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Health Technology Assessment (HTA)

HTA Report

Tumour treating fields (TTFields) therapy for patients with glioblastoma

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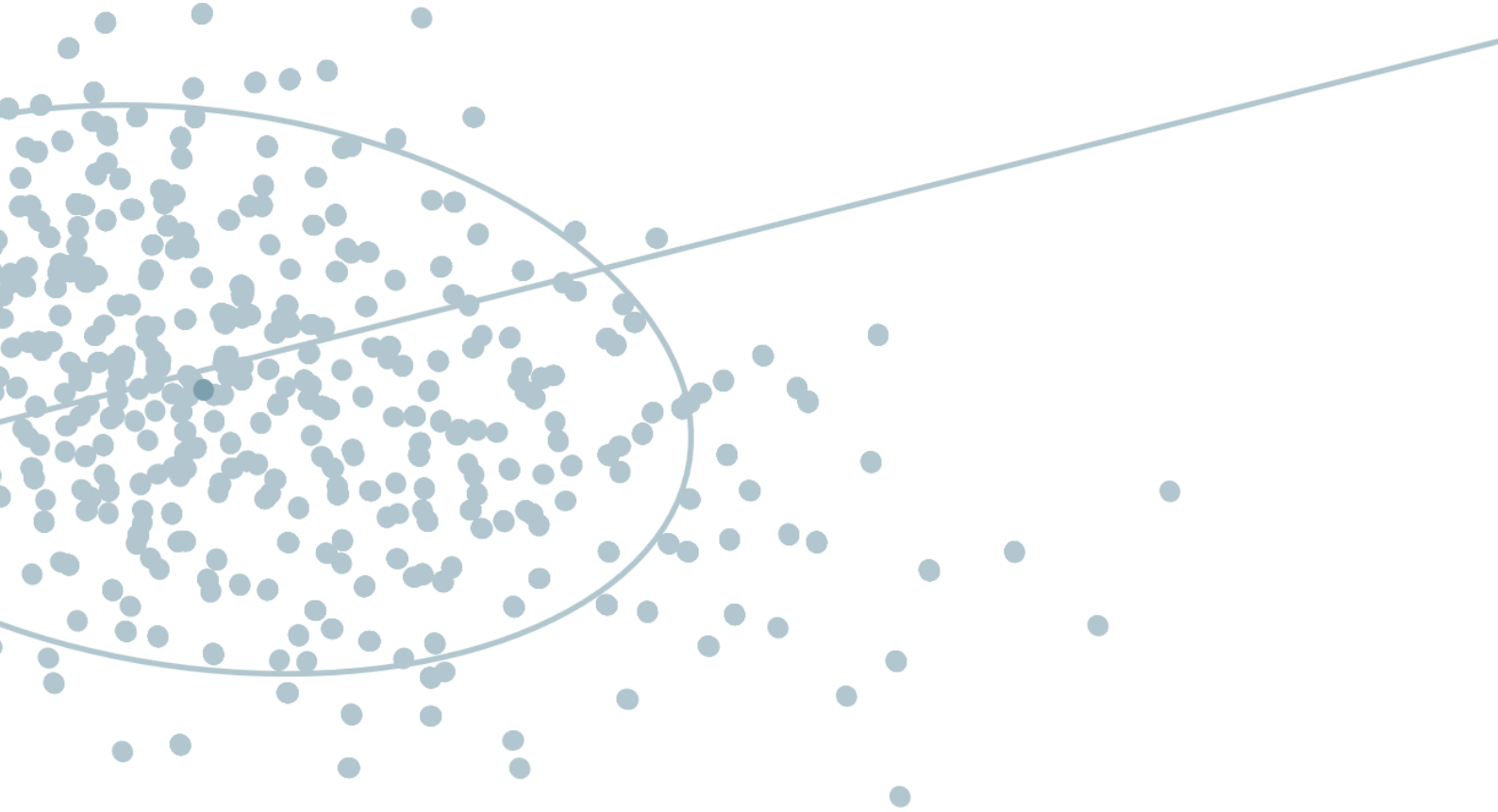

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Authors report no conflict of interest.

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Cover image: Simplified representation of a fictional probabilistic sensitivity analysis on a cost-effectiveness plane with the diagonal willingness-to-pay line.

Executive Summary

BACKGROUND

Glioblastoma (GBM) is an aggressive type of brain cancer characterised by poor prognosis, with an estimated median survival of 13.1 months on a population level. A surgical resection or biopsy of the tumour followed 3-6 weeks later by radiochemotherapy, and maintenance chemotherapy with temozolomide (TMZ) represents the standard of care for patients with newly diagnosed GBM (ndGBM). Treatment at recurrence is varied; the majority of recurrent GBM (rGBM) patients receive systemic treatment, mostly lomustine or less frequently rechallenge with TMZ, or patients can receive bevacizumab, second surgery is an option for subgroups of patients, and re-irradiation can be administered for patients with small tumours. Tumour treating fields (TTFields) are an additional treatment option in combination with TMZ maintenance chemotherapy starting 4–7 weeks after radiochemotherapy. In Switzerland, TTFields are temporarily covered by the mandatory health insurance and limited to ndGBM up to first progression, and a maximum treatment duration of 2 years. In Switzerland, TTFields are not covered for the treatment of rGBM. Whether the medical technology qualifies for statutory health insurance coverage is reconsidered in 2024 based on re-evaluation of the available and new evidence.

OBJECTIVE

This health technology assessment (HTA) report assesses the efficacy, effectiveness, safety, cost-effectiveness and budget impact as well as ethical, legal, social, and organisational benefits and harms of: 1) either TTFields in combination with maintenance chemotherapy or TTFields alone after maintenance chemotherapy has stopped in the treatment of ndGBM adult patients until 1st progression 2) TTFields alone or in combination with second-line systemic therapy (physician's choice chemotherapy) in the treatment of adult GBM patients at 1st progression.

METHODS

For the clinical review, a systematic literature search of the PubMed (MEDLINE), Embase.com, and Cochrane Library databases was conducted adhering to international methodological standards. A stepwise approach was implemented to search for studies on TTFields in patients with GBM, first for randomised controlled studies (RCTs) and an additional search for comparative non-randomised studies. Studies were selected by applying pre-specified exclusion criteria during the selection process. The included studies were critically appraised with the revised Cochrane Risk of Bias tool for randomised trials (RoB 2) and the Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool, and the extracted data were summarised in tables and narrative text. Based on the

heterogeneity of the study populations, the results were stratified in 3 populations: patients with ndGBM, patients with GBM at first recurrence, and patients with GBM at all recurrences.

The systematic literature search for the economic review followed a procedure similar to the one described above. The searches were conducted in PubMed (MEDLINE), Embase.com, Cochrane Library, as well as the economic databases of Cost Effectiveness Analysis (CEA) Registry, Tufts Medical Centre Cost-Effectiveness Analysis Registry, and National Health Service Economic Evaluation Database (NHS EED). The quality of the studies was assessed using the Consolidated health Economic Evaluation Reporting Standards (CHEERs) and the Consensus Health Economic Criteria (CHEC) checklists. Two partitioned survival models (one for ndGBM and one for rGBM) were built to estimate the cost-effectiveness of TTFields plus TMZ compared with TMZ only. Efficacy inputs, costs and utilities were collected from literature. A Swiss healthcare payer perspective and a lifetime time horizon were used. Starting age in the model was 56 years. Cycle length was one month.

Ethical, legal, social, and organisational (ELSO) issues were searched through the systematic literature searches and pragmatic searches, and described narratively.

RESULTS

In the clinical review, 5 articles reporting data on 2 RCTs (one in patients with ndGBM and one in patients with rGBM) and 2 retrospective cohort studies in patients with ndGBM were included.

One multi-country RCT in patients with **ndGBM** treated with TTFields plus TMZ compared with TMZ alone showed a statistically significant longer median overall survival of 20.9 months versus 16.0 months from randomisation (HR for death 0.63 [95% CI 0.53-0.76], p<0.001; 1 RCT; moderate certainty evidence) and a statistically significant longer median progression-free survival of 6.7 months versus 4.0 months from randomisation (HR for progression 0.63 [95% CI 0.52-0.76], p<0.001; 1 RCT; moderate certainty evidence). Furthermore, health-related quality of life (HRQoL) was comparable, only itchy skin was statistically significant worse compared with TMZ alone (1 RCT; low certainty evidence), and there was no statistically significant difference in grade 3-4 severe adverse events (RR 1.09 [95% CI 0.91-1.30], p=0.58; 1 RCT; low certainty evidence). Effectiveness data of TTFields plus TMZ compared with TMZ alone in patients with ndGBM showed discrepant results in two single-centre retrospective cohort studies: no statistically significant difference in overall survival was found in the USA (HR for death 0.93 [95% CI 0.58-1.47], p=0.741; very low certainty evidence) and a statistically significant longer overall and progression-free survival was found in China (HR for death 0.19 [95% CI 0.09-0.41], p<0.001; HR for progression 0.35 [95% CI 0.14-0.91], p=0.031; low certainty evidence).

