ACE BRIEF FOR NEW AND EMERGING HEALTH TECHNOLOGIES

Optune for the Treatment of Newly Diagnosed and Recurrent Glioblastoma

Document Number: HSB-M 03/2023

Date: Feb 2023

ACE
agency for
care effectiveness

Summary of Key Points

- Glioblastoma (GBM) is the most common and aggressive form of brain tumour in adults. Prognosis is poor, with a five-year survival rate of around 5%.
- The conventional treatment modalities for patients with GBM, including surgical resection, radiation, and chemotherapy, are associated with substantial side effects and limited efficacy.
- Optune (Novocure) is a locoregional, portable and non-invasive device that generates alternating electrical fields, known as tumour-treating fields (TTFields), which inhibit tumour growth while sparing healthy cells. It is indicated by the US Food and Drug Administration to treat patients with newly diagnosed (ndGBM) or recurrent GBM (rGBM).
- In the meta-analyses analysed in this brief, the TTFields group included TTFields used alone or together with other adjuvant therapies. The control group included comparators such as best supportive care, single or combination chemotherapy regimens.
- Overall, TTFields therapy demonstrated a good safety profile and no known systemic toxicity. Array-associated mild-to-moderate dermatologic adverse events (AEs) are the predominant reported AE.
- In terms of clinical effectiveness, pooled data showed that TTFields significantly improved survival outcomes with no meaningful difference in health-related quality-of-life compared to the control group.
    - In patients with GBM, TTFields led to a significant improvement in pooled median overall survival (OS) and progression-free survival (PFS) by 3.29 and 2.35 months (both $p<0.00001$), respectively.
    - Greater improvements in pooled median OS were observed in patients with ndGBM than rGBM (7.48 vs. 2.55 months) with the use of TTFields.
    - Treatment compliance with TTFields therapy was reported to be a key prognostic factor of survival outcomes.
- At the healthcare system level, TTFields may potentially reduce healthcare spending from lowered incidence of systemic AEs. The technology may also enable treatment out of the hospital settings.
- However, the results are limited by a paucity of randomised controlled trial (RCT) data and high heterogeneity of studies in the meta-analyses. Additionally, pooled findings from the meta-analysis are limited for rGBM.
- When used by patients with ndGBM, TTFields with maintenance temozolomide (TMZ) was not cost-effective compared to TMZ alone. Incremental cost-effectiveness ratios (ICERs) ranged from S$198,898 to S$786,975 per life-year gained. The cost-effectiveness of TTFields for rGBM remains uncertain.
- The Optune system costs S$27,762 per patient per month, with the cost of TTFields identified as a key driver of the ICER.
- Key implementation considerations include high cost at the national and individual level, clinician training and credentialing, and patient acceptance and compliance.
- Of note, international clinical practice guidelines issued mixed recommendations for the use of TTFields for the management of ndGBM and rGBM.

I. Background

Glioblastoma (GBM), also referred to as grade IV astrocytoma, is the most common and aggressive form of brain tumour in adults.[1] While GBM occurs primarily in the brain, it may also spread to the brain stem, cerebellum and spinal cord.[2,3] It is characterised by a poor prognosis and high tumour heterogeneity, leading to treatment resistance and frequent recurrence.[1] The majority of GBM cases arise without a known precursor, while some cases may originate from a low-grade tumour that transforms into GBM over time.[3] Clinically, the manifestation of GBM vary based on the size and location of the tumour, with symptoms including headache, neurological deficits and seizures.[3]

The global incidence of GBM is less than 10 per 100,000 person and is increasing.[4] The National Neuroscience Institute (NNI) has reported seeing approximately 100 new cases of glioma, including GBM and lower-grade gliomas each year.[5] GBM is a highly lethal cancer with a rapid disease course, presenting a five-year survival rate of around 5% and a median survival of around 10 months.[4] Despite maximal treatment efforts, GBM presents a recurrence rate of 70% within one year of diagnosis.[3]

The current multimodal strategies used to treat GBM, including surgical resection, radiation and chemotherapy, remains limited as GBM remains an incurable disease with poor outcome.[6] Furthermore, the current treatment options present substantial side effects. As such, there is a clinical need for an improved or novel treatment strategy to improve the outcome of patients with GBM.

II. Technology

Optune (Novocure) is a locoregional, portable and non-invasive device that generates low intensity, intermediate frequency (200 kHz) and alternating electrical fields, known as tumour-treating fields (TTFields), through transducer arrays placed on the scalp.[7] TTFields inhibit tumour growth through various mechanisms, including disrupting cell mitosis by altering tumour cell polarity, delaying DNA repair, promoting autophagy, and inhibiting cell metabolism, migration and angiogenesis.[1] This inhibitory effect on tumour growth was reported to only affect rapidly dividing tumour cells while sparing the healthy cells.

As illustrated in Figure 1, Optune is comprised of an electric field generator, transducer arrays, power supply, portable battery and charger, a connectable cable and carrying case.[7] As a portable device, Optune can be operated by a battery pack that allow patients to be mobile while receiving treatment. Alternatively, it may also be plugged into an electrical outlet when the patient is seated or asleep.[8] Of note, the transducer arrays have to be replaced at least twice per week and patients need to re-shave their scalp to maintain optimal contact with the transducer.[7] In addition, optimal placement of the transducer can be guided by the company's NovoTAL System software, which requires the patient's magnetic resonance imaging (MRI) data.

Figure 1: Illustration of the Optune device. Image adapted from https://www.optune.com/hcp/therapy/quick-facts

TTFields represents a novel approach to cancer treatment that produce an anti-mitotic effect targeted at rapidly dividing tumour cells in a non-invasive and portable manner.[9] Increasingly it is known as the fourth novel, physical cancer treatment modality following surgery, chemotherapy and radiotherapy.[1]

III. Regulatory and Subsidy Status

Optune has been approved by the US Food and Drug Administration (FDA) since April 2011, as a monotherapy for adult patients older than 22 years, with recurrent GBM (rGBM) who remain refractory to standard medical therapies. In 2015, the FDA expanded their indication for Optune to include patients with newly diagnosed GBM (ndGBM), following maximal debulking surgery and completion of radiation therapy, together with concomitant standard of care chemotherapy.

The device is publicly reimbursed in the US, Switzerland, Israel and Japan for the treatment of patients with ndGBM.[10-13] For patients with rGBM, Optune is reimbursed by a number of private insurers in the US.[14]

IV. Stage of Development in Singapore

While it is not registered with the Health Sciences Authority (HSA), Optune appears to be locally available in the private care setting as a treatment option for patients with GBM.[15,16] In addition, local clinicians have referred a limited number of patients to overseas centre for TTFields therapy (Personal communication: Senior Consultant from NNI, 15 February 2023).

☐	Yet to emerge	☐	Established
☒	Investigational / Experimental (subject of clinical trials or deviate from standard practice and not routinely used)	☐	Established *but* modification in indication or technique
☐	Nearly established	☐	Established *but* should consider for reassessment (due to perceived no/low value)

V. Treatment Pathway

According to the National Institute of Health and Care Excellence (NICE) guidelines on the management of glioblastoma (NG99),[17] the standard of care for patients with ndGBM consists of maximal safe surgical resection, followed by radiotherapy with concomitant chemotherapy with temozolomide (TMZ). Adjuvant treatment with TMZ is administered following completion of chemoradiotherapy.[17] The decision for chemoradiotherapy is contingent upon the patient's age, tolerance to therapy as indicated by the Karnofsky performance status (KPS) and *MGMT* methylation status which determines sensitivity towards alkylating agents.[17] Best supportive care may also be considered for patients aged 70 or over with a poor performance status (KPS<70).[17] In contrast, approaches for patients with rGBM are not well-defined. In the absence of standard-of-care, treatment options include further surgical resection, reirradiation, systemic therapies or supportive care alone.[17,18]

In addition to standard medical therapies, the introduction of Optune into clinical pathways presents a new modality for the treatment of GBM. TTFields has been included in the treatment algorithm for the management of ndGBM and rGBM by the National Comprehensive Cancer Network (NCCN; see Figure A1 in Appendix A).[19] Despite this, international clinical practice guidelines have mixed recommendations regarding the use of TTFields (see Table 1 below and Table B1 in Appendix B). Of note, NICE recommended that TTFields should not be used as it was not cost-effective and would not be an efficient use of the National Health Service (NHS) resources.[17]

Table 1: Summary of clinical practice guideline recommendations on the use of TTFields for the management of GBM

Organisation (year)	Guideline recommendation for TTFields	
	ndGBM	rGBM
National Institute for Health and Care Excellence (NICE, 2021)[17]	×	×
National Comprehensive Cancer Network (NCCN, 2022)[19]	✓	✓
American Association of Neurosciences Nurses (AANN, 2016)[20]	—	✓
Medical Oncology Spanish Society (SEOM, 2017)[21]	—	×
European Association for Neuro-Oncology (EANO, 2017)[22]	×	×
European Society for Medical Oncology (ESMO, 2014)[23]	—	×
"✓" = recommended; "×" = not recommended; "—" = no recommendation reported.		

Abbreviations: ndGBM, newly diagnosed glioblastoma; rGBM, recurrent glioblastoma; TTFields, tumour-treating fields.
Note: Refer to Table B1 in Appendix B for detailed guideline recommendation and strength of evidence.

If introduced into local clinical pathways, Optune may be used as an add-on treatment option to standard therapy for ndGBM, and as an alternative salvage therapy option for rGBM once other treatment options like surgery, radiation and chemotherapy have been exhausted.

