings is comparable to that of using best standard chemotherapy Primary endpoint: Overall survival at 5-year follow-up	1/2018
A Phase II Study of the NovoTTF-100A[a] System, Enhanced by Genomic Analysis to Identify the Genetic Signature of Response in the Treatment of Recurrent Glioblastoma Multiforme Washington University School of Medicine (St. Louis, MO, USA) NCT01954576	n = 30 patients at least 22 years of age with radiologic and histologic evidence of recurrent GBM and life expectancy of at least 3 months	Single-group assignment study assessing "how well Novocure's tumor treating electric fields therapy works in treating patients with recurrent glioblastoma multiforme." Primary endpoints: Complete response + partial response + stable disease (bevacizumab-naive) at 6 months, complete response + partial response + stable disease (bevacizumab-refractory) at 4 months	5/2018
Other Indications			
A Phase II Randomized Study of TTField Therapy Versus Supportive Care in Non-small Cell Lung Cancer Patients With 1-5 Brain Metastases Following Optimal Standard Local Treatment 5 international sites NCT01755624	n = 60 patients at least 18 years of age with non-small cell lung cancer with a new diagnosis of brain metastases and a life expectancy ≥3 months	Randomized controlled trial testing the efficacy, safety, and neurocognitive outcomes of the NovoTTF-100A[a] to treat patients with non-small cell lung cancer with controlled systemic disease following optimal standard local treatment for 1 to 5 brain metastases. Primary endpoint: Time to local and distant progression in the brain up to 2 years	7/2017

Study Name/Clinical Site NCT Identifier	Planned Enrollment	Study Design and Objective Primary Endpoints	Estimated Completion Date
LCI-NEU-NOV-001: A Phase II Study of NovoTTF-100A[a] System in Combination With Bevacizumab (BEV) and Temozolomide (TMZ) in Patients With Newly Diagnosed Unresectable Glioblastoma (GBM) Levine Cancer Institute (Charlotte, NC, USA) NCT02343549	n = 46 patients at least 22 years of age with pathologic evidence of GBM and a life expectancy of at least 3 months	Single-group assignment study assessing the safety and efficacy of best standard of care radiation, temozolomide and bevacizumab, followed by treatment with the NovoTTF-100A[a] system and maintenance temozolomide and bevacizumab. Primary endpoint: survival at 12 months	6/2017

[a] Renamed Optune Treatment Kit
BCNU: 1,3-bis(2-chloroethyl)1-nitrosourea
GBM: Glioblastoma

Discussion

The choice of BSC used in Stupp et al.[21] to treat patients with recurrent GBM may not reflect optimal treatment. According to one clinical expert who provided comments to ECRI Institute about this technology, after FDA approved bevacizumab for treating recurrent GBM, it has typically been used alone or in combination with lomustine for treating a majority of patients with recurrent GBM in the United States.[19,65,66] However, in Stupp et al. only 31% of patients in the BSC treatment arm received bevacizumab. Selection of BSC in the clinical trial was performed according to local practice and informed by patient's previous treatments.[21] Low representation of bevacizumab in Stupp et al. is likely because bevacizumab was not approved for treating recurrent GBM in the United States until May 2009,[67] and Stupp et al. enrolled patients between September 2006 to May of 2009.[21] Thus, a shift in standard of care is not adequately reflected in Stupp et al. A *post hoc* analysis performed on the population enrolled in Stupp et al., comparing patients treated with TTF therapy with the patients treated with bevacizumab, shows a small but statistically significant increase in overall survival in patients treated with TTF therapy.[68] In the same *post hoc* analysis, comparison of patients who received TTF therapy with patients who received BSC minus bevacizumab resulted in no difference in overall survival.[68] This *post hoc* study did not examine overall survival between patients treated with bevacizumab compared with patients who received any other BSC therapy.[68] Additional studies comparing TTF therapy with bevacizumab for treating patients with recurrent GBM may facilitate a better understanding of TTF therapy's safety and effectiveness.