A post-hoc analysis of the multi-country RCT in patients with **GBM at first recurrence** treated with TTFields plus chemotherapy compared with chemotherapy alone showed a statistically significant longer overall survival, with a median of 11.8 months versus 9.2 months from progression (HR for death 0.70 [95% CI 0.48-1.00], p=0.049; 1 RCT - post-hoc analysis; low certainty evidence), and there was borderline no statistically significant difference in grade 3-4 severe adverse events (RR 1.48 [95% CI 0.997-2.19], p not reported; 1 RCT - post-hoc analysis; very low certainty evidence).

A second multi-country RCT in patients with **GBM at all recurrences** (i.e. 12% at 1st recurrence, 47% at 2nd recurrence, and 41% at ≥3rd recurrence) treated with TTFields compared with chemo-therapyreported no statistically significant difference in overall survival with a median overall survival of 6.6 months versus 6.0 months from randomisation (HR for death 0.86 [95% CI 0.66-1.12], p=0.27; 1 RCT; low certainty evidence), but overall survival became statistically significant longer in a post-hoc analysis of this RCT when limiting the study population to patients receiving at least one course of TTFields therapy with a median overall survival of 7.8 versus 6.0 months from randomisation (HR for death 0.69 [95% CI 0.52-0.92], p=0.0093; 1 RCT - post-hoc analysis; low certainty evidence). The RCT also did not show a statistically significant difference in progression-free survival, with a median of 2.2 versus 2.1 months from randomisation (HR for progression 0.81 [95% CI 0.60-1.09], p=0.16; 1 RCT; low certainty evidence); no post-hoc analysis was conducted for the outcome pro-gression-free survival. The HRQoL domains did not seem to differ or seemed in favour of TTFields, except for physical functioning (1 RCT; very low certainty evidence) and statistically significant less grade 3-4 severe adverse events were reported for TTFields compared with chemotherapy (RR 0.37 [95% CI 0.16-0.86], p=0.022; 1 RCT; moderate certainty evidence).

In the economic review 3 cost-effectiveness studies on TTFields for patients with ndGBM were in-cluded: 2 from a French healthcare payer perspective using different model structures (a partitioned survival model and a Markov model) and one from a US healthcare payer perspective. While the first 2 studies concluded that TTFields were not cost-effective, the latter concluded the opposite, under local cost-effectiveness thresholds. The results of the cost-effectiveness model developed for Switzerland showed that, for the ndGBM population, treatment with TTFields plus TMZ leads to higher costs, but also additional benefit compared with treatment only with TMZ, with an ICER of CHF 555,465 per QALY gained. Scenario analyses and sensitivity analyses showed the robustness of the results. An ICER of CHF 6,552,337 per QALY gained was estimated for the rGBM population as the additional benefit was smaller and the estimated costs higher. Finally, according to the budget impact analysis, reimbursement of TTFields in Switzerland can result in additional expenses of CHF 31 million over the span of 5 years, for the ndGBM population. Expanding reimbursement to the

rGBM population is associated to a budget impact of CHF 49 million over the span of 5 years.

Sixteen articles on ELSO domains were included. In the ethical domain, physician recommendations and patient perspectives on treatment challenges are discussed. Additionally, patient's socioeconomic status, conflicts of interest for academic centers, and the high cost of TTFields are identified as potential barriers to patient access to treatment with TTFields. Discrepancies regarding TTFields treatment in international clinical practice guidelines exist. No relevant legal issues were identified. In the social domain, it is discussed that the use of TTFields in GBM patients is heavily reliant on social support, necessitating the involvement of caregivers in both the physician's and patient's decision-making process. Compliance to the treatment of both patients and caregivers is emphasized in order for optimal benefits of the treatment to be achieved. Finally, the expanding role of oncology nurses is highlighted, as they play a pivotal role in guiding patients and caregivers through the initiation and adherence to TTFields therapy.

CONCLUSION

The clinical evidence is based on 1 RCT and 2 retrospective cohort studies in patients with ndGBM, 1 RCT in patients with GBM at all recurrences (i.e. 88% at ≥2nd recurrence), and 2 unplanned post-hoc analyses of these RCTs. In patients with ndGBM, treatment with TTFields plus TMZ compared with TMZ alone is probably efficacious in terms of survival (1 RCT; moderate certainty evidence), may result in little or no difference in severe adverse events (1 RCT; low certainty evidence), and may have little or no effect on HRQoL except for itchy skin (1 RCT; low certainty evidence). Two single-centre retrospective cohort studies in patients with ndGBM showed inconclusive results for the effectiveness of TTFields plus TMZ compared with TMZ alone. In patients with GBM at first recurrence, treatment with TTFields plus chemotherapy compared with chemotherapy alone may be efficacious in terms of survival (1 RCT – post-hoc analysis; low certainty evidence) and may result in little or no difference in severe adverse events but the evidence is very uncertain (1 RCT – post-hoc analysis; very low certainty evidence). In patients with GBM at all recurrences, TTFields treatment alone compared with chemotherapy may result in little or no difference in efficacy in terms of survival (1 RCT; low certainty evidence), probably shows less severe adverse events than chemotherapy (1 RCT; moderate certainty evidence), and may show little or no difference in HRQoL but the evidence is very uncertain (1 RCT; very low certainty evidence).

From a health economic perspective, for both ndGBM and rGBM at first recurrerence, the reimbursement of TTFields is likely to improve survival and QALYs and to increase costs. The budget impact analyses showed that the budgetary impact of TTFields is mainly driven by the costs of TTFields. Finally, the use of TTFields is associated with important ethical, social and organisational

issues.

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Abbreviations and acronyms

BI	Budget Impact
BIA	Budget Impact Analysis
CE	Cost-effectiveness
CEA	Cost Effectiveness Analysis
CEAC	Cost-effectiveness acceptability curve
CHEC	Consensus Health Economic Criteria
CHEERs	Consolidated Health Economic Evaluation Reporting Standards
CHF	Swiss Franc
CI	Confidence interval
CMA	Comprehensive Meta-Analysis
CNEDiMTS	Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé
CNS	Central Nervous System
DARTH	Decision Analysis in R for Technologies in Health
DGHO	Deutsche Gesellschaft fur Hamatologie und Medizinische Onkologie e.V.
DNA	Deoxyribonucleic acid
EAE	Effectiveness, appropriateness, and economic efficiency
EANO	European Association of Neuro-Oncology
ELSO	Ethical, legal, social, and organisational
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of life questionnaire
EORTC QLQ-BN20	European Organisation for Research and Treatment of Cancer Quality of life questionnaire for brain cancer
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FOPH	Federal Office of Public Health
GBM	Glioblastoma
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HAS	Haute Autorité de santé
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio

IDH	Isocitrate dehydrogenase
INE	Insulated transducer array
IPD	Individual patient data
ITT	Intention-to-treat
KPS	Karnofsky-Performance-Status
LYs	Life years
MGMT	O^6-methylguanine DNA methyltransferase
MIGEL	Mittel und Gegenständeliste (Swiss Devices and Items List)
mITT	Modified intention-to-treat
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
ndGBM	Newly diagnosed glioblastoma
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NOS	Not otherwise specified
OECD	Organisation for Economic Co-operation and Development
ÖGHO	Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie
OKP	Obligatorische Krankenpflegeversicherung (Obligatory health insurance)
OS	Overall survival
OWSA	One-way sensitivity analyses
PFS	Progression-free survival
PICO	Population, intervention, comparator, outcome
PRISMA	Preferred Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
QALYs	Quality-adjusted life years
QoL	Quality of Life
RCT	Randomised controlled trial
rGBM	Recurrent glioblastoma
RoB 2	Revised Cochrane Risk of Bias tool for randomised trials
ROBINS-I	Risk of Bias in Non-randomised Studies – of Interventions
RR	Risk ratio
SF-36	Short-form 36
SGH-SSH	Schweizerische Gesellschaft fur Hämatologie
SoC	Standard of care

SSMO	Swiss Society of Medical Oncology
TLV	Tandvårds-Läkemedelförmånsverket (Dental and Pharmaceutical Benefits Agency)
TMZ	Temozolomide
TTFields	Tumour treating fields
UK	United Kingdom
USA	United States of America
WHO	World Health Organisation

Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology, their execution and the results are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in an HTA report include clinical efficacy, effectiveness and safety, costs, cost-effectiveness and budget impact, ethical, legal, social and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system.