VI. Summary of Evidence

The assessment was conducted based on the Population, Intervention, Comparator and Outcome (PICO) criteria presented in Table 2. Based on literature searches conducted in health technology assessment (HTA) databases, PubMed, Embase and the Cochrane Library, four systematic reviews with meta-analysis (SRMAs)[24-27] were included in the key evidence base. Notably, the four SRMAs[24-27] have considerable overlap in the studies included, most of which were single-arm trials along with the only two randomised controlled trials (RCTs) available to date for ndGBM (EF-14) and rGBM (EF-11). Due to its recency and coverage, the review by Regev et al. (2021)[27] provided the basis for evidence review and was complemented by other SRMAs where relevant. Among the studies included in the SRMAs, TTFields was used alone or with other adjuvant therapies, while the comparators included best supportive care, single or combination chemotherapy regimens, and were referred to as the TTFields and control group in the pooled analysis, respectively.

Seven other studies served as supplementary evidence including: two horizon scanning (HS) reports from the Canadian Agency for Drugs and Technologies in Health (CADTH)[8] and ECRI Institute[28]; one HTA report from NICE (NG99)[17]; a network meta-analysis (NMA)[29]; two comparative studies[30,31] that provided further information on the external validity of TTFields; and one real-world study[32] on health-related quality-of-life (HRQoL). The primary studies included in the HS and HTA reports were pooled in the SRMAs. The study design and characteristics of the included studies are presented in Tables C1 and C2 (Appendix C).

Table 2: Summary of PICO criteria

Population	Patients with newly diagnosed or recurrent glioblastoma
Intervention	Optune, alone or in combination with standard medical therapies
Comparator	Standard medical therapies, including surgical resection, radiation and chemotherapy
Outcome	Safety, clinical- and cost-effectiveness

Safety

Overall, findings from three SRMAs[25-27] and the HTA report by NICE (NG99)[17] found TTFields to be generally safe. Owing to the localised mechanism of action, TTFields demonstrated a good safety profile and no known systemic toxicity, with significantly fewer incidence of severe adverse events (SAEs) compared to the control group.[27] The rate of adverse events (AEs) between both arms, such as cognitive, dermatologic, vascular, metabolic and neurological disorders, were also found to be comparable (Table 3).[17,26,27] Across the studies,[25,27] array-associated mild-to-moderate dermatological AEs including mechanical lesions, skin infection and dermatitis, were the predominant AEs reported, accounting for a prevalence of 38% to 48% among patients with GBM treated with TTFields therapy (Table 3).

In contrast, severe dermatologic AEs were uncommon and were reported in ≤2% of patients, in two out of 12 studies consisting of 11,558 patients who received TTFields.[27]

Table 3: Summary of adverse events

Study	N	Tumour type	Type of AE	Comparison arm(s)	Pooled effect size (95% CI)	p-value
NICE NG99	237	rGBM	Cognitive disorders (grade ≥2)	TTFields *vs.* control	RR=0.89 (0.11 to 5.46)	—
	204		Grade 3 or 4 AEs		RR=1.46 (0.98 to 2.17)	—
Magouliotis et al. (2018)[26]	1,440	ndGBM, rGBM	Skin reactions	TTFields *vs.* control	OR=2.12 (0.97 to 4.64)	0.06
	1,440		Vascular disorders		OR=1.07 (0.68 to 1.67)	0.77
	896		Metabolic/nutritional disorders		OR=0.69 (0.35 to 1.36)	0.29
	1,440		Neurological disorders		OR=0.81 (0.62 to 1.07)	0.15
Regev et al. (2021)[27]	11,558		Mild to moderate dermatologic AEs	TTFields	Prev=0.38 (0.32 to 0.45)*	—
Li et al. (2022)[25]	790	rGBM	Skin toxicity	TTFields	HR=0.48 (0.22 to 0.75)	—

* Based on a random effects model.

Abbreviations: AE, adverse event; CI, confidence interval; HR, hazard ratio; ndGBM, newly diagnosed glioblastoma; OR, odds ratio; prev, prevalence; rGBM, recurrent glioblastoma; RR, risk ratio; TTFields, tumour-treating fields.

In addition, TTFields was found to be safe for concomitant use with ventriculoperitoneal shunt implants, which are used to treat symptoms of hydrocephalus in patients with GBM.[27]

Effectiveness

Patient benefit

Pooled clinical-effectiveness outcomes were reported in all four SRMAs.[24-27] In patients with ndGBM or rGBM, TTFields generally prolonged survival, with no significant changes in HRQoL compared to standard care.

Survival outcome

Overall, the pooled data demonstrated that TTFields led to a statistically significant survival benefit in patients with ndGBM and rGBM. Pooled Kaplan-Meier (KM) curves by Regev et al. (2021)[27] showed that TTFields improved median overall survival (OS) and progression-free survival (PFS) in patients with ndGBM and rGBM when compared to historical controls (ndGBM: radiotherapy with TMZ; rGBM: best standard care; see Figure D1 in Appendix D). Similarly in patients with GBM, pooled data by Magouliotis et al. (2018)[26] demonstrated that compared to the control group, TTFields significantly improved median OS and PFS by 3.29 and 2.35 months (both p<0.00001), respectively (Table 4). In particular, greater improvement in median OS was observed in patients with ndGBM than those with rGBM (7.48 *vs.* 2.55 months; Table D1 in Appendix D), indicating better efficacy of TTFields in patients with ndGBM.[26] Moreover, in patients with GBM, TTFields improved the odds of survival at one and two years postoperatively by 1.81 and 2.33 folds compared to chemotherapy (both p<0.00001), while reducing the risk of death by 25% compared to the control group in the recurrence setting (hazard ratio [HR], 0.75; 95% CI, 0.63 to 0.89; p=0.001; Table 4).[25,26]

Of note, caution is warranted when interpreting the pooled results for rGBM. Published findings from the only RCT in this patient group (EF-11) reported a non-significant difference in median OS between TTFields and the control arm (6.6 *vs.* 6 months; p=0.27), while improved median OS was demonstrated in subsequent non-RCT studies.[27]

Table 4: Pooled clinical efficacy of TTFields *vs.* control

Study	N	Tumour type	Clinical outcome	Pooled effect size (95% CI)	p-value
Magouliotis et al. (2018)[26]	1,769	ndGBM, rGBM	Median OS	WMD=3.29 (2.37 to 4.21)	<0.00001
	346		Median PFS	WMD=2.35 (1.76 to 2.93)	<0.00001
	1,506		1-year OS	OR=1.81 (1.41 to 2.32)	<0.00001
			2-year OS	OR=2.33 (1.73 to 3.14)	<0.00001
Li et al. (2022)[25]	1,473	rGBM	Median OS	HR=0.75 (0.63 to 0.89)	0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; ndGBM, newly diagnosed glioblastoma; OR, odds ratio; OS, overall survival; PFS, progression-free survival; rGBM, recurrent glioblastoma; WMD, weighted mean difference.

In addition, findings from a NMA[29] demonstrated that the concurrent use of TTFields with TMZ was the most effective treatment strategy in improving OS in elderly patients with ndGBM compared to ten other therapeutic options (see Table D2 and Figure D2 in Appendix D).

These findings may have applicability to the local population, where GBM was found to occur predominantly in people above the age of 60.[33] Subgroup analyses of a cohort aged ≥65 years in the pivotal EF-14 trial, along with a retrospective study on Chinese patients, demonstrated improved survival benefit for patients with ndGBM with TTFields plus maintenance TMZ, compared to TMZ alone (see Table D3 and Figure D3 in Appendix D).[30,31]

It is also worthwhile to note that survival outcome was found to be associated with treatment compliance. In patients with ndGBM or rGBM, multiples studies have shown a stepwise increase in median OS as treatment compliance rate increased (Table D4 in Appendix D).[27] Pooled data reported in two SRMAs[25,27] consistently showed that a high daily TTFields compliance of ≥75% prolonged survival of patients with GBM compared to those with a daily compliance of less than 75% (HR, 0.57; 95% CI, 0.46 to 0.70; p<0.00001; see Figures D4 and D5 in Appendix D).

Health-related quality-of-life

In patients with rGBM, the pivotal EF-11 trial showed no meaningful between group differences in the global health and social functioning domains of the EORTC-QLQ-C30 questionnaire.[27] The scores of the cognitive, emotional and role functioning domains were higher for the TTFields group than the control group, while physical functioning was slightly worse.[27] Similarly, in patients with ndGBM, the pivotal EF-14 trial demonstrated no significant differences in HRQoL metrics between the TTFields plus maintenance TMZ group and the TMZ monotherapy group, except for a higher incidence of skin itching in the TTFields group.[27] Aside from the clinical trial setting, a large-scale, real-world study of HRQoL in patients with GBM (n=1,106) found that longer duration of TTFields use was strongly associated with improved HRQoL, particularly in progressed patients.[32]

However, given the need for patients to be alopecic and continuously wear the device, the impact of TTFields on quality-of-life (QoL) aside from health-related aspects remains to be investigated.[34]

Healthcare system benefits

As noted by CADTH, the use of TTFields in patients with rGBM may reduce healthcare costs associated with systemic SAEs caused by chemotherapy and radiation therapy.[8] Unpublished manufacturer's information has reported that TTFields treatment reduced hospitalisation and length of stay compared to chemotherapy.[8]

The ECRI Institute also reported that patients with rGBM may receive TTFields therapy out of the hospital setting, potentially leading to a slight reduction in patient flow at cancer treatment centres.[28] This is in contrast to conventional medical therapies such as bevacizumab, which requires intravenous administration.[28]