A strength of Stupp et al.[21] is that patients with several GBM recurrences were allowed to participate in the RCT. Many patients (85%) enrolled in the study after a second or third recurrence[14,21] Furthermore, approximately 20% of patients enrolled had tumors resistant to bevacizumab treatment, which are typically very resistant to other treatment regimens.[14] *Post hoc* analysis demonstrated that in patients who failed bevacizumab treatment, TTF therapy was significantly more effective than any other BSC selection and increased overall survival by an average of approximately three months.[68] However, overall survival for this subgroup was not different from overall survival of patients treated with TTF therapy or BSC who did not experience bevacizumab treatment failure.[68] Because patients with multiple recurrences typically have tumors that acquired resistance to treatments and are difficult to treat, patients with more than two recurrences are often excluded from most GBM trials.[14]

A limitation that may have affected the findings of Stupp et al. is the lack of consideration for *MGMT* (O^6-methylguanine DNA-methyltransferase) promoter methylation. *MGMT* promoter methylation is considered a prognostic factor for temozolomide response[65] and has been associated with better responses to temozolomide treatment.[5,69] Some patients (11%) in the BSC arm of Stupp et al. were treated with temozolomide. Uneven distribution of patients harboring *MGMT* promoter methylation into treatment groups may have affected patient response to temozolomide compared with TTF therapy.

Evidence Base Conclusions

This report addresses four key questions. Below are the conclusions regarding each key question.

Key Question 1: How does the effectiveness of TTF therapy compare with that of other treatment options for patients with recurrent GBM?

- At 24-month follow-up, overall survival of patients treated with TTF therapy and patients treated with BSC was not different. Strength of evidence: Moderate.
- The evidence does not permit us to determine how QOL compares between patients who received TTF therapy and patients who received BSC because study authors reported insufficient information to draw a conclusion. Strength of evidence: Very low.

Key Question 2: How does the effectiveness of TTF therapy compare with that of palliative therapy alone for treating recurrent GBM?

Our searches did not identify any studies that provided data to address this question.

Key Question 3: How do AEs reported for TTF therapy compare with AEs reported for other treatments for recurrent GBM?

- TTF causes a lower rate of treatment-emergent serious hematologic AEs than BSC. Strength of evidence: Moderate.
- Treatment-emergent serious metabolism and nutrition disorders or vascular disorders of patients treated with TTF therapy and those treated with BSC are not different. Strength of evidence: Low.
- The evidence does not permit us to determine how treatment-emergent serious gastrointestinal AEs or nervous system disorders of patients treated with TTF therapy and patients treated with BSC compare because study authors reported too few events on which to base a conclusion. Strength of evidence: Very low.
- TTF causes a lower rate of thrombocytopenia, leukopenia, diarrhea, and infections than BSC. Strength of evidence: Moderate.
- TTF causes a lower rate of nausea, anorexia, muscle weakness, and alopecia than BSC. Strength of evidence: Low.
- TTF causes a higher rate of skin site reactions, falls, and rashes than BSC. Strength of evidence: Low. (No skin site reaction AEs were severe or life threatening.)

Key Question 4: What AEs are reported in studies of TTF therapy?

The most common reported AE for TTF therapy is skin reaction at the site where the electrodes contact the scalp.[16,21,62] This AE was easily treated with antibiotics, corticosteroids, or electrode relocation.[16,21,62] Other common AEs reported by Mrugala et al.[62] include neurologic disorders, seizures, headaches, pain and discomfort, and falls.[62]

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Classifications

Technology Class

Device, Procedure

Clinical Category

Treatment–Therapeutic

Clinical Specialty

Neurology, Neurosurgery, Oncology, Palliative Care

UMDNS

Stimulators, Electromagnetic, Low-Intensity, Brain/Spinal Cord [22-840]; Stimulators, Electrical, Brain [18-467]

MeSH

Brain Neoplasms; Electric Stimulation Therapy; Glioblastoma; Neoplasm Recurrence, Local

ICD-9-CM

Malignant neoplasm of brain, unspecified [191.9]

FDA SPN

Stimulator, Low Electric Field, Tumor Treatment [NZK]

HCPCS

Electrical stimulation device used for cancer treatment, includes all accessories, any type [E0766]

SNOMED CT

Glioblastoma [63634009]; Malignant neoplasm of brain [428061005]; Neoplasm of brain [126952004]; Therapeutic electrical stimulation [57942008]; Recurrent tumor [25173007]

Publication History

Date	Action	Comments
7/2/2012	Published	Initial publication
4/24/2013	Updated	Guidelines, Diffusion, Reimbursement, Ongoing Trials
1/15/2014	Updated	Regulatory, Future Trends, Reimbursement, Ongoing Trials
9/25/2015	Updated	Comprehensive Update
11/11/2015	Updated	Minor Update: Editor's Note, Regulatory Status, Reported Indications and Contraindications, Competing and Complementary Technologies, Future Trends

Search Strategy

OVID syntax (EMBASE and MEDLINE were searched together):

1. exp Electrical Stimulation Therapy/ or electrostimulation/ or electrostimulation therapy/ or electromagnetic field/ or Electromagnetic Fields/ or electric field/ or (ttfield$ or tumor treating field$ or electrochemotherapy or electroporation or (electric$ adj field$) or electrode$).mp.
2. Glioblastoma/ or (gbm or glioblastoma$ or glyoblastoma$ or gliadel or (malignan$ adj2 glioma$) or (anaplastic adj2 astrocytoma)).mp.
3. (novocure$ or novottf$ or novo-ttf$).mp.
4. (1 or 3) and 2
5. Remove duplicates from 4
6. 5 not (letter/ or editorial/ or news/ or comment/ or case reports/ or note/ or conference paper/ or (conference or letter or editorial or news or comment or case reports).pt.)