1 Policy question and context

Glioblastoma (GBM) is an aggressive form of tumour originating in the brain or very rarely spinal cord. With an estimated incidence rate between 3.19 and 4.17 per 100,000 people worldwide, the condition is the most common primary brain tumour in adult patients. [1] GBM has a poor prognosis, with a median survival of 13.1 months found in a population-level study of GBM patients in Switzerland. [2] Standard treatment for patients with newly diagnosed GBM (ndGBM) consists of surgical removal of the tumour or biopsy with subsequent radio- and chemotherapy with temozolomide (TMZ), and maintenance chemotherapy with TMZ. Treatment at recurrence is varied; the majority of recurrent GBM (rGBM) patients receive systemic treatment, mostly chemotherapy with lomustine or less frequently rechallenge chemotherapy with TMZ, or patients can receive targeted therapy agents such as bevacizumab, second surgery is an option for subgroups of patients, and re-irradiation can be administered for patients with small tumours. [3] According to Roth et al 2020, patients who received radiotherapy or alkylating chemotherapy in the first-line setting should be placed on a different therapeutic modality at recurrence. [4]

Tumour treating fields (TTFields) are a non-invasive, out-patient treatment option for patients with GBM and are used in combination with maintenance TMZ treatment. [4] The U.S. Food and Drug Administration (FDA) approved TTFields as a treatment option for patients with rGBM in 2011 and for patients with ndGBM in 2015. In Switzerland, TTFields are, since July 2021, temporarily covered by the Swiss mandatory health insurance (OKP) under the condition of a re-evaluation of the available and new evidence until July 2024. The technology has to fulfil the constitution-defined “Effectiveness, Appropriateness and Economic Efficiency (EAE)” criteria to qualify for full or restricted coverage. [5] Currently, reimbursement is limited to specific indications (ndGBM up to first progression) and a maximum treatment duration of 2 years. Also, specific requirements are in place to qualify for reimbursement, such as an initial user instruction of the product including compliance control. [5]

To inform the policy reimbursement question in 2024, an HTA report was issued including the typical HTA domains regarding TTFields for ndGBM patients. [6] Additionally, the HTA report includes evidence for a potential policy investment of expanding TTFields to rGBM patients. For the latter, the economic effectiveness evidence is in the form of a scenario analysis in the cost-effectiveness and budget impact analyses. As such, the economic evaluation of expanding TTFields to rGBM patients does not include sensitivity analyses.

2 Research question

The HTA report addresses 2 research questions:

The primary question - in the treatment of ndGBM adult patients until 1st progression in Switzerland, what is the efficacy, effectiveness, safety, cost-effectiveness, and budget impact, as well as ethical, legal, social, and organisational benefits and harms of either TTFields in combination with maintenance chemotherapy or TTFields alone after maintenance chemotherapy has stopped, compared with maintenance chemotherapy alone?

In addition, the HTA report answers the secondary question - in the treatment of ndGBM and GBM adult patients at 1st progression in Switzerland, what is the efficacy, effectiveness, safety, cost-effectiveness and budget impact, as well as ethical, legal, social, and organisational benefits and harms of TTFields alone or in combination with second-line systemic therapy (i.e. physician's choice chemotherapy) compared with second-line systemic therapy (i.e. physician's choice chemotherapy) alone?

3 Medical background

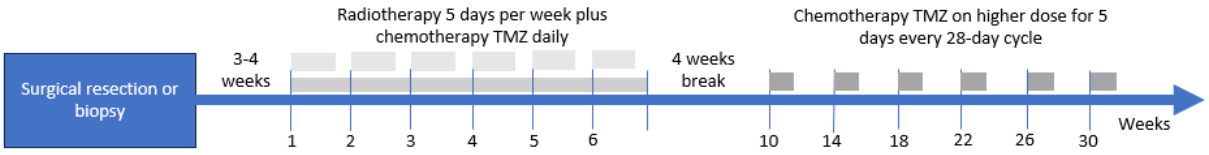
Gliomas form a heterogeneous group of tumours that originate in the central nervous system. Grade 4 is the most aggressive tumour and is named glioblastoma, previously known as glioblastoma multiforme. [7] Currently, the term glioblastoma is the most commonly used, however the term glioblastoma multiforme can be found in relevant literature and therefore is also included in the current HTA. The 2021 World Health Organisation (WHO) classification of the Central Nervous System (WHO CNS5) reduces the more than 15 entities of adult type diffuse gliomas listed in the 2016 update (WHO CNS4) to 3 types with better characterised biology and prognosis. [8] One of the major changes between WHO CNS5 and WHO CNS4 consists of the restriction of the diagnosis of GBM only to tumours that are *IDH* wild type, while previously GBMs were divided into (1) glioblastoma, isocitrate dehydrogenase (IDH)-wild type; (2) glioblastoma, IDH-mutant; and (3) glioblastoma, not otherwise specified (NOS). [7,8] For the purpose of this HTA report, GBM will be used, covering both glioblastoma and glioblastoma multiforme.

While the pathological diagnosis of GBM had been historically based on morphological features, specific biomarkers are included in the diagnosis criteria according to WHO CNS5. [9] As such, clinical endpoints from randomised controlled trials (RCTs) and observational studies will likely be based on classification definitions somewhat different from the most recent WHO definitions. GBM has a global incidence between 3.19 and 4.17 per 100,000 people and accounts for more than 60% of all gliomas in adults. [1,10] In Switzerland, between 500 and 700 adults are diagnosed with gliomas each year. [11] Between 2010 and 2014, the incidence rate of GBM in Switzerland was estimated at 3.54 per 100,000 and it occurred more

often in men than in women, with an incidence rate of 4.72 per 100,000 and 2.47 per 100,000 respectively. [12] The median age at diagnosis of these patients was 65 years. [12] Median survival after GBM diagnosis is about 13.1 months.[13] Estimates of survival without treatment suggests a median survival of 6-10 months.[14] Survival has improved over time, mainly as a consequence of the introduction of TMZ in addition to radiotherapy. [11,15] Depending on the size and location of the tumour, the clinical presentation of patients with GBM varies widely. GBM often presents with a short clinical history of 3 to 6 months, with signs like focal neurological deficits and cognitive impairments as well as dizziness, headaches, nausea, lethargy, seizures, hemiparesis, and stroke-like symptoms and signs. [10,16,17]

GBM is suspected through magnetic resonance imaging (MRI) in combination with a contrast-enhancing agent, but the definitive diagnosis can only be made by histopathology. [11] Standard of care (SoC) for patients with ndGBM includes surgical removal of the tumour as feasible, followed by radiation plus concomitant TMZ therapy, as well as subsequent TMZ maintenance therapy.[18] The European Association of Neuro-Oncology (EANO) 2021 Guideline suggests that surgical resection should aim to remove as much tumour tissue as safely feasible without compromising neurological function, or biopsy. 3-4 weeks after surgical resection or biopsy, radiotherapy and chemotherapy are started for the 6 subsequent weeks. [17] In general, patients receive radiotherapy 5 times per week and chemotherapy daily. Once radiotherapy is completed and after a 4-week break, chemotherapy is given at a higher dosage for 5 days during a 5-out-of-28-day cycle. [11,15] A visual presentation of the treatment regime is shown in ***Figure 1***. TTFields can be provided as an additional non-invasive, out-patient treatment option for patients with GBM used in combination with maintenance chemotherapy.