Cost-effectiveness

Findings from three cost-effectiveness analyses (CEAs) showed that, for patients with ndGBM, TTFields in combination with maintenance TMZ was not a cost-effective treatment option compared to TMZ alone (Table 5). Based on survival outcomes from the EF-14 trial, two CEAs from the French national health insurance perspective reported incremental cost-effectiveness ratios (ICERs) of €510,273 to €549,909 (S$730,252 to S$786,975)[a] per life-year gained (LYG), while a CEA from the US payer perspective reported an ICER of US$150,452 (S$198,898)[a] per LYG (Table 5).[27] In terms of quality-adjusted life-year (QALY), the US CEA reported an ICER of US$197,336 (S$260,878)[a] per QALY gained.[27] Across these CEAs, one-way sensitivity analyses showed that the ICERs were sensitive to the cost of TTFields therapy.[35-37]

Although the US CEA suggested that TTFields may be considered cost-effective within the reported range of willingness-to-pay thresholds in the US, NICE concluded that given the prohibitive cost of TTFields, any ICER would almost certainly be above thresholds conventionally held by NICE for accepting new technologies.[17,37]

Table 5: Cost-effectiveness of TTFields plus TMZ *vs.* TMZ alone for patients with ndGBM

Study	Perspective	Model	Time horizon	Cost input	ICER
Bernard-Arnoux et al. (2016)[35]	French national health insurance	Markov	Lifetime	Direct cost*	€549,909 per LYG
Connock et al. (2019)[36]		PSM	20-year		€510,273 per LYG
Guzauskas et al. (2019)[37]	US healthcare system	PSM	Lifetime	Direct cost†	US$150,452 per LYG
					US$197,336 per QALY gained

* Includes cost of TTFields therapy, TMZ, chemotherapy at recurrence, hospital stays, outpatient procedures and medical transportation.

† Includes cost of TTFields therapy, TMZ, adverse events and supportive care.

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-year gained; PSM, partitioned survival model; QALY, quality-adjusted life-year; TMZ, temozolomide; TTFields, tumour-treating fields

[a] Based on the Monetary Authority of Singapore exchange rate as of 17 January 2023: US$1=S$1.3220; €1=S$1.4311. Figures were rounded to the nearest dollar.

On the other hand, the cost-effectiveness of TTFields remains uncertain for patients with rGBM.[27] Notably, on the basis of indirect economic evidence in patients with ndGBM, NICE indicated that there was insufficient clinical effectiveness to make TTFields cost-effective for patients with rGBM.[17]

Ongoing trials

Seventeen ongoing trials involving the use of TTFields in patients with GBM were identified from the ScanMedicine database (NIHR Innovation Observatory; see Table E1 in Appendix E). These trials mainly aim to provide further evidence on the optimal line of TTFields therapy for patients with ndGBM and its clinical effectiveness as a concurrent treatment modality in patients with rGBM.[34] Several key trials are summarised in Table 6, including the pivotal EF-32 trial investigating the use of TTFields with concomitant chemoradiotherapy for patients with ndGBM and the EF-33 trial evaluating a new high-intensity transducer array for patients with rGBM.

Table 6: Key ongoing trials

Study (Trial ID)	N	Tumour type	Brief description	Estimated completion date
TIGER (NCT03258021)	710	ndGBM	A prospective observational study to obtain real life data on the use of TTFields in patients with ndGBM in routine clinical care in Germany.	July 2021
EF-33 (NCT04492163)	25	rGBM	A prospective, open-label, single arm, historical control pilot study to test the effectiveness and safety of TTFields delivered through high intensity arrays in rGBM.	January 2022
TIGER PRO-Active (NCT04717739)	500	ndGBM	A non-interventional study to investigate change over time in cognitive function, sleep quality, and activity in daily life as important determinants of QoL in GBM patients treated with TTFields in routine clinical care using low-threshold, electronic PRO and modern automated tracking data analyses.	February 2025
EF-32 (NCT04471844)	950	ndGBM	A RCT to test the effectiveness and safety of TTFields given concomitantly with RT and TMZ in patients with ndGBM, compared to RT and TMZ alone. In both arms, TTFields maintenance TMZ are continued following RT.	August 2026
OptimalTTF-2 (NCT04223999)	70	rGBM	A RCT to test a new potential treatment, skull remodeling surgery combined with TTFields and best practice medical oncological therapy against TTFields (intervention) and best practice medical oncological therapy alone (control)	March 2024

Abbreviations: GBM, glioblastoma; ndGBM, newly diagnosed glioblastoma; rGBM, recurrent glioblastoma; QoL, quality-of-life; RCT, randomised controlled trial; RT, radiotherapy; TMZ, temozolomide; TTFields, tumour-treating fields.

Summary

Overall, TTFields was found to be generally safe and effective for patients with GBM. It demonstrated a good safety profile and had no known systemic toxicity. Array-associated mild-to-moderate dermatologic AEs were the predominant AEs. In terms of clinical effectiveness, pooled data showed that TTFields led to significant improvement in survival outcomes, but with no meaningful difference in patient's HRQoL, compared to the control group. In patients with GBM, the use of TTFields significantly improved median OS and PFS by 3.29 and 2.35 months, respectively (both $p<0.00001$), compared to the control group. Of note, greater improvements in median OS were observed in patients with ndGBM than rGBM

(7.48 *vs.* 2.55 months). Treatment compliance of TTFields therapy was reported to be a key prognostic factor of survival outcomes. There may be some potential healthcare system benefits with the use of TTFields, including reduced healthcare spending from lowered incidence of systemic AEs, as well as the ability to allow out-of-hospital treatment for patients with rGBM. In terms of cost-effectiveness, TTFields with maintenance TMZ was not cost-effective compared to TMZ alone in patients with ndGBM, with ICERs ranging from S$198,898 to S$786,975 per LYG reported. In contrast, the cost-effectiveness of TTFields for rGBM remains uncertain.

These findings should be interpreted with caution as the pooled data in this brief were largely based on single-arm trials and were limited by a paucity of RCTs. In addition, there were several limitations in the landmark RCTs included in the pooled analyses, including unblinded study design, lack of a sham or placebo device, and high rates of missing longitudinal HRQoL data. High heterogeneity was also present across the primary studies included in the meta-analyses, due to differences in study designs and treatment regimens used.

VII. Estimated Costs

The cost of TTFields therapy with the Optune system was reported to be US$21,000 (S$27,762)[a] per patient per month.[8] This includes the Optune system, a month's supply of transducer arrays and 24-hour technical support.[8]

VIII. Implementation Considerations

Uptake of the Optune system involves a concerted effort between policymakers, healthcare providers, patients and their caregivers. For example, the current high cost of TTFields therapy may serve as a barrier to adoption at the national and individual level.[8,38] It was suggested that TTFields may become more affordable with competing technologies in the market, as well as ongoing studies investigating its optimal place in care pathway that may improve its therapeutic efficacy, rendering it more cost-effective.[38] While no additional hospital infrastructure is required to support its uptake, it should be noted that there may be an increase in MRI needs to plan the transducer layout for each patient and during subsequent follow-ups every two to three months.[8]

In addition, healthcare providers would require formal training and credentialing to customise the layout of the transducer array for patients. This entails a four-hour program provided by the manufacturer that involves training, hands-on demonstration and practice of system assembly and transducer array application.[28] Further training to use the NovoTAL simulation software may also be completed.[28] In the US, 31% of healthcare providers surveyed lacked TTFields-certified physicians, highlighting the importance of adequate training to ensure patient access to TTFields.[39] Aside from credentialing requirements, clinicians may also be sceptical in adopting TTFields due to the lack of a clear mechanism of action, especially in complex and variably localised tissues, along with the paucity of high-quality evidence.[40]

[a] Based on the Monetary Authority of Singapore exchange rate as of 17 January 2023: US$1=S$1.3220; €1=S$1.4311. Figures were rounded to the nearest dollar.

Patient's acceptance and compliance are also key enablers to uptake of the Optune system. The need for patients to shave their scalp along with prolonged wearing of a device with prominent transducer arrays and wires may lead to cancer-related stigma, and be a burden for some patients.[8] Most patients would also require assistance to prepare their scalp for placement of the arrays.[8] Furthermore, it would be necessary to ensure treatment compliance as this impacts the effectiveness of the TTFields therapy. Compliance would require sustained efforts from the patient, caregiver and healthcare providers. Interestingly, anecdotal evidence showed that TTFields encouraged patients to take ownership of their own treatment in contrast to other cancer treatment strategies where patients remained as passive recipients of care.[8]

IX. Concurrent Developments

Two similar technologies to Optune are in ongoing development (Table 7). Both utilise electromagnetic field or radiofrequency energy to inhibit the spread of cancerous cells. There are indications that EMulate Therapeutics is ready to initiate a pivotal trial to submit the Voyager system for FDA approval.[41]

Table 7: Similar technologies in development

Technology (Manufacturer/Institution)	Brief description	Status
Voyager (EMulate Therapeutics, Inc)	A medical device that uses localised, ultra-low radio frequency energy, in the range of 0–22 kHz, for the treatment of malignant solid tumours including GBM.	Investigational device
Electromagnetic fields that hinder cancer division (Ohio State University)	An early investigational concept that uses electromagnetic fields to hinder the spread of cancer cells.	Early device concept phase
Abbreviation: GBM, glioblastoma.		