This search may be executed in PubMed using the following strategy:

1. Electrical Stimulation Therapy[mh] OR Electromagnetic Fields[mh] OR (ttfield*[tiab] or tumor treating field*[tiab] OR electrochemotherapy[tiab] OR electroporation[tiab] OR OR “electric field”[tiab] OR “electric fields”[tiab] OR electrode*[tiab])
2. Glioblastoma[mh] OR (gbm[tiab] OR glioblastoma*[tiab] OR glyoblastoma*[tiab] OR gliadel[tiab] OR (malignan*[tiab] AND glioma*[tiab]) OR (anaplastic[tiab] AND astrocytoma[tiab]))
3. (novocure*[tiab] OR novottf*[tiab] OR novo-ttf*[tiab])
4. (1 OR 3) AND 2
5. 4 NOT (letter[pt] OR editorial[pt] OR news[pt] OR comment[pt] OR case reports[pt])

Appendix A. Strength-of-evidence Assessment Methods

We grade strength of evidence (SOE) for selected patient outcomes in this report. Our grading approach is based on the concepts and methods proposed by the GRADE working group. Our approach also incorporates the evidence assessment methods adopted by the Agency for Healthcare Research and Quality's Evidence-based Practice Centers. Detailed descriptions of the GRADE and EPC methods are accessible using the links we provided above. To grade evidence in this report, we consider seven domains that may affect strength of evidence: risk of bias, consistency, directness, precision, magnitude of effect, dose-response gradient, and plausible confounders that would reduce a demonstrated effect. For each selected outcome, we assign a grade of "high," "moderate," "low," or "very low." The definitions of the grades are provided in Table A-2.

Table A-1. Strength-of-evidence Grade Definitions

Grade	Definition
High	We have high confidence in the findings for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions).
Moderate	We have moderate confidence in the findings for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence in the findings for this outcome. The body of evidence has major or numerous deficiencies. We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Very low	We have no confidence in the findings for this outcome. No conclusion is appropriate, either because no evidence is available, or the existing evidence has unacceptable deficiencies.

We assessed each comparative study as having low, medium, or high risk of bias using the items in Table A-2.

Table A-2. Items Used for Risk-of-bias Assessment

Item	Comment
Were patients randomly or pseudorandomly (e.g., using instrumental variable analysis) assigned to the study groups?	Instrumental variable analysis can account for both measured and unmeasured confounders as long as the chosen variables have a strong association with treatment choice but no association with health outcomes. Studies using this method received a "yes" for this item. Studies using propensity scoring or multivariate regression received a "no."
Was there concealment of group allocation?	—
Were data analyzed based on the intention-to-treat-principle?	—
Were the patients blinded to the group assigned?	—
Were those who treated the patient blinded to the group to which the patients were assigned?	—
Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	—
Was the outcome measure of interest objective, and was it objectively measured?	The following were considered objective outcomes: median overall survival, serious hematologic adverse events, thrombocytopenia, leukopenia, diarrhea, infections, serious metabolism and nutrition disorders, and serious vascular disorders. The following were considered subjective outcomes: quality of life, skin site reaction adverse events, abdominal pain, nausea, falls, anorexia, muscle weakness, alopecia, rash, serious gastrointestinal adverse events, and serious nervous system disorders.
Was there a 15% or less difference in the length of follow-up for the 2 groups?	—
Did 85% or more of enrolled patients provide data at the time point of interest?	—
Was there fidelity to the protocol?	—