Figure 1. Treatment regime

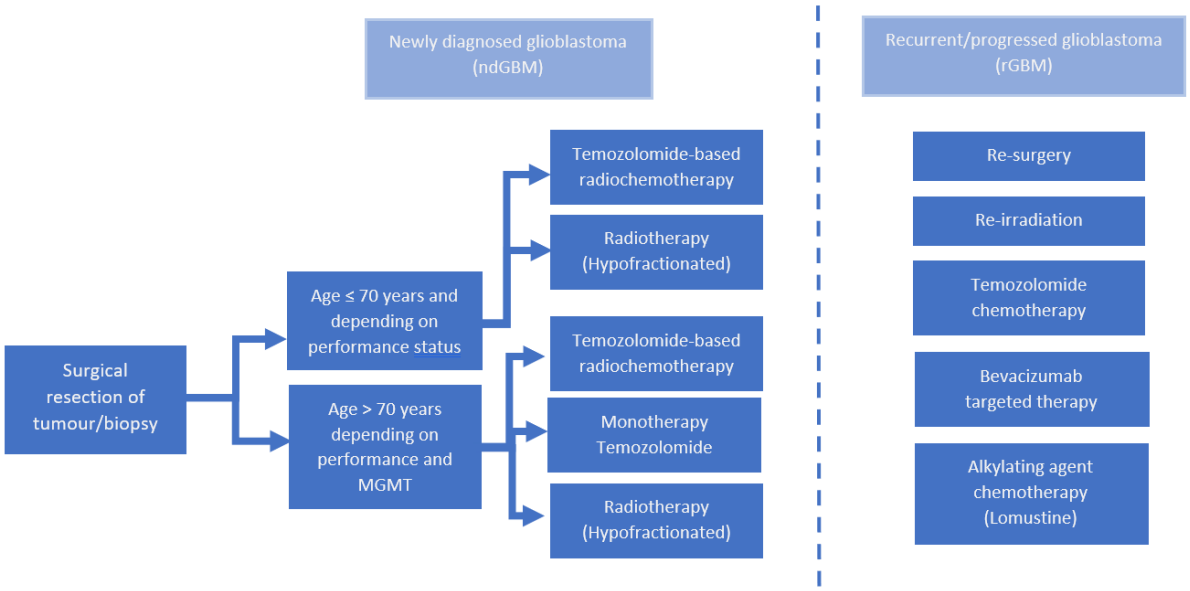


In a review of diagnosis and treatment of diffuse gliomas in adults in Switzerland, Roth and colleagues described that most neuro-oncological centres treat GBM patients below the age of 70 years with combined TMZ-based radiochemotherapy, due to its overall good tolerability and in the absence of convincing alternatives. Patients older than 70 years may receive combined TMZ-based radiochemotherapy or monotherapy with TMZ or irradiation, as considered appropriate by the treating physician depending on the performance status and on the O^6-methylguanine DNA methyltransferase (MGMT) promoter methylation status. [4,17]

Since surgical resection, radiotherapy and chemotherapy are no curative treatments, in GBM patients the tumour progresses or recurs almost always despite these treatments. Treatment options for patients with progressive or recurrent disease consist of inclusion into a clinical trial, re-operation, re-exposure to chemotherapy, re-irradiation, combinations thereof, and palliative care. [19] Roth et al 2020 described that the treatment of rGBM is less standardised than the treatment of ndGBM. [17] While re-exposure to TMZ was more frequent in the past, lomustine is now increasingly being considered SoC. [17,20] The targeted therapy bevacizumab is also considered a useful option to reduce clinical symptoms burden in rGBM by blocking the growth of blood vessels. Roth et al 2020 suggest rGBM patients who were initially only treated with radiotherapy or alkylating chemotherapy (e.g. lomustine) should receive a different therapeutic modality than previously treated with**.** ***Figure 2*** presents the treatment pathway for patients with GBM. While the figure is based on the clinical practice in Switzerland as reported by Roth and colleagues, additional treatment options were included based on the EANO guidelines and reviewer feedback. [17]

A review in 2018 showed that 13 different labels were used to describe progression in GBM. The label most frequently used to describe progression was recurrence (99% of studies used recurrence). [21] In this HTA report, progression and recurrence are therefore used interchangeably as considered in the Cochrane review by McBain et al 2018. [19]

Figure 2. Treatment pathway glioblastoma (GBM), newly diagnosed and recurrent



4 Technology

4.1 Technology description

TTFields have emerged as a potential treatment option in addition to conventional radiochemotherapy for the management of GBM. TTFields are administered by delivering low-intensity, intermediate-frequency, alternating electric fields to human GBM using 4 non-invasive transducer arrays, which are placed on the skin close to the tumour, and can be seen in ***Figure 3.*** TTFields function through different mechanisms of action, including by disturbing cell mitosis, delaying DNA repair enhancing autophagy, inhibiting cell metabolism and angiogenesis, cancer cell migration and activating anti-tumour immune responses. After training by nursing staff, patients operate the device independently, in an outpatient setting. Patients should wear the device for as long as possible to maximise treatment effect, at least 18 hours per day. The preparation for TTFields includes regularly shaving of the patient's head and changing the insulated transductor arrays (INE) twice a week. Shaving of the patient's head, changing of the transductor arrays, and connecting the device to the arrays may be done by the patient, or by a caretaker if the patient is unable to. Optimal placement of the transducer arrays on the patient's head is based on software provided by the manufacturer, using data from patient's MRI scans. Throughout treatment, the optimal placement might be adjusted using information provided by the software. Further, TTFields are provided with 4 interchangeable batteries and patients or caretakers are required to recharge the battery every 2-3 hours for 2-4 hours at the accompanying charging station and turn the device off and on, while it is also possible to power the device directly via the power grid when the patient is stationary (e.g. during the night). The device can be carried in a bag, thus allowing patients to partake in normal daily life.

TTFields are manufactured by Novocure,and are available under the trade name Optune®. There are no other companies manufacturing TTFields.

Figure 3. TTFields (Optune®) device

Notes: Reproduced with permission from Novocure GmbH ©2022 Novocure GmbH – All rights reserved. [22]

4.2 Regulatory status / provider

In Switzerland, TTFields are temporarily covered by the OKP with evidence developing until July 2024 and are listed in the Mittel- und Gegenständeliste (MiGeL) under position number 09.04.01.00.2 for the treatment of ndGBM. The reimbursement is limited to: [5]

- adults (≥18 years)
- who have a Karnofsky-Performance-Status (KPS) ≥70
- and start therapy 4-7 weeks after radiochemotherapy
- only in combination with concomitant TMZ maintenance therapy
- show no tumour progression after concomitant radiochemotherapy.

Further limitations include:

- reimbursement arrest in case of tumour progression
- no reimbursement for rGBM
- compliance control from the prescribing physician after 3 months and continuously for further treatment. Stop of reimbursement if patients are wearing TTFields <18 hours per day

- maximum treatment duration 2 years.

This list of limitations is not exhaustive (see **Appendix *14.2.3***). Maximum covered costs of TTFields are Swiss Franc (CHF) 14,320 per month for self-administration and CHF 13,604 per month for care-administration. [5]

5 Population, Intervention, Comparator, Outcome (PICO)

The GBM population (distinguished as ndGBM and rGBM) and treatment strategies are presented in the medical background section. For the purposes of including all relevant studies, the population is defined broadly by including both WHO CNS4 and CNS5 classifications. The PICO is derived from the pre-scoping report in which the clinically relevant outcomes were defined/selected and is defined as follows:

Table 1. PICO

PICO	
P:	Adult patients with glioblastoma (newly diagnosed and recurrent) after tumour resection/biopsy and radiochemotherapy
I:	TTFields either in combination with chemotherapy or alone after maintenance chemotherapy has stopped
C:	Maintenance chemotherapy
O:	Efficacy and effectiveness • Overall survival (OS) • Progression-free survival (PFS)[a] • Health-related quality of life (HRQoL)[b] Safety • Serious adverse events • Drop-out due to serious adverse events Compliance • Adherence • Drop-out due to non-adherence

	Economics • Incremental/total costs, life years (LYs), and quality-of-life-adjusted life-years (QALYs) • Incremental cost-effectiveness ratio (ICER) • Budget impact analysis (BIA)

Notes
a = Preferably, progression of GBM is radiologically confirmed. When magnetic resonance imaging is not available, progression can be assessed clinically.
b = HRQoL as assessed with validated questionnaires.

6 HTA key questions

For the evaluation of the technology, the following key questions covering the central HTA domains are addressed for the primary (TTFields for ndGBM patients) and secondary (TTFields expanded to rGBM patients) research questions:

1. Is the technology efficacious/effective compared with the comparator treatment?
2. Is the technology safe compared with the comparator treatment?
3. What are the costs of the technology?
4. Is the technology cost-effective compared with the comparator treatment?
5. What is the budget impact burden of the technology compared with the comparator treatment?
6. Are there ethical, legal, social, or organisational issues related to the technology?

7 Efficacy, effectiveness and safety

Summary statement efficacy, effectiveness and safety

Efficacy of TTFields

In patients with **ndGBM** treated with TTFields plus TMZ compared with TMZ alone, overall and progression-free survival were statistically significant longer (HR 0.63 [95% CI 0.53-0.76]; HR 0.63 [95% CI 0.52-0.76]; 1 RCT; moderate certainty evidence). During 12 months of TTFields plus TMZ treatment HRQoL was comparable between the 2 treatment arms, only itchy skin was statistically significant worse in the TTFields plus TMZ arm compared with TMZ alone (1 RCT; low certainty evidence). In patients with **GBM at first recurrence** overall survival was statistically significant longer when treated with TTFields plus chemotherapy versus chemotherapy alone (HR 0.70 [95% CI 0.48-1.00]; 1 RCT - post-hoc analysis; low certainty evidence). Progression-free survival and HRQoL were not reported. In patients with **GBM at all recurrences** (i.e. 12% at 1st recurrence, 47% at 2nd recurrence, and 41% at ≥3rd recurrence) treated with TTFields compared with chemotherapy there was no statistically significant difference in overall and progression-free survival (HR 0.86 [95% CI 0.66-1.12]; HR 0.81 [95% CI 0.60-1.09]; 1 RCT; low certainty evidence). When limiting the study population to patients receiving at least one course of TTFields therapy a statistically significant longer overall survival was reported versus chemotherapy (HR 0.69 [95% CI 0.52-0.92] 1 RCT - post-hoc analysis; low certainty evidence). At 3 months follow-up, the HRQoL domains did not seem to differ or seemed in favour of TTFields, except for the HRQoL domain physical functioning (1 RCT; very low certainty evidence).