Optune is also being investigated for use in other cancer types, including meningioma, pancreatic, lung and ovarian cancers.[8] Separately, the device has also been branded as Optune Lua, and approved by FDA for the treatment of malignant pleural mesothelioma.[42]

It is also worth highlighting a microfluidic device, developed by the Singapore-MIT Alliance for Research and Technology with funding from the National Research Foundation, that can rapidly screen the effect of TTFields on cancerous and non-cancerous cells in an in vivo-like microenvironment.[43] This can potentially enable clinicians to optimise treatment protocols and evaluate synergies between TTFields therapy and chemotherapy.[44]

X. Additional Information

Local clinical expert opinion is that although the current cost presents a substantial barrier for widespread local adoption, TTFields therapy should still be made available locally as a therapeutic option for patients with GBM, as it is an effective device for a detrimental disease.

References

1. Du X, Chen C, Xiao Y, et al. Research on application of tumor treating fields in glioblastoma: A bibliometric and visual analysis. Front Oncol. 2022;12:1055366. doi: 10.3389/fonc.2022.1055366.

2. American Association of Neurological Surgeons (AANS). Glioblastoma Multiforme [Internet]. Illinois: AANS; c2023 [cited 2023 January 20]. Available from: https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Glioblastoma-Multiforme.

3. Davis ME. Glioblastoma: Overview of Disease and Treatment. Clin J Oncol Nurs. 2016;20(5 Suppl):S2-8. doi: 10.1188/16.CJON.S1.2-8.

4. Taylor OG, Brzozowski JS, Skelding KA. Glioblastoma Multiforme: An Overview of Emerging Therapeutic Targets. Front Oncol. 2019;9:963. doi: 10.3389/fonc.2019.00963.

5. SingHealth Duke-NUS Academic Medical Centre. Nearly S$10 million awarded to research on new diagnostic and treatment possibilities for deadly brain tumour [Internet]. Singapore: SingHealth; 2021 [cited 2023 January 20]. Available from: https://www.singhealthdukenus.com.sg/news/research/nearly-s10-million-awarded-to-research-on-new-diagnostic-and-treatment-possibilities-for-deadly-brain-tumour.

6. Rong L, Li N, Zhang Z. Emerging therapies for glioblastoma: current state and future directions. J Exp Clin Cancer Res. 2022;41(1):142. doi: 10.1186/s13046-022-02349-7.

7. Novocure. Optune Instructions for Use [Internet]. New Hampshire: Novocure; 2019 [cited 2023 January 20]. Available from: https://www.optune.com/pdfs/Optune_IFU_8.5x11.pdf.

8. Canadian Agency for Drugs and Technologies in Health (CADTH). Alternating Electric Fields ("Tumour- Treating Fields") for the Treatment of Glioblastoma [Internet]. Ontario: CADTH; 2018 [cited 2023 January 22]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513128.

9. Mehta M, Wen P, Nishikawa R, Reardon D, Peters K. Critical review of the addition of tumor treating fields (TTFields) to the existing standard of care for newly diagnosed glioblastoma patients. Crit Rev Oncol Hematol. 2017;111:60-5. doi: 10.1016/j.critrevonc.2017.01.005.

10. Novocure nabs reimbursement for Optune in Japan [Internet]. Drug Delivery Business News; 2017 [cited 2023 January 20]. Available from: https://www.drugdeliverybusiness.com/novocure-nabs-reimbursement-optune-japan.

11. Novocure. Medicare Releases Final Local Coverage Determination Providing Coverage of Optune® for Newly Diagnosed Glioblastoma [Internet]. Jersey: Novocure; 2019 [cited 2023 January 20]. Available from: https://www.novocure.com/medicare-releases-final-local-coverage-determination-providing-coverage-of-optune-for-newly-diagnosed-glioblastoma.

12. Novocure. Novocure Announces National Reimbursement in Switzerland for Optune® in Combination With Temozolomide for the Treatment of Newly Diagnosed Glioblastoma [Internet]. Jersey: Novocure; 2020 [cited 2023 January 20]. Available from: https://www.novocure.com/novocure-announces-national-reimbursement-in-switzerland-

for-optune-in-combination-with-temozolomide-for-the-treatment-of-newly-diagnosed-glioblastoma.

13. Novocure. Novocure Announces National Reimbursement in Israel for Optune® in Combination with Temozolomide for the Treatment of Newly Diagnosed Glioblastoma [Internet]. Jersey: Novocure; 2020 [cited 2023 January 20]. Available from: https://www.novocure.com/novocure-announces-national-reimbursement-in-israel-for-optune-in-combination-with-temozolomide-for-the-treatment-of-newly-diagnosed-glioblastoma.

14. Washington State Health Care Authority (WSHCA). Tumor treating fields (Optune®), - re-review [Internet]. Washington: WSHCA; 2018 [cited 2023 January 22]. Available from: https://www.hca.wa.gov/about-hca/programs-and-initiatives/health-technology-assessment/tumor-treating-fields-optune.

15. Brain Tumour Society (Singapore). Glioma Treatment Guide [Internet]. Singapore: Brain Tumour Society (Singapore); c2023 [cited 2023 January 25]. Available from: https://www.braintumoursociety.org.sg/glioma-treatment-guide-2.

16. Icon Cancer Centre. The latest in treatment for aggressive brain cancer [Internet]. Singapore: Icon Cancer Centre; 2021 [cited 2023 January 25]. Available from: https://iconcancercentre.sg/en/the-latest-in-treatment-for-aggressive-brain-cancer.

17. National Institute for Health and Care Excellence (NICE). Brain tumours (primary) and brain metastases in over 16s (NG99) [Internet]. England: NICE: 2018 [updated 2021 January 29; cited 2023 January 26]. Available from: https://www.nice.org.uk/guidance/ng99.

18. Tan AC, Ashley DM, López GY, et al. Management of glioblastoma: State of the art and future directions. CA Cancer J Clin. 2020;70(4):299-312. doi: 10.3322/caac.21613.

19. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Central Nervous System Cancers. Version 2.2022 [Internet]. Pennsylvania: NCCN; 2022 [cited 2023 February 5]. Available from: https://www.nccn.org/guidelines/category_1.

20. Blissitt PA. Clinical practice guideline series update: care of the adult patient with a brain tumor. J Neurosci Nurs. 2014;46(6):367-8. doi: 10.1097/JNN.0000000000000088.

21. Martínez-Garcia M, Álvarez-Linera J, Carrato C, et al. SEOM clinical guidelines for diagnosis and treatment of glioblastoma (2017). Clin Transl Oncol. 2018;20(1):22-8. doi: 10.1007/s12094-017-1763-6.

22. Weller M, van den Bent M, Tonn JC, et al. European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. Lancet Oncol. 2017;18(6):e315-e329. doi: 10.1016/S1470-2045(17)30194-8.

23. Stupp R, Brada M, van den Bent MJ, Tonn JC, Pentheroudakis G. High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25 Suppl 3:iii93-101. doi: 10.1093/annonc/mdu050.

24. Li S, Dong J, Wang X, Meng X, Jiang C, Cai J. Dexamethasone and compliance affect TTFields efficacy to glioblastoma patients: a systematic review and meta-analysis. Chin Neurosurg J. 2022;8(1):24. doi: 10.1186/s41016-022-00294-0.

25. Li X, Jia Z, Yan Y. Efficacy and safety of tumor-treating fields in recurrent glioblastoma: a systematic review and meta-analysis. Acta Neurochir (Wien). 2022;164(8):1985-93. doi: 10.1007/s00701-022-05192-z.

26. Magouliotis DE, Asprodini EK, Svokos KA, Tasiopoulou VS, Svokos AA, Toms SA. Tumor-treating fields as a fourth treating modality for glioblastoma: a meta-analysis. Acta Neurochir (Wien). 2018;160(6):1167-74. doi: 10.1007/s00701-018-3536-6.

27. Regev O, Merkin V, Blumenthal DT, Melamed I, Kaisman-Elbaz T. Tumor-Treating Fields for the treatment of glioblastoma: a systematic review and meta-analysis. Neurooncol Pract. 2021;8(4):426-40. doi: 10.1093/nop/npab026.

28. ECRI Institute. Tumor Treating Fields Therapy (Optune) for Recurrent Glioblastoma [Internet]. United States: ECRI Institute: 2015 [cited 2023 January 27]. Available from: https://www.ecri.org/Resources/AHCJ/2016_Resources/Tumor_Treating_Fields_Therapy_Optune_for_Recurrent_Glioblastoma.pdf.

29. Zhao B, Wu J, Xia Y, et al. Comparative efficacy and safety of therapeutics for elderly glioblastoma patients: A Bayesian network analysis. Pharmacol Res. 2022;182:106316. doi: 10.1016/j.phrs.2022.106316.

30. Chen C, Xu H, Song K, et al. Tumor Treating Fields Combine with Temozolomide for Newly Diagnosed Glioblastoma: A Retrospective Analysis of Chinese Patients in a Single Center. J Clin Med. 2022;11(19):5855. doi: 10.3390/jcm11195855.

31. Ram Z, Kim CY, Hottinger AF, Idbaih A, Nicholas G, Zhu JJ. Efficacy and Safety of Tumor Treating Fields (TTFields) in Elderly Patients with Newly Diagnosed Glioblastoma: Subgroup Analysis of the Phase 3 EF-14 Clinical Trial. Front Oncol. 2021;11:671972. doi: 10.3389/fonc.2021.671972.

32. Palmer JD, Chavez G, Furnback W, et al. Health-Related Quality of Life for Patients Receiving Tumor Treating Fields for Glioblastoma. Front Oncol. 2021;11:772261. doi: 10.3389/fonc.2021.772261.