Appendix B. Results of Risk-of-bias and Strength-of-evidence Assessment

Table B-1. Results of Risk-of-Bias Assessment

Study Author/Year	Outcome(s)	Q1. Were patients randomly assigned to treatment groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were the patients blinded to the group assigned?	Q5. Were those who treated the patient blinded to the group to which the patients were assigned?	Q6. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q7. Was the outcome measure of interest objective, and was it objectively measured?	Q8. Was there a 15% or less difference in the length of follow-up for the 2 groups?	Q9. Did 85% or more of enrolled patients provide data at the time point of interest?	Q10. Was there fidelity to protocol?	Risk-of-bias Category
Stupp et al. 2012[21]	Median overall survival[a]	Yes	NR	Yes	No	No	No	Yes	Yes	Yes	Yes	Low
	Quality of Life	Yes[b]	NR	No	No	NR	NR	No	Yes	No	Yes	Medium
	Serious hematologic AEs	Yes	NR	Yes	No	No	No	Yes	Yes	Yes	Yes	Low
	Serious gastrointestinal AEs	Yes	NR	Yes	No	No	No	No	Yes	Yes	Yes	Medium
	Serious metabolism and nutrition disorders AEs	Yes	NR	Yes	No	No	No	No	Yes	Yes	Yes	Low
	Serious nervous system disorders AEs	Yes	NR	Yes	No	No	No	No	Yes	Yes	Yes	Medium
	Serious vascular disorders AEs	Yes	NR	Yes	No	No	No	Yes	Yes	Yes	Yes	Low
	Thrombocytopenia AEs	Yes	NR	Yes	No	No	No	Yes	Yes	Yes	Yes	Low
	Leukopenia AEs	Yes	NR	Yes	No	No	No	Yes	Yes	Yes	Yes	Low
	Abdominal pain AE	Yes	NR	Yes	No	No	No	No	Yes	Yes	Yes	Medium
	Diarrhea AEs	Yes	NR	Yes	No	No	No	Yes	Yes	Yes	Yes	Low
	Nausea AEs	Yes	NR	Yes	No	No	No	No	Yes	Yes	Yes	Medium
	Infections AEs	Yes	NR	Yes	No	No	No	Yes	Yes	Yes	Yes	Low
	Fall AEs	Yes	NR	Yes	No	No	No	No	Yes	Yes	Yes	Medium
	Anorexia AEs	Yes	NR	Yes	No	No	No	No	Yes	Yes	Yes	Medium

Study Author/Year	Outcome(s)	Q1. Were patients randomly assigned to treatment groups?	Q2. Was there concealment of group allocation?	Q3. Were data analyzed based on the intention-to-treat-principle?	Q4. Were the patients blinded to the group assigned?	Q5. Were those who treated the patient blinded to the group to which the patients were assigned?	Q6. Were those who assessed the patient outcomes blinded to the group to which the patients were assigned?	Q7. Was the outcome measure of interest objective, and was it objectively measured?	Q8. Was there a 15% or less difference in the length of follow-up for the 2 groups?	Q9. Did 85% or more of enrolled patients provide data at the time point of interest?	Q10. Was there fidelity to protocol?	Risk-of-bias Category
	Skin site reaction AEs	Yes	NR	Yes	No	No	No	No	Yes	Yes	Yes	Medium
	Muscle weakness AEs	Yes	NR	Yes	No	No	No	No	Yes	Yes	Yes	Medium
	Alopecia AEs	Yes	NR	Yes	No	No	No	No	Yes	Yes	Yes	Medium
	Rash AEs	Yes	NR	Yes	No	No	No	No	Yes	Yes	Yes	Medium

[a] Reporting for 24 months

[b] Because of high attrition (174/237 [73%]), the initial randomization may be compromised.

AE: Adverse event

NR: Not reported

Table B-2. Results of Strength-of-evidence Assessment

Comparison/ Reference	Outcome	Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
Tumor treating fields vs. best standard chemotherapy Stupp et al. 2012[21]	Median overall survival	Low	Unknown	Direct	Precise	Neither	Moderate
	Quality of Life	Medium	Unknown	Direct	Imprecise	Neither	Very low
	Serious hematologic AEs	Low	Unknown	Direct	Precise	TTF	Moderate
	Serious gastrointestinal AEs	Medium	Unknown	Direct	Imprecise	Neither	Very low
	Serious metabolism and nutrition disorders AEs	Low	Unknown	Direct	Imprecise	Neither	Low
	Serious nervous system disorders AEs	Medium	Unknown	Direct	Imprecise	Neither	Very low
	Serious vascular disorders AEs	Low	Unknown	Direct	Imprecise	Neither	Low
	Thrombocytopenia AE	Low	Unknown	Direct	Precise	TTF	Moderate
	Leukopenia AEs	Low	Unknown	Direct	Precise	TTF	Moderate
	Abdominal pain AEs	Medium	Unknown	Direct	Precise	TTF	Low
	Diarrhea AEs	Low	Unknown	Direct	Precise	TTF	Moderate
	Nausea AEs	Medium	Unknown	Direct	Precise	TTF	Low