Effectiveness of TTFields

In patients with **ndGBM** treated with TTFields plus TMZ versus TMZ alone, no statistically significant difference in overall survival was found in a single-centre retrospective cohort study in the USA (HR 0.93 [95% CI 0.58-1.47]; 1 non-randomised study; very low certainty evidence) and a statistically significant longer overall and progression-free survival was found in a single-centre retrospective cohort study in China (HR 0.19 [95% CI 0.09-0.41]; HR 0.35 [95% CI 0.14-0.91]; 1 non-randomised study; low certainty evidence).

Safety of TTFields

There was no statistically significant difference in grade 3-4 severe adverse events for TTFields plus TMZ versus TMZ alone in patients with **ndGBM** (RR 1.09 [95% CI 0.91-1.30]; 1 RCT; low certainty evidence) and borderline no statistically significant difference for TTFields plus chemotherapy versus chemotherapy alone in patients with **GBM at first recurrence** (RR 1.48 [95% CI 0.997-2.19)] 1 RCT - post-hoc analysis; very low certainty evidence). In patients with **GBM at all recurrences** treated with

TTFields compared with chemotherapy there were statistically significant less grade 3-4 severe adverse events (RR 0.37 [95% CI 0.16-0.86]; 1 RCT; moderate certainty evidence).

7.1 Methodology efficacy, effectiveness and safety

The systematic review methodology described in this HTA report is developed in line with the Cochrane Handbook for Systematic Reviews of Interventions (Version 6.3) [23] and the report is drafted in adherence to the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. [24]

7.1.1 Databases and search strategy

A stepwise systematic literature search approach was implemented: 1) a systematic literature search for RCTs (3 April 2023), and 2) an additional systematic literature search for comparative non-randomised studies (26 April 2023). Systematic literature searches were conducted in 3 databases: PubMed (MEDLINE), Embase.com, and the Cochrane Library. To gain insight in ongoing RCTs on TTFields in patients with ndGBM or rGBM, with study characteristics in line with our PICO, searches were conducted on the websites of ClinicalTrials.gov (https://clinicaltrials.gov) and the European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu) on 25 April 2023.

The search strategy was developed based on the PICO criteria reported in ***Chapter 5***. Search strings were compiled for the GBM population (i.e. newly diagnosed or recurrent patients) and the intervention TTFields. A large number of duplicate records was retrieved, caused by conference abstracts in the database Embase.com. Therefore, in addition to the approach described in the HTA protocol a search limit was added to exclude conference abstracts. The syntax of the search strategy was composed for one medical database, PubMed (MEDLINE), and customised to the other databases. The details of the search strategies are outlined in ***Appendix 14.1.1***.

Electronic records of the articles retrieved by the searches were stored with Endnote reference manager software (Clarivate Analytics, United States of America (USA)). This Endnote file was uploaded in Rayyan software (Rayyan Systems Inc., USA) for the selection of the articles. [25] Duplicate records were deleted, and this number was registered in the PRISMA flow diagram.

7.1.2 Other sources

Relevant systematic reviews to our research question were selected during the screening of titles and abstracts. During the full-text screening phase, the reference lists of these systematic reviews were checked for possibly missed individual articles. Narrative reviews were excluded directly and not

checked for references. The systematic review itself was excluded after the reference check, with a documented reason for exclusion in the PRISMA flow diagram. In addition, the supplementary search technique backward citation chasing was applied, i.e. by finding other studies cited within the included articles. No additional studies were found in these other sources.

7.1.3 Study selection

Relevant articles were selected in duplicate by a systematic approach by 2 independent researchers. Firstly, the major topics of the articles were assessed on relevancy to the objectives by title and abstract. Articles that seemed to contain relevant data for the objectives were selected for full-text screening. Articles without relevancy to the objectives were excluded, without documenting the reason for exclusion. If the 2 researchers disagreed on the relevance of an article, this was discussed. If the differences remained after discussion, the article was assessed in full-text. Secondly, the articles were assessed in full-text based on the pre-specified eligibility criteria (***Table 2***). Articles were included in the systematic review if they fulfilled the inclusion criteria; the remaining articles were excluded and the primary reason for exclusion was listed. Any differences between the researchers were resolved by discussion, if needed a third researcher was consulted.

Table 2. Inclusion and exclusion criteria for clinical evaluation studies

	Inclusion criteria	**Exclusion criteria**
Publication year	All	None
Language of publication	English, French, German, Italian	All other languages
Country of study	Worldwide	None
Study design/ publication type	- RCTs - Comparative non-randomised studies (i.e. prospective or retrospective cohort studies)	- Systematic reviews (i.e. only used for a reference check) - Narrative reviews - Non-comparative studies (e.g. single-arm trials) - Simulation studies - Case series or case reports - Irrelevant publication types (e.g. letter, comment, expert opinion, editorial, abstract only, conference presentation, book chapter)
Population	- Adult patients with ndGBM (WHO Grade IV) after tumour resection/biopsy and radiochemotherapy	- Animal studies - Patients age <18 years - Patients without tumour resection and

	- Adult patients with rGBM (WHO Grade IV) after tumour resection/biopsy and radiochemotherapy	radiochemotherapy - Mixed study population of patients with ndGBM and rGBM, without stratification of the results
Intervention	TTFields either in combination with maintenance chemotherapy/second-line systemic therapy (i.e. physician's choice chemotherapy) or alone	TTFields in addition to other therapies than maintenance chemotherapy/second-line systemic therapy (i.e. physician's choice chemotherapy)
Comparator	Maintenance chemotherapy/second-line systemic therapy (i.e. physician's choice chemotherapy)	- Other comparators - No comparator
Outcome	- Overall survival - Progression-free survival - HRQoL - Serious adverse events - Drop-out due to serious adverse events - Compliance/adherence - Drop-out due to non-adherence	- Inadequate data (e.g. missing relevant data or unexplained important errors in patient flow) - Studies with duplicate data (study with the largest sample size or most extended follow-up was included for data extraction of the results) - Unclear follow-up duration - Other outcomes

Abbreviations
HRQoL = health-related quality of life, ndGBM = newly diagnosed glioblastoma, RCTs = randomised controlled trials, rGBM = recurrent glioblastoma, TTFields = tumour treating fields, WHO = World Health Organisation.

7.1.4 Assessment of quality of evidence

The included studies were critically appraised by one researcher using different tools depending on the study design and fully reviewed by and discussed with a second researcher. The risk of bias of the RCTs was assessed with the revised Cochrane Risk of Bias tool for randomised trials (RoB 2). [23,26] The comparative non-randomised studies were assessed with the Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool. [27] The risk of bias was assessed on a per outcome basis and was visualised in plots with the web application Robvis. [28]

The overall certainty of the evidence on outcome level was appraised using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. [23,29] The certainty of a body of evidence is defined as the extent to which one can be confident that the estimated effect of an intervention is close to the true effect. A GRADE assessment of this certainty involved appraisal of 5 domains: (1) risk of bias (i.e. study limitations; as assessed with the RoB 2 and ROBINS-I tools), (2) inconsistency (i.e. heterogeneity or variability in the estimates of treatment effect across studies), (3) indirectness of evidence (i.e. the degree of differences between the PICOs of this HTA and the PICOs of the primary studies), (4) imprecision of the effect estimates, and (5) the risk of publication bias. Based on the

assessments for each domain, the overall evaluation of the certainty of the evidence per outcome was classified as high, moderate, low, or very low. The overall certainty of the evidence was summarised in GRADE summary of findings tables, together with key information concerning the magnitudes of effects of the intervention and the amount of available evidence. [23,29] GRADEpro GDT software (Evidence Prime Inc., Canada) was used to construct the summary of findings tables. [30]

7.1.5 Methodology data extraction, analysis and synthesis of the domains efficacy, effectiveness and safety

7.1.5.1 Data extraction

Relevant data from the included studies was independently extracted by one researcher into a standardised data-extraction spreadsheet in Microsoft Excel and was fully reviewed by a second researcher. This spreadsheet included:

- bibliographic reference
- study characteristics (study design, study name, study objective, country, setting, study period, length of follow-up, inclusion/exclusion criteria, source of funding)
- study population (diagnosis, sample size, age, sex, pre-treatment KPS, MGMT status)
- intervention (hours/day and duration of TTFields; type, dose and duration of maintenance chemotherapy/second-line systemic therapy (i.e. physician's choice chemotherapy))
- comparator (type, dose, and duration of maintenance chemotherapy/second-line systemic therapy (i.e. physician's choice chemotherapy))
- outcomes (overall survival, progression-free survival, HRQoL, serious adverse events, drop-out due to serious adverse events, compliance/adherence)
- additional comments (study limitations or issues that need to be considered not identifiable from other extracted data).