33. Cheo ST, Lim GH, Lim KH. Glioblastoma multiforme outcomes of 107 patients treated in two Singapore institutions. Singapore Med J. 2017;58(1):41-5. doi: 10.11622/smedj.2016044.

34. Guo X, Yang X, Wu J, et al. Tumor-Treating Fields in Glioblastomas: Past, Present, and Future. Cancers (Basel). 2022;14(15). doi: 10.3390/cancers14153669.

35. Bernard-Arnoux F, Lamure M, Ducray F, Aulagner G, Honnorat J, Armoiry X. The cost-effectiveness of tumor-treating fields therapy in patients with newly diagnosed glioblastoma. Neuro Oncol. 2016;18(8):1129-36. doi: 10.1093/neuonc/now102.

36. Connock M, Auguste P, Dussart C, Guyotat J, Armoiry X. Cost-effectiveness of tumor-treating fields added to maintenance temozolomide in patients with glioblastoma: an updated evaluation using a partitioned survival model. J Neurooncol. 2019;143(3):605-11. doi: 10.1007/s11060-019-03197-w.

37. Guzauskas GF, Pollom EL, Stieber VW, Wang BCM, Garrison Jr LP. Tumor treating fields and maintenance temozolomide for newly-diagnosed glioblastoma: a cost-effectiveness study. J Med Econ. 2019;22(10):1006-13. doi: 10.1080/13696998.2019.1614933.

38. Rominiyi O, Vanderlinden A, Clenton SJ, Bridgewater C, Al-Tamimi Y, Collis SJ. Tumour treating fields therapy for glioblastoma: current advances and future directions. Br J Cancer. 2021;124(4):697-709. doi: 10.1038/s41416-020-01136-5.

39. McClelland S 3rd, Sosanya O, Mitin T, et al. Application of tumor treating fields for newly diagnosed glioblastoma: understanding of nationwide practice patterns. J Neurooncol. 2018;140(1):155-8. doi: 10.1007/s11060-018-2945-y.

40. Wick W. TTFields: where does all the skepticism come from? Neuro Oncol. 2016;18(3):303-5. doi: 10.1093/neuonc/now012.

41. United States Securities and Exchange Commission (SEC). FORM S-1 [Internet]. Washington: SEC; 2022 [cited 2023 February 6]. Available from: https://www.sec.gov/Archives/edgar/data/1254348/000149315222023239/forms-1.htm.

42. Novocure. Novocure Announces Optune Lua™ as the Brand Name for the NovoTTF-100L™ System [Internet]. Jersey: Novocure; 2020 [cited 2023 February 6]. Available from: https://www.novocure.com/novocure-announces-optune-lua-as-the-brand-name-for-the-novottf-100l-system.

43. Pavesi A, Adriani G, Tay A, et al. Engineering a 3D microfluidic culture platform for tumor-treating field application. Sci Rep. 2016;6(1):26584. doi: 10.1038/srep26584.

44. Singapore-MIT Alliance for Research and Technology (SMART). SMART advances cancer therapy – Tumour Treating Fields – with a novel microfluidic device [Internet]. Singapore: SMART; 2016 [cited 2023 February 6]. Available from: https://smart.mit.edu/news-events/news/smart-advances-cancer-therapy--tumour-treating-fields--with-a-novel-microfluidic-device.

Appendix

Appendix A: Treatment algorithm for the management of GBM

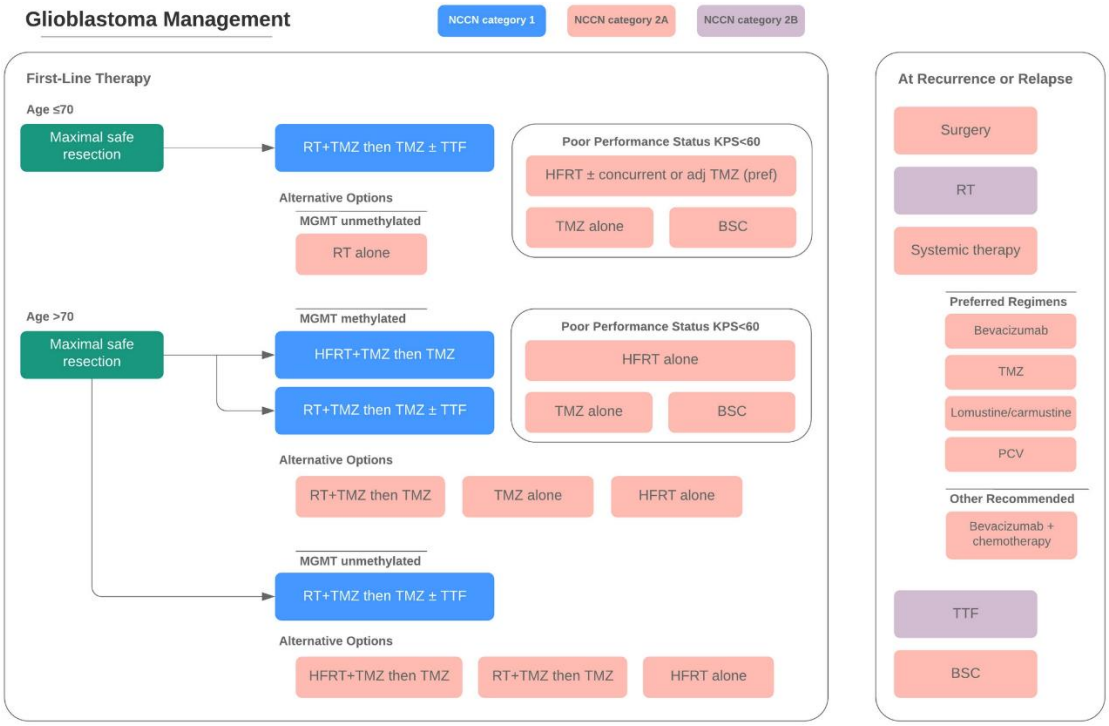

Figure A1: Treatment algorithm for GBM as per the National Comprehensive Cancer Network (NCCN) guidelines. Abbreviations: adj, adjuvant; BSC, best supportive care; HFRT, hyperfractionated radiotherapy; KPS, Karnofsky performance status; MGMT, O6-methylguanine-DNA methyltransferase; NCCN, National Comprehensive Cancer Network; pref, preferred; PCV, procarbazine, lomustine, and vincristine regimen; RT, radiotherapy; TMZ, temozolomide; TTF, tumour-treating fields. Note: (i) Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate (ii) Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate (iii) Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. Figure adapted from Tan et al. (2020).[18]

Appendix B: Clinical practice guidelines for the management of GBM

Table B1: Detailed summary of recommendations from clinical practice guidelines for the management of GBM that included TTFields

Organisation; Guideline title (year); Quality rating*	Recommendation	Rating/strength of evidence
NCCN; *NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers Version 2.2022 (2022)*[19] Quality rating: 5 out of 7	For patients with ndGBM of any age with a good performance status (KPS ≥60) regardless of MGMT promoter status: Recommend standard brain RT + concurrent TMZ and adjuvant TMZ + **alternating electric fields therapy** For patients with rGBM: Consider **alternating electric field therapy**	Category 1 for ndGBM; Category 2B for rGBM†
NICE; *Brain tumours (primary) and brain metastases in over 16s (2018; Updated in 2021)*[17]	For patients with ndGBM: Do not offer **TTF** For patients with rGBM: Do not offer **TTF**	Not reported
AANN; *Care of the Adult Patient with a Brain Tumor (2014; Revised in 2016)*[20] Quality rating: 7 out of 7	Nurses should be aware that use of electrical **tumour treatment fields** may be considered a comparable treatment option to chemotherapy for patients with recurrent malignant glioma, particularly when hematologic, infectious, or GI toxicities limit treatment options (Level 1). When **tumour treatment fields** are used, nurses should assess the skin for topical dermatitis (Level 1). Nurses should educate patients about measures to improve comfort and compliance with the system (Level 3).	Two Level 1 and one Level 3 recommendations§
SEOM; *SEOM clinical guidelines for diagnosis and treatment of glioblastoma (2017)*[21] Quality rating: 3 out of 7	For rGBM, **TTFields** failed to prolong survival compared with second-line chemotherapy.	Level II, Grade D¶
EANO; *EANO guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas (2017)*[22] Quality rating: Overall, 5 out of 7. 3 out of 7 for the guidelines pertaining to TTFields	**TTFields** was not recommended. The following two statements were included in the text: ndGBM: "Questions regarding mode of action, interpretation of data and impact on quality of life have been raised,58 and the place and cost-effectiveness of **TTF** in the standard of care for newly diagnosed glioblastoma remain to be defined." rGBM: "**TTF** were not superior to best physician`s choice in a randomised phase III trial."	Not reported
ESMO; *High-grade glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2014)*[23] Quality rating: 2 out of 7	**TTFields** was not recommended. The following statement was included in the guideline for rGBM: "**TTF** failed to prolong survival compared with second-line chemotherapy"	Level I, Grade A**

Abbreviations: AANN, American Association of Neuroscience Nurses; AGREE II, Appraisal of Guidelines for Research and Evaluation II; EANO, European Association for Neuro-Oncology; ESMO; European Society for Medical Oncology; GI, gastrointestinal; KPS, Karnofsky Performance Score; MGMT, 06-methyguanine-DNA methyltransferase; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Care and Health Excellence; ndGBM, newly diagnosed glioblastoma; rGBM, recurrent glioblastoma; RT, radiotherapy; SEOM, Medical Oncology Spanish Society; TMZ, temozolomide; TTF/TTFields, tumour-treating fields.