Comparison/ Reference	Outcome	Risk of Bias	Consistency	Directness	Precision	Evidence Favors	SOE Grade
	Infections AEs	Low	Unknown	Direct	Precise	TTF	Moderate
	Fall AEs	Medium	Unknown	Direct	Precise	BSC	Low
	Anorexia AEs	Medium	Unknown	Direct	Precise	TTF	Low
	Skin site reaction AEs	Medium	Unknown	Direct	Precise	BSC	Low
	Muscle weakness AEs	Medium	Unknown	Direct	Precise	TTF	Low
	Alopecia AEs	Medium	Unknown	Direct	Precise	TTF	Low
	Rash AEs	Medium	Unknown	Direct	Precise	BSC	Low

AE: Adverse events
BSC: Best standard of care
SOE: Strength of evidence
TTF: Tumor treating field

Appendix C. Impact Ratings Definitions

Reimbursement Status

Definition: The extent to which third-party payer coverage and coding are in effect to enable insured patients' access to the intervention.

(4) Wide coverage: Medicare has a positive national coverage determination and/or ≥8 private payers provide coverage.

(3) Expanding coverage: Medicare has no national coverage determination; some local Medicare carriers provide coverage; 4 to 7 major private payers provide coverage; others deny coverage, have no published policy in place, or decide coverage on a case-by-case basis.

(2) Limited coverage: Medicare has no national coverage determination or provides coverage only in the context of a clinical trial (i.e., coverage with evidence development); 1 to 3 major private payers provide coverage.

(1) No coverage: Medicare has a national coverage determination that denies coverage. Most private third-party payers explicitly state that they do not cover the technology because they consider the technology or intervention to be "investigational" or "experimental" or consider the evidence insufficient.

Diffusion Status

Definition: The extent to which the technology or intervention has been adopted into clinical care at this time. Considerations include the proportion of clinicians or healthcare facilities that report or advertise using the technology or intervention.

(4) Wide: Adopted by ≥50% of healthcare providers and facilities expected to use this technology.

(3) Middle: Adopted by >25% and up to 50% of healthcare providers and facilities expected to use this technology.

(2) Early: Adopted by about >10% and up to 25% of healthcare providers and facilities expected to use this technology.

(1) Innovative: use limited to clinical trials or adopted by <10% of healthcare providers and facilities that would be expected to use this technology after it is clinically and commercially available.

Effect on Staffing and Care Processes

Definition: The extent to which most providers need to change their staffing model and/or care processes if adopting this technology. Staffing impacts include need for additional staff or different model/team. Process impacts include shifts in amount of care delivered, care setting, and changes in patient volume and/or throughput.

(4) Substantial: Significant staffing changes and/or care process changes needed.

(3) Moderate: Some staffing changes and/or care process changes needed.

(2) Low: Limited staffing changes and/ or care process changes needed.

(1) Negligible: Current staffing and/or care processes are probably sufficient.

Infrastructure Needs

Definition: The extent of new or expanded infrastructure that most providers will need if adopting the technology (e.g., new or expanded existing facilities, new capital equipment, supplies).

(4) Substantial: Significant additional infrastructure needed to adopt the technology.

(3) Moderate: Some additional infrastructure needed to adopt the technology.

(2) Small: Limited additional infrastructure needed to adopt the technology.

(1) Negligible: No additional infrastructure needed to adopt the technology.

Technology Cost Impact on Providers

Definition: The costs to implement and use the technology initially and ongoing; considers acquisition and maintenance, additional staff and training, additional infrastructure needed.

(4) Substantial costs associated with acquisition, implementation (estimated >$100,000).

(3) Moderate costs associated with acquisition, implementation (estimated >$50,000 up to <$100,000).

(2) Small costs associated with acquisition, implementation (estimated <$25,000 up to $50,000).

(1) Negligible costs associated with acquisition, implementation, and ongoing use. Resources and supplies required to use the technology are on hand at most healthcare facilities that would use the technology (estimated <$25,000).

Technology Cost Impact on Payers

Definition: The costs to payers (health plans and patients) for use of the new technology (drug, device, procedure). Considerations include cost per patient, size of the patient population expected to use it, and patient copay scenarios.

(4) Substantial per-patient costs (estimated >$50,000) and copays or substantial number of patients expected to use the technology.

(3) Moderate per-patient costs (>$25,000 to $50,000) and copays or moderate number of patients expected to use the technology

(2) Small per-patient costs ($5,000 to <$25,000) and copays or small number of patients expected to use the technology.

(1) Negligible per-patient costs (<$5,000) and copays or negligible number of patients expected to use the technology.

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