7.1.5.2 Data analysis and synthesis

The extracted data of the included studies was summarised in study characteristics tables, risk of bias figures, summary tables, and GRADE summary of findings tables. The options for clinically relevant data merging/stratification were explored and discussed with the HTA team and the FOPH. Based on the heterogeneity of the study populations in the included studies, the results were stratified for 3 populations: 1) patients with ndGBM, 2) patients with GBM at first recurrence, and 3) patients with GBM at all recurrences.

Due to the low number of RCTs on TTFields in patients with GBM and the difference between the study populations, it was not possible to calculate pooled estimates for the outcomes reported in the RCTs. It was decided not to pool the effectiveness data for overall survival of the 2 comparative non-randomised studies, in order to show the discrepancy between these results. The outcomes were analysed narratively and presented in summary tables.

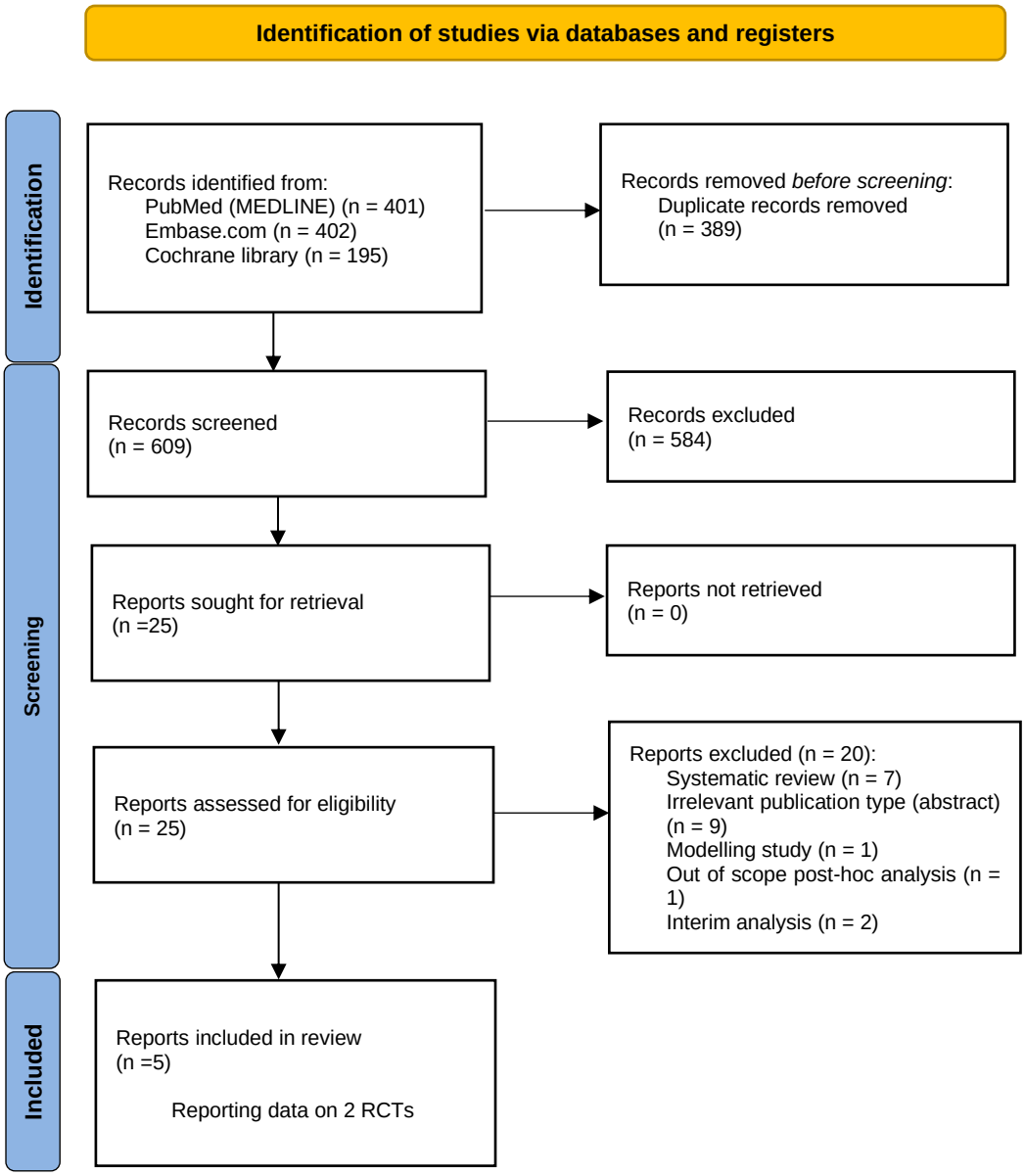
7.2 Results efficacy, effectiveness and safety

7.2.1 PRISMA flow diagram

7.2.1.1 Search step 1: search for randomised controlled trials

The results of the systematic literature search for RCTs are summarised in ***Figure 4.*** In total, 609 unique records were identified in PubMed (MEDLINE), Embase.com and Cochrane Library with the search conducted on 3 April 2023. Of those, 584 records were excluded based on title and abstract, leaving 25 articles for review in full-text. A total of 5 articles reporting data on 2 RCTs were included in the systematic review. The reasons for exclusion were irrelevant publication type, i.e. abstracts (9 articles), systematic reviews which were excluded after the reference check (7 articles), interim analyses (2 articles), post-hoc analyses out of scope for our objectives (1 article), and a modelling study (1 article). An overview of the reason for exclusion by each excluded article is enclosed in ***Appendix 14.1.2***.

Figure 4. PRISMA flow diagram [24] of the clinical evaluation systematic literature search: RCTs



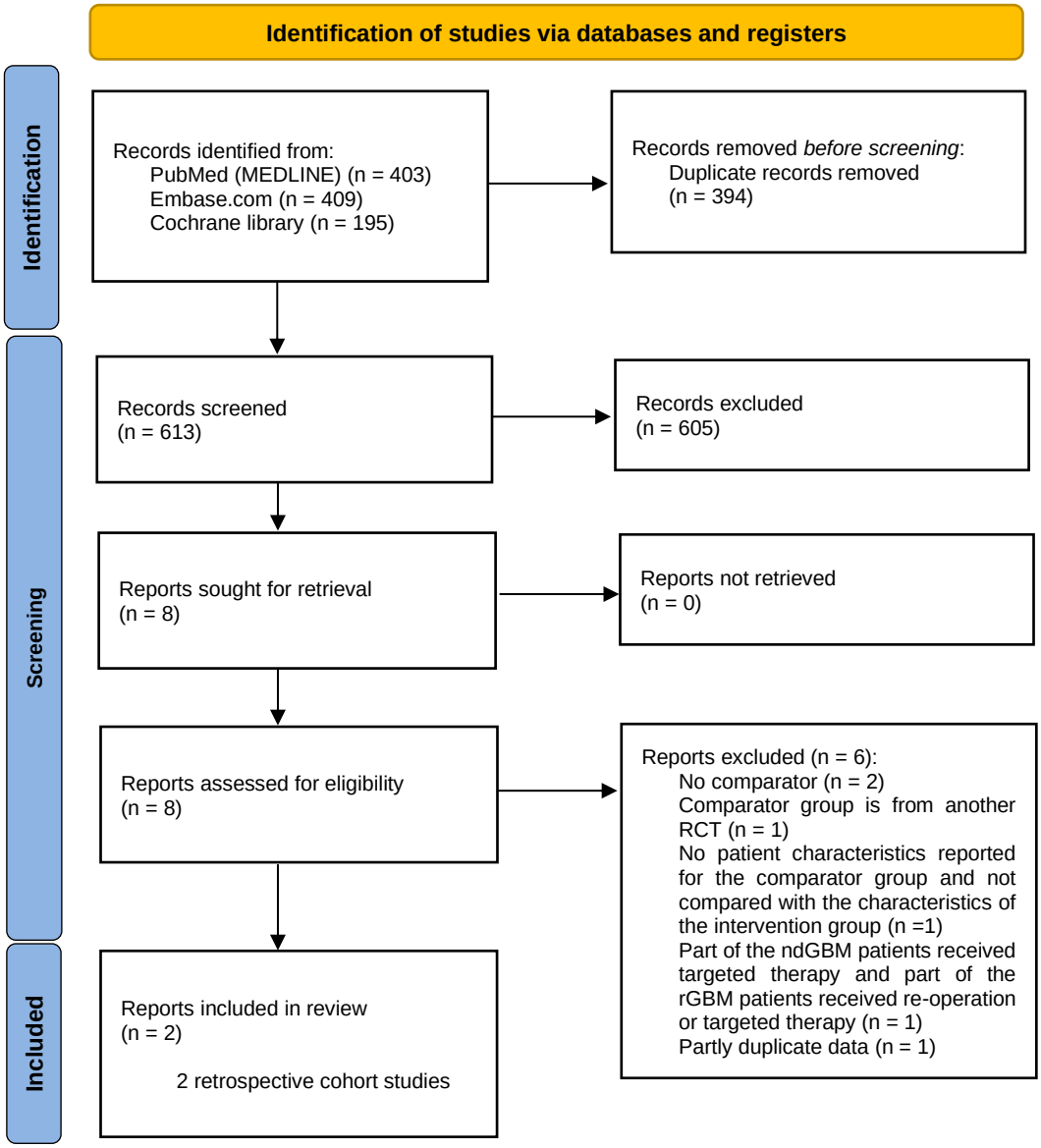
Notes
Search date 3 April 2023.