* Quality rating was based on the AGREE II tool as graded by the Washington State Health Care Authority Health Technology Assessment Program.

† Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate; Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate

§ Level 1 recommendations are supported by Class 1 evidence. Class I = Randomised controlled trials without significant limitations or meta-analysis. Level 3 recommendations are supported by Class III and IV evidence. Class III = Qualitative study, case study, or series Class IV = Evidence from expert committee reports and expert opinion of the AANN guideline panel; standards of care and clinical protocols that have been identified.

¶ Level 2 Evidence = Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity. Grade D = Moderate evidence against efficacy or for adverse outcome, generally not recommended.

** Level 1 = Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity, Grade A= Strong evidence for efficacy with a substantial clinical benefit, strongly recommended.

Table adapted from the Washington State Health Care Authority[14].

Appendix C: Studies identified and study design

Table C1: List of included studies

Type of study	Key evidence base	Supplementary evidence base
Systematic reviews with meta-analysis	4	—
Health technology assessment report	—	1
Horizon scanning reports	—	2
Network meta-analysis	—	1
Real-world evidence	—	1
Comparative studies (subgroup analysis)	—	2

Note:

1. Inclusion criteria
   a. Studies that fulfil the PICO criteria listed in Table 2.
2. Exclusion criteria
   b. Studies only available in the abstract form.

Table C2: Design and characteristics of included studies

Study	Study design	Number of studies/patients	Tumour type
Key evidence base			
Regev et al. (2021)[27]	SRMA	20 studies	ndGBM, rGBM
Magouliotis et al. (2018)[26]	SRMA	6 studies	ndGBM, rGBM
Li et al. (2022)[25]	SRMA	9 studies	rGBM
Li et al. (2022)[24]	SRMA	5 studies	ndGBM, rGBM
Supplementary evidence base			
NICE NG99 (2018)[17]	HTA report	3 studies*	ndGBM, rGBM
CADTH (2018)[8]	Horizon scanning report	4 studies†	ndGBM, rGBM
ECRI (2015)[28]	Horizon scanning report	3 studies	rGBM
Zhao et al. (2022)[29]	NMA	17 studies	ndGBM, rGBM
Ram et al. (2021)[31]	Subgroup analysis of RCT	134 patients	ndGBM
Palmer et al. (2021)[32]	RWE	1,106 patients	ndGBM, rGBM
Chen et al. (2022)[30]	Retrospective, propensity-matched study	267 patients	ndGBM

* Number of studies relating to TTFields.

† Number of key studies included.

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CEA, cost-effectiveness analysis; HTA, health technology assessment; ndGBM, newly diagnosed glioblastoma; NICE, National Institute of Health and Care Excellence; NMA, network meta-analysis; RCT, randomised controlled trial; rGBM, recurrent glioblastoma; RWE, real-world evidence; SRMA, systematic review with meta-analysis.

Appendix D: Supplementary tables and figures

Table D1: Supplemental pooled survival outcomes of TTFields

Study	N	Tumour type	Intervention arm(s)	Clinical outcome	Pooled effect size (95% CI)	p-value
Regev et al. (2021)[27]	512	ndGBM	TTFields	Median OS	21.7 months (19.6 to 23.8 months)	—
				1-year OS rate	73.5% (69.5% to 77.6%)	—
				2-year OS rate	45.1% (40.6% to 50.0%)	—
				3-year OS rate	29.3% (24.8% to 34.7%)	—
	522			Median PFS	7.2 months (6.1 to 8.2 months)	—
				6-month PFS rate	55.9% (50.9% to 61.4%)	—
				12-month PFS rate	32.4% (27.9% to 37.5%)	—
				18-month PFS rate	21.7% (17.9% to 26.2%)	—
	984	rGBM		Median OS	10.3 months (8.3 to 12.8 months)	—
				1-year OS rate	43.7% (34.4% to 55.4%)	—
				2-year OS rate	21.3% (14.0% to 32.2%)	—
				3-year OS rate	14% (8.7% to 22.6%)	—
	201			Median PFS	5.7 months (2.8 to 10.0 months)	—
				6-month PFS rate	47.8% (29.0% to 78.7%)	—
				12-month PFS rate	29.3% (18.4% to 46.7%)	—
				18-month PFS rate	19.7% (10.3% to 37.6%)	—
Magouliotis et al. (2018)[26]	723	ndGBM	TTFields *vs.* control	Median OS	WMD=7.48 (5.11 to 9.86)	<0.00001
	1,046	rGBM			WMD=2.55 (1.56 to 3.55)	<0.00001
Li et al. (2022)[25]	856	rGBM	TTFields	1-year OS rate	47.3% (28.6% to 66.7%)	—

Abbreviations: CI, confidence interval; HR, hazard ratio; ndGBM, newly diagnosed glioblastoma; OR, odds ratio; OS, overall survival; PFS, progression-free survival; rGBM, recurrent glioblastoma; TTFields, tumour-treating fields; WMD, weighted mean difference.

Table D2: Network meta-analysis of overall survival in elderly patients with ndGBM

Intervention	HR for OS (95% CI)	SUCRA	Ranking
TTFields + temozolomide	0.11 (0.02 to 0.67)	0.918	1st
Temozolomide + hyperfractionated radiotherapy	0.17 (0.03 to 0.95)	0.804	2nd
Bevacizumab + standard radiotherapy	0.25 (0.05 to 1.22)	0.637	3rd
Rindopepimut + temozolomide	0.25 (0.04 to 1.60)	0.620	4th
Temozolomide	0.26 (0.07 to 1.14)	0.572	5th
Hyperfractionated radiotherapy	0.31 (0.08 to 1.20)	0.524	6th
Bevacizumab + hyperfractionated radiotherapy	0.35 (0.06 to 2.16)	0.467	7th
Standard radiotherapy	0.34 (0.10 to 1.09)	0.447	8th
Hydroxychloroquine + standard radiotherapy	0.58 (0.09 to 3.83)	0.266	9th
CpG-oligodeoxynucleotides + supportive care	1.10 (0.30 to 4.10)	0.127	10th

Note: The HRs of each intervention were compared to supportive care.

Abbreviations: CI, confidence interval; HR, hazard ratio; **ndGBM, newly diagnosed glioblastoma;** OS, overall survival; SUCRA, surface under the cumulative ranking curve; TTFields, tumour-treating fields.

Data adapted from Zhao et al. (2022)[29].

Table D3: Clinical efficacy of TTFields in a subgroup of elderly patients in the EF-14 trial

Clinical outcomes	TTFields plus maintenance TMZ (n=89)	TMZ alone (n=45)	HR (95% CI)	p-value
PFS (95% CI), months	6.5 (4.5 to 8.4)	3.9 (2.4 to 4.2)	0.47 (0.30 to 0.74)	0.0236
OS (95% CI), months	17.4 (12.8 to 23.0)	13.7 (9.3 to 16.6)	0.51 (0.33 to 0.77)	0.0204
PFS-6, % (95% CI)	52.5 (41.0 to 62.8)	26.1 (13.1 to 41.1)	—	0.002
1-year OS, % (95% CI)	63.3 (52.7 to 72.7)	52.5 (36.9 to 65.9)	—	0.11
2-year OS, % (95% CI)	39.4 (29.2 to 49.5)	26.9 (14.8 to 40.6)	—	0.072
3-year OS, % (95% CI)	19.1 (10.8 to 29.3)	11.4 (3.9 to 23.4)	—	0.135
4-year OS, % (95% CI)	14.6 (7.0 to 24.8)	0	—	—
5-year OS, % (95% CI)	14.6 (7.0 to 24.8)	0	—	—

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PFS-6, progression-free survival at 6-month; TMZ, temozolomide; TTFields, tumour-treating fields.

Table adapted from Ram et al. (2021).[31]

Table D4: Impact of treatment compliance on median OS

Study; study type	Tumour type	N	Compliance	Median OS (months)
Murgala et al. (2014), PRiDe; Post-marketing surveillance	rGBM	127	≥75%	13.5
		160	<75%	4
Kanner et al. (2014), EF-11; RCT	rGBM	92	≥75%	7.7
		28	<75%	4.5
		10	<60%	5.8
		33	60% to 79%	6
		77	≥80%	7.7
Zhu et al. (2020), EF-19; Post-approval registry	rGBM	82	≥75%	9.83
		102	<75%	6.67
Toms et al. (2019), EF-14; RCT	ndGBM	43	>90%	24.9
		166	80% to 90%	21.5
		91	70% to 80%	21.7
		46	60% to 70%	19.9
		42	50% to 60%	18
		40	30% to 50%	17.9
		22	<30%	18.2

Abbreviations: ndGBM, newly diagnosed glioblastoma; OS, overall survival; RCT, randomised controlled trial; rGBM, recurrent glioblastoma.

Table adapted from Regev et al. (2021)[27].

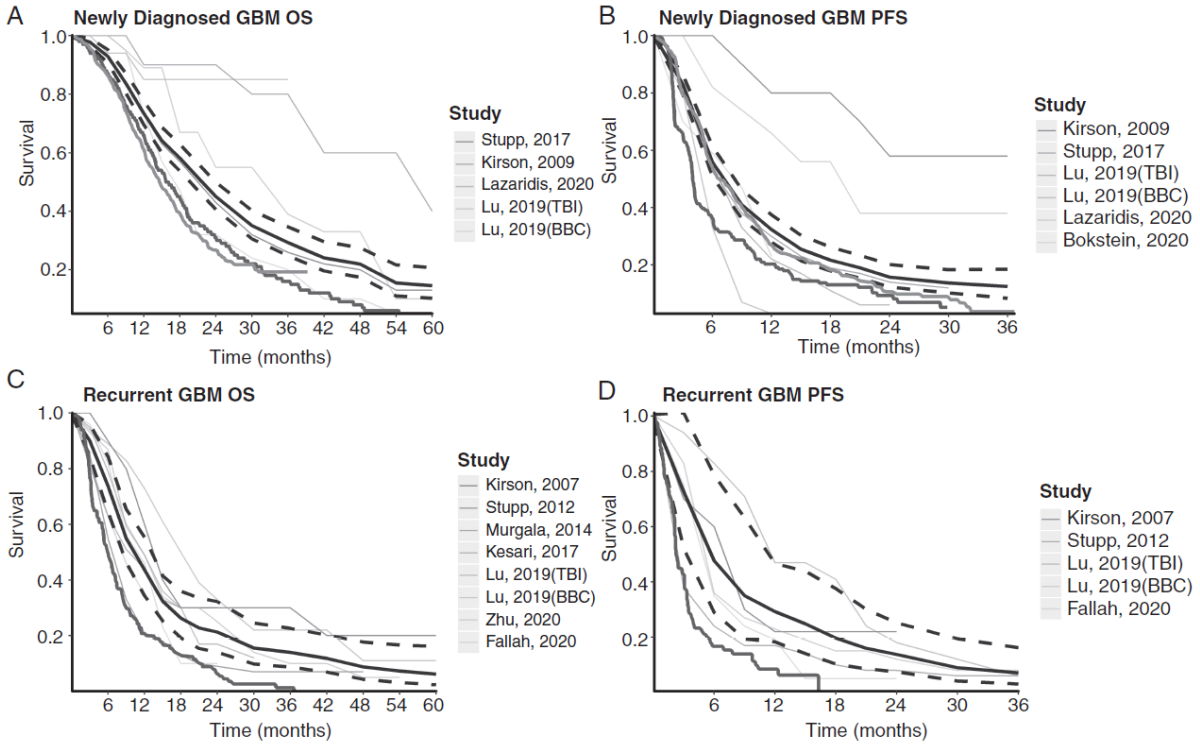

Figure D1: Pooled Kaplan-Meier curves of patients with GBM treated with TTFields. Pooled KM survival curves for OS (**A, C**) and PFS (**B, D**). The thin grey lines represent the survival curve in each individual study. The thick black lines represent the pooled survival curves with the 95% CI represented by the dashed black lines. The thick dark grey line represents the original survival curve of controls according to EF-11 (rGBM: best standard of care) and EF-14 (ndGBM: radiotherapy + temozolomide). The thick bright grey line represents the original survival curve of ndGBM patients treated with radiotherapy + temozolomide in the historic study by Stupp et al. (2005) which established the current standard of care for ndGBM (EORTC protocol). Abbreviations: GBM, glioblastoma; KM, Kaplan-Meier; ndGBM, newly diagnosed glioblastoma; OS, overall survival; PFS, progression-free survival; TTFields, tumour-treating fields. Figure adapted from Regev et al. (2021)[27].

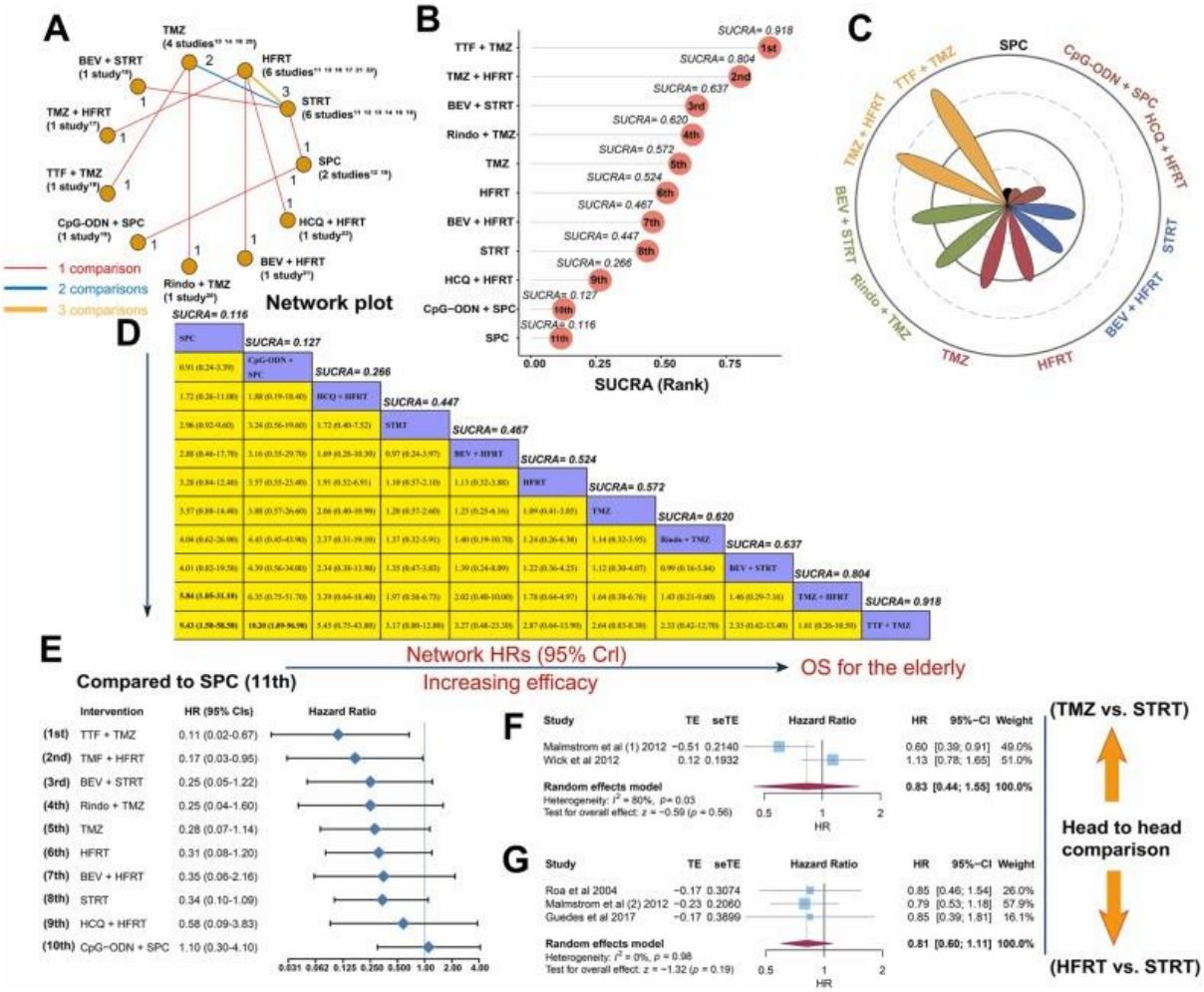

Figure D2: Results of overall survival for elderly patients with newly diagnosed GBM. (A) Network plot for 11 available treatments. (B) SUCRA results among 11 treatments, with better treatment efficacy with a higher SUCRA value. (C) Radar diagram depicting the SUCRA results of the 11 treatments. (D) Comparison between each treatment, with the hazard ratio and 95% confidence interval indicated within each yellow box. (E) Forest plot of the top 10 treatments compared to SPC. (F) Head-to-head comparison between TMZ and STRT. (G) Head-to-head comparison between HFRT and STRT. Abbreviations: BEV, bevacizumab; CpG-ODN, CpG-oligodeoxynucleotides; GBM, glioblastoma; HCQ, hydroxychloroquine; HFRT, hyperfractionated radiotherapy; HR, hazard ratio; OS, overall survival; Rindo, rindopepimut; SPC, supportive care; STRT, standard radiotherapy; SUCRA, surface under the cumulative ranking curve; TMZ, temozolomide; TTF, tumour treating field . Figure adapted from Zhao et al. (2022)[29].

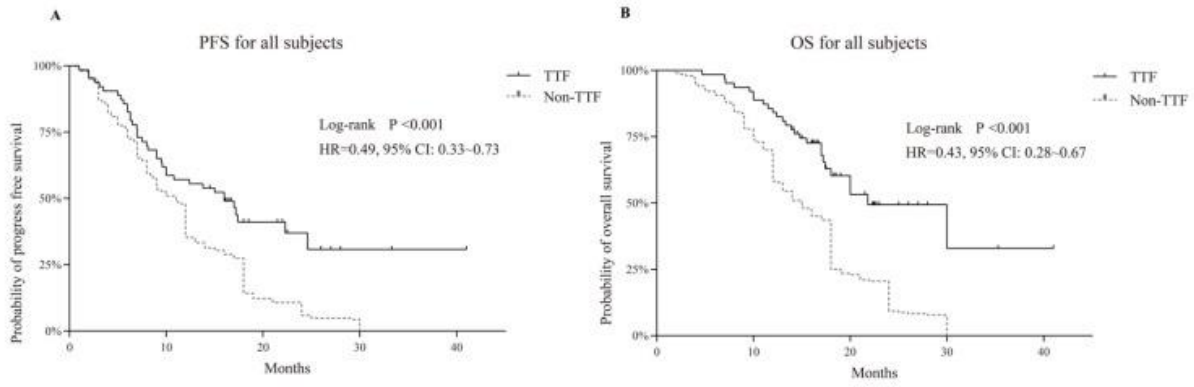

Figure D3: Kaplan-Meier curves comparing TTFields plus maintenance TMZ with TMZ alone in a retrospective cohort of Chinese patients with GBM, indicating potential applicability of TTFields efficacy to the local population. Compared to the TMZ alone group, patients in the TTFields/TMZ group had significantly higher **(A)** median progression-free survival (HR, 0.49; 95% CI, 0.33 to 0.73; p<0.001) and **(B)** median overall survival (HR, 0.43; 95% CI, 0.38 to 0.67; p<0.001). Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TMZ, temozolomide; TTFields, tumour-treating fields. Figure adapted from Chen et al. (2022)[30].