7.2.1.2 Search step 2: search for comparative non-randomised studies

For the second search step, the search strategy was rerun on 26 April 2023 to search for comparative non-randomised studies on TTFields in patients with GBM. The results of this systematic literature search are summarised in ***Figure 5***. In total 613 unique records were retrieved, 605 records were excluded based on title and abstract, resulting in 8 articles selected to be screened in full-text. Two comparative non-randomised studies were finally included. Articles were excluded for the reasons no comparator reported (2 articles), comparator group is from another RCT (1 article), no patient characteristics reported for the comparator group (1 article), the study was partly based on duplicate data already

included in an RCT (1 article), and part of the patients with ndGBM received targeted therapy and part of the patients with rGBM received re-operation or targeted therapy (1 article). In ***Appendix 14.1.2*** an overview of the reason for exclusion by each excluded article is enclosed.

Figure 5. PRISMA flow diagram [24] of the clinical evaluation systematic literature search: comparative non-randomised studies



Notes

Search date 26 April 2023.

7.2.2 Study characteristics and quality assessment of included studies

7.2.2.1 Randomised controlled trials

Two RCTs on TTFields treatment, one in a population of patients with ndGBM and another in patients with rGBM, form the evidence base of the clinical evaluation in this HTA report. In total, 5 articles reporting data on these 2 RCTs were selected for full analysis. These studies were conducted by the same research group and funded by Novocure Ltd., the device manufacturer of TTFields. The study characteristics are summarised in ***Table 3*** and stratified in 3 populations: 1) patients with ndGBM, 2) patients with GBM at first recurrence, and 3) patients with GBM at all recurrences.

ndGBM

In the EF-14 trial, Stupp et al 2017 studied the efficacy and safety of TTFields treatment in adult patients with nGBM who, according to the Stupp protocol, had undergone maximal safe debulking surgery or biopsy and had completed standard radiochemotherapy with a minimal dose of 45 Gy. [31] The EF-14 trial was a multicentre open-label phase III RCT conducted in 12 countries with study enrolment from July 2009 to December 2014 and follow-up through December 2016, with a median follow-up of 40 months. Patients were randomised in a 2:1 ratio to TTFields treatment for ≥18 hours/day plus maintenance TMZ (n=466, median age 56 years, 68% male) or TMZ alone (n=229, median age 57 years, 69% male). If tumour progression occurred, second-line therapy was offered per local practice and in the intervention arm TTFields could be continued until second radiologic progression. In total, 51% (n=237) of the patients in the intervention arm continued TTFields after the first progression. Stupp et al 2017 reported data on the outcomes overall survival, progression-free survival, compliance, drop-out due to non-adherence and serious adverse events. The outcome HRQoL of the EF-14 trial was analysed in a secondary analysis in the patients of the original EF-14 trial population who completed at least one HRQoL scale at baseline and published in an additional article by Taphoorn et al 2018. [32] The baseline characteristics of the patients who provided HRQoL data were comparable to those of the intention-to-treat (ITT) population and were well balanced between the intervention and control arm in this subpopulation.

GBM at first recurrence

Based on the ndGBM population of the EF-14 trial, an unplanned post-hoc analysis was conducted by Kesari et al 2017 in adults with GBM at first recurrence. [33] At first tumour progression, second-line therapy (including reoperation, radiosurgery, chemotherapy, bevacizumab or combination therapy) was offered per local practice. In December 2014, 228 of the 466 patients in the TTFields plus TMZ arm had

a first recurrence of whom 131 received second-line chemotherapy in addition to continued TTFields treatment. In the TMZ arm 121 of the 229 patients had a first recurrence and 73 patients received second-line chemotherapy. Thirteen patients randomised in the TMZ arm crossed over to TTFields, resulting in 144 patients with GBM at first recurrence included in the post-hoc analysis in the TTFields plus chemotherapy intervention arm (median age 57 years, 75% male) and 60 patients in the chemotherapy control arm (median age 58 years, 75% male). Patients' characteristics were well balanced between the intervention and control arm. TTFields treatment continued until the second radiologic progression or clinical deterioration, for a maximum of 24 months. The median follow-up was 12.6 months.

GBM at all recurrences

Stupp et al 2012 studied the efficacy and safety of TTFields treatment in adult patients with radiologically confirmed rGBM in an open-label phase III RCT, the EF-11 trial. [34] This multicentre study enrolled patients in 7 countries between September 2006 and May 2009, with a median follow-up of 39 months. Patients who had debulking surgery or biopsy and radiotherapy with/without TMZ with all recurrences were included: 12% had a first recurrence, 47% a second recurrence, and 41% a third or greater recurrence. A total of 237 patients were included in the RCT, among whom 120 were randomised to TTFields treatment for 22-24 hours/day (median age 54 years, 77% male) and 117 to physician's best choice chemotherapy (median age 54 years, 62% male). Physician's best choice chemotherapy consisted of chemotherapy agents and targeted therapy agents (i.e. bevacizumab, imatinib), prescribed alone or in combination.

In the TTFields group of the EF-11 trial, 27 of the 120 randomised patients (23%) discontinued treatment early – often within a few days – due to non-compliance or inability to handle the device. [34] An unplanned post-hoc analysis on overall survival in the EF-11 trial was published by Kanner et al 2014. They analysed a modified intention-to-treat (mITT) population of the 93 patients receiving at least one full cycle of TTFields treatment (i.e. 22-24 hours/day for ≥1 predefined treatment cycle of 4 weeks) compared with the 117 patients receiving physician's best choice chemotherapy. [35] No patient characteristics were reported for this modified TTFields population.

Table 3. Study characteristics of the included RCTs

Reference Study name	Study design Funding	Country Enrolment period Follow-up	Study population						Intervention	Comparator	Outcome
			I or C	Sample size	age (median; range)	sex (% male)	KPS (median; range)	MGMT status methylated			
ndGBM											
Stupp et al 2017 [31] EF-14	RCT; multicentre Novocure Ltd.	12 countries[a] July 2009-Dec 2014 median: 40 months	Patients ≥18 years with ndGBM						TTFields + TMZ	TMZ	OS PFS Compliance Drop-out non adherence SAEs
			I	r: 466 a: 466	56 years (19-83)	68%	90% (60-100)	36%			
			C	r: 229 a: 229	57 years (19-80)	69%	90% (70-100)	42%			
Taphoorn et al 2018 [32] EF-14	RCT – secondary analysis; multicentre Novocure Ltd.	12 countries[a] July 2009-Dec 2014 total: 12 months	Patients ≥18 years with ndGBM and at least 1 HRQoL scale at baseline						TTFields + TMZ	TMZ	HRQoL
			I	r: 466 a: 437	56 years (19-83)	68%	90% (60-100)	NR			
			C	r: 229 a: 202	57 years (19-80)	69%	90% (70-100)	NR			
GBM at first recurrence											
Kesari et al 2017 [33] EF-14	RCT – post-hoc analysis; multicentre Novocure Ltd.	12 countries[a] July 2009-Dec 2014 median: 13 months	Patients ≥18 years with GBM at first recurrence						TTFields + chemo-therapy[b]	Chemo therapy[c]	OS SAEs
			I	r: 466 a: 144	57 years (29-83)	75%	90% (60-100)	24%			
			C	r: 229 a: 60	58 years (22-75)	75%	90% (70-100)	23%			
GBM at all recurrences											
Stupp et al 2012 [34] EF-11	RCT; multicentre Novocure Ltd.	7 countries[d] Sept 2006-May 2009 median: 39 months	Patients ≥18 years with GBM at all recurrences[e] (intention-to-treat population)						TTFields	Chemo therapy[f]	OS PFS HRQoL Compliance Drop-out non adherence SAEs
			I	r: 120 a: 120	54 years (24-80)	77%	80% (50-100)	NR			
			C	r: 117 a: 117	54 years (29-74)	62%	80% (50-100)	NR			
Kanner et al 2014 [35] EF-11	RCT – post-hoc analysis; multicentre Novocure Ltd.	7 countries[d] Sept 2006-May 2009 NR	Patients ≥18 years with GBM at all recurrences[e], receiving ≥1 full cycle of TTFields or chemotherapy (modified intention-to-treat population)						TTFields	Chemo therapy[f]	OS
			I	r: 120 a: 93	NR	NR	NR	NR			
			C	r: 117 a: 117	54 years (29-74)	62%	80% (50-100)	NR			

Abbreviations

a = analysed (i.e. sample size analysed population), HRQoL = health-related quality of life, KPS = Karnofsky performance status, MGMT = O^6-methylguanine-DNA methyltransferase, ndGBM = newly diagnosed glioblastoma, NR = not reported, OS = overall survival, PFS = progression-free survival, r = randomised (i.e. sample size randomised population), SAEs = serious adverse events, TMZ = temozolomide, TTFields = tumour treating fields.

Notes

a = Austria, Canada, Czech Republic, France, Germany, Israel, Italy, Korea, Spain, Sweden, Switzerland, USA.
b = Second-line chemotherapy: bevacizumab 55%; lomustine, carmustine, fotemustine 36%; temozolomide 17%; irinotecan 2%; carboplatin 2%.
c = Second-line chemotherapy: bevacizumab 50%; lomustine, carmustine, fotemustine 38%; temozolomide 12%; irinotecan 3%; carboplatin 2%; procarbazine 2%.
d = Austria, Czech Republic, France, Germany, Israel, Switzerland, USA.
e = First recurrence 12%; second recurrence 47%; third or greater recurrence 41%.
f = Chemotherapy physician's best choice (multiple listings possible, some agents given in combination): bevacizumab 31%; irinotecan 31%; BCNU/CCNU 25%; PCV 9%; temozolomide 11%; procarbazine 1%; carboplatin 13%; etoposide 3%; imatinib 2%; hydroxyurea 1%; none received 3%.

7.2.2.2 Comparative non-randomised studies

Two comparative non-randomised studies on TTFields treatment in patients with ndGBM were included in this HTA report. These studies were conducted by different research groups in the USA and China.

ndGBM

Study characteristics of 2 included retrospective cohort studies in adult patients with ndGBM are outlined in ***Table 4***. Liu et al 2020 studied 104 patients in a single centre in the USA between January 2014 and July 2019, among them 37 patients received TTFields treatment plus TMZ (median age 61 years, 62% male) compared with 67 patients receiving TMZ alone (median age 65 years, 57% male). [36] Study funding was not reported. Chen et al 2022 conducted a single-centre study in China between January 2016 and February 2021 and included 63 patients treated with TTFields plus TMZ and 204 patients treated with TMZ alone. [37] They used propensity score-matching and inverse probability treatment weighting analysis to reduce the influence of selection bias, resulting in a matched dataset of 49 patients treated with TTFields plus TMZ (mean age 49 years, 45% male) and 87 patients treated with TMZ alone (mean age 49 years, 52% male). The study was funded by the National Natural Science Foundation of China and Chinese Society of Clinical Oncology.

rGBM

No comparative non-randomised studies were identified on TTFields in combination with maintenance chemotherapy or TTFields alone compared with maintenance chemotherapy in adult patients with rGBM.

Table 4. Study characteristics of the included comparative non-randomised studies

Reference Study name	Study design Funding	Country Enrollment period Follow-up	Study population						Intervention	Comparator	Outcome
			I or C	Sample size	Age (median; range or mean ± SD)	sex (% male)	KPS (median; range or mean ± SD)	MGMT status methylated			
ndGBM											
Liu et al 2020 [36] NR	Retrospective cohort study; single-centre NR	USA Jan 2014-July 2017 median (range): 42 (29-58) months	Patients ≥18 years with ndGBM						TTFields + TMZ	TMZ	OS
			I	37	61 years (28-81)	62%	90% (70-100)	16%			
			C	67	65 years (28-83)	57%	90% (50-100)	36%			
Chen et al 2022 [37] NR	Retrospective cohort study; single-centre NSFC; CSCO	China I: Aug 2018-Feb 2021 C: Jan 2016-Oct 2017 NR	Patients ≥18 years with ndGBM (matched dataset)						TTFields + TMZ	TMZ	OS PFS Compliance
			I	49	49.4±13.3 years	45%	81.8±11.9 %	24%			
			C	87	49.3±14.6 years	52%	82.2±15.2 %	37%			

Abbreviations

C = comparator, CSCO = Chinese Society of Clinical Oncology, I = intervention, KPS = Karnofsky performance status, MGMT = O^6-methylguanine-DNA methyltransferase, ndGBM = newly diagnosed glioblastoma, NR = not reported, NSFC = National Natural Science Foundation of China, OS = overall survival, PFS = progression-free survival, TMZ = temozolomide, TTFields = tumour treating fields, USA = United States of America.

7.2.3 Quality assessment of included studies

7.2.3.1 Randomised controlled trials

The risk of bias of the 5 included articles reporting on 2 RCTs was evaluated with the RoB 2 tool. [26] The risk of bias was assessed for 5 domains on a per outcome basis for overall survival (***Table 5***), progression-free survival (***Table 6***), HRQoL (***Table 7***), and serious adverse events (***Table 8***). These 5 domains include bias due to the randomisation process, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. [26] Summary figures of the risk of bias are enclosed in ***Appendix 14.1.3***.

*7.2.3.1.1 **Survival outcomes***

ndGBM

For the outcomes overall survival (***Table 5***) and progression-free survival (***Table 6***) the overall risk of bias was some concerns for the EF-14 trial. [31] Randomisation was performed using a central web-based

randomisation system with randomly varying block sizes (e.g. 3, 6 or 9 patients) within each stratum. The median time from diagnosis to randomisation was 3.8 months and 82 patients (8%) were excluded prior to randomisation due to progressive disease. This might have resulted in selection bias towards patients with a better prognosis. Due to the lack of a placebo as control arm, the participants, carers and people delivering the interventions were not blinded. No information was provided if there were deviations from the intended intervention that arose because of the trial context. Analyses were conducted according to the intention-to-treat (ITT) principle. Overall survival is an objective outcome and progression was assessed by an independent neuro-radiologist who was blinded to the treatment allocation of the patients, so that outcome measurement was deemed at low risk of bias.

GBM at first recurrence

The overall risk of bias was assessed as high for the outcome overall survival reported by Kesari et al 2017 (***Table 5***). [33] The unplanned post-hoc analysis in patients with GBM at first recurrence from the EF-14 trial was not in accordance with the pre-specified analysis plan of this RCT. The original patients with ndGBM were randomised in the EF-14 trial and the post-hoc analysis was based on a subset of these patients receiving second-line chemotherapy at first recurrence. Confounding might have been caused by the heterogeneity in second-line systemic therapy (i.e. reoperation, radiosurgery, chemotherapy, bevacizumab or combination therapy), because this was based on local practice. Furthermore, 9 percent of the patients in the TTFields plus chemotherapy arm crossed over from the TMZ arm and initiated TTFields at first recurrence instead of since randomisation in the EF-14 trial. The other patients who continued TTFields after recurrence had relapsed after first-line TTFields treatment.

GBM at all recurrences

The overall risk of bias for the outcomes overall survival (***Table 5***) and progression-free survival *(**Table 6***) was some concerns for the EF-11 trial in patients with GBM at all recurrences [34] and high risk of bias for the outcome overall survival (***Table 5***) for the unplanned post-hoc analysis of the EF-11 trial. [35] In the EF-11 trial randomisation was performed using random block sizes stratified by centre and prior surgery for the latest recurrence. No details were reported on the allocation concealment. Due to the lack of a placebo as control arm, the participants, carers and people delivering the interventions were not blinded. No information was provided if there were deviations from the intended intervention that arose because of the trial context. Stupp et al 2012 conducted the analyses according to the ITT principle. The unplanned post-hoc analysis in patients with rGBM receiving at least one full cycle of TTFields treatment was not in accordance with the pre-specified analysis plan of this RCT. A modified ITT analysis

was applied. The baseline patient characteristics were balanced in the ITT population, but no characteristics were reported for the mITT population. Since standard therapy for rGBM was lacking, patients in the intervention and control arm received different types and combinations of chemo and targeted therapy. Overall survival is an objective outcome and progression was assessed by blinded central radiology review, so that outcome measurement was deemed at low risk of bias .

Table 5. Risk of bias RCTs assessed with the RoB 2 tool – Outcome OS