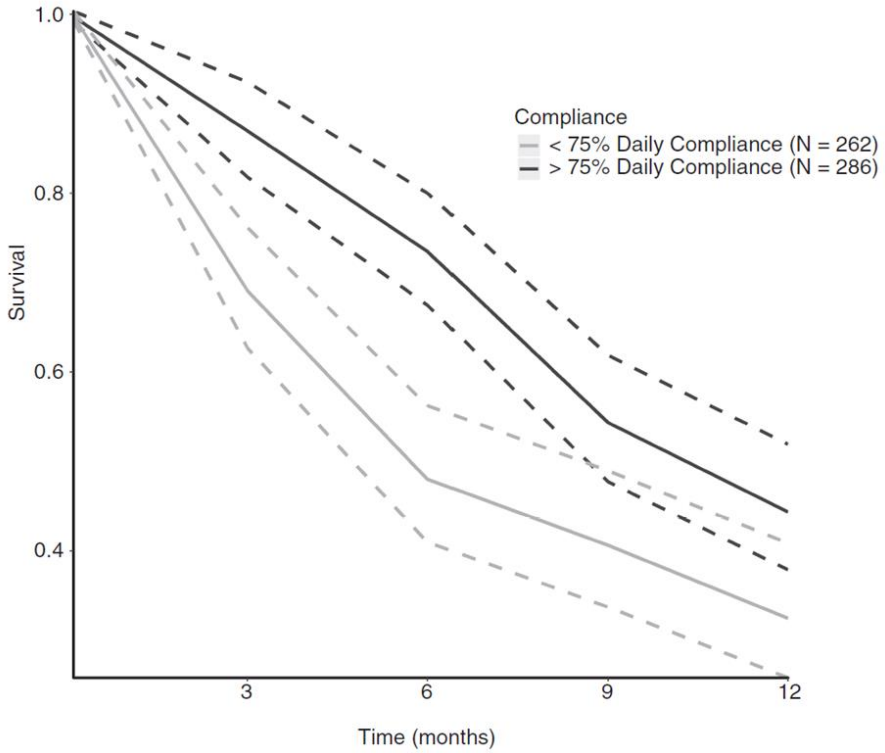

Figure D4: Pooled Kaplan-Meier overall survival curves for treatment compliance with TTFields in patients with recurrent GBM. The dark grey and light grey dashed lines represent the 95% confidence interval for ≥75% and <75% compliance KM curves. The pooled OS curves for daily compliance of ≥75% and <75% were 10.3 months (95% CI, 8.6 to 12.3 months) and 5.7 months (95% CI, 4.8 to 8.1 months), respectively. Abbreviation: GBM, glioblastoma; KM, Kaplan-Meier; OS, overall survival; TTFields, tumour-treating fields. Figure adapted from Regev et al. (2021)[27].

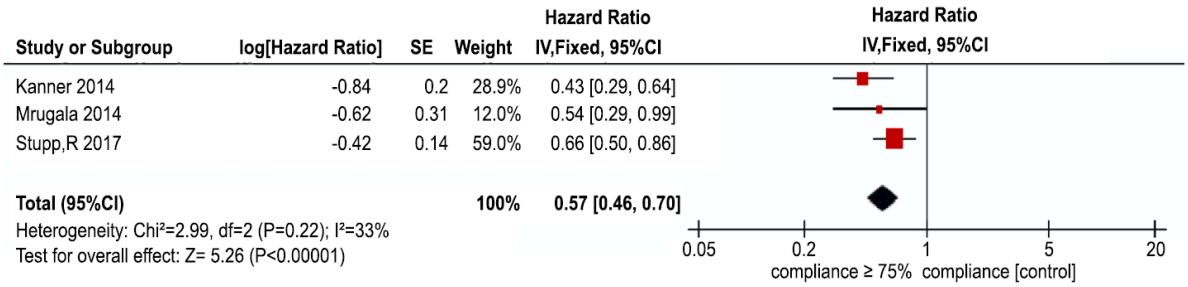

Figure D5: Forest plot of the impact of compliance on the efficacy of TTFields in patients with newly diagnosed or recurrent GBM. Patients with a compliance of TTFields treatment ≥75% have a significantly lower risk of death than patients with a compliance of <75%. Abbreviations: GBM, glioblastoma; TTFields, tumour-treating fields. Figure adapted from Li et al. (2022)[24].

Appendix E: Ongoing clinical trials of TTFields for GBM

Table E1: Ongoing clinical trials

Study (Trial ID)	N	Tumour type	Brief description	Estimated completion date
TIGER (NCT03258021)	710	ndGBM	A prospective observational study to obtain real life data on the use of TTFields in patients with ndGBM in routine clinical care in Germany.	July 2021
TaRRGET (NCT04671459)	40	rGBM	A single-arm study to investigate the use of TTFields with SRS.	December 2023
ECTG001 (NCT04902586)	30	ndGBM, rGBM	A RCT to investigate the efficacy and safety of concurrent chemoradiotherapy with and without TTFields.	July 2022
Niraparib/TTFields in GBM (NCT04221503)	30	rGBM	A non-randomised controlled trial to evaluate the efficacy and safety of niraparib and TTFields in rGBM.	December 2025
EF-33 (NCT04492163)	25	rGBM	A prospective, open-label, single-arm, historical control pilot study to test the effectiveness and safety of TTFields delivered through high intensity arrays in rGBM.	January 2022
TIGER PRO-Active (NCT04717739)	500	ndGBM	A non-interventional study to investigate change over time in cognitive function, sleep quality, and activity in daily life as important determinants of QoL in GBM patients treated with TTFields in routine clinical care using low-threshold, electronic PRO and modern automated tracking data analyses.	February 2025
WBSI Guided Personalized Delivery of TTFields (NCT05086497)	155	ndGBM, rGBM	A RCT to investigate the efficacy of array mapping with regular contrast enhanced MRI compared to whole brain spectroscopy in patients who received TTFields therapy.	June 2026
EF-32 (NCT04471844)	950	ndGBM	A RCT to test the effectiveness and safety of TTFields given concomitantly with RT and TMZ in patients with ndGBM, compared to RT and TMZ alone. In both arms, TTFields maintenance TMZ are continued following RT.	August 2026
Study of Tumor Treating Fields With Hypofractionated Chemoradiotherapy in Newly Diagnosed Glioblastoma (NCT04474353)	12	ndGBM	A single-arm study to determine the safety and efficacy of the combination therapy of TTFields + SRS + TMZ for ndGBM.	May 2024
2-THE-TOP (NCT03405792)	31	ndGBM	A single-arm study to determine whether the triple combination of pembrolizumab when added to TTFields and adjuvant TMZ increases PFS in patients with ndGBM as compared to historical control data.	February 2023
NovoTTF Treatment Signatures in Glioblastoma Patients at Autopsy (NCT03194971)	20	ndGBM, rGBM	An observational study to determine the underlying pathological signatures of TTFields at autopsy.	May 2024
OptimalTTF-2 (NCT04223999)	70	rGBM	A RCT to test a new potential treatment, skull remodeling surgery combined with TTFields and best practice medical oncological therapy against TTFields (intervention) and best practice medical oncological therapy alone (control)	March 2024
Optune for Children With High-Grade Glioma or	80	rGBM	A feasibility trial to investigate (i) the safety and tolerability of concurrent TTFields and RT, and (ii) the feasibility of	November 2027

Ependymoma, and Optune With Radiation Therapy for Children With DIPG (NCT03033992)			concurrent TTFields and RT and the efficacy associated with this approach compared to historical controls in children.	
Unity (NCT03705351)	7	ndGBM	A single-arm study to investigate the safety and efficacy of TTFields with concurrent chemoradiation in patients with ndGBM.	November 2025
Safety and Immunogenicity of Personalized Genomic Vaccine and TTFields to Treat Glioblastoma (NCT03223103)	13	ndGBM	A single-arm study to test the safety, tolerability, and immunogenicity of MTA-based personalised vaccine in patients with ndGBM along with the use of continual TTFields.	May 2023
NeoGlioma (NCT05030298)	40	ndGBM	A study to evaluate the safety of preoperative radiosurgery in the treatment of patients with biopsy-proven, high-grade glioma prior to conventional therapy, as well as the acute clinical toxicity profile.	September 2025
Partial Brain RT, Temozolomide, Chloroquine, and TTF Therapy for the Treatment of Newly Diagnosed Glioblastoma (NCT04397679)	10	ndGBM	A study to evaluate the side effects of partial brain radiation therapy, TMZ, chloroquine, and TTF therapy for the treatment of ndGBM.	March 2024
Abbreviation: DIPG, diffuse intrinsic pontine glioma; GBM, glioblastoma; MTA, mutation-derived tumour antigen; ndGBM, newly diagnosed glioblastoma; PFS, progression-free survival; PRO, patient-reported outcome; QoL, quality-of-life; RCT, randomised controlled trial; rGBM, recurrent glioblastoma; RT, radiotherapy; SRS, stereotactic radiosurgery; TMZ, temozolomide; TTFields, tumour-treating fields; WBSI, whole-brain spectroscopic imaging.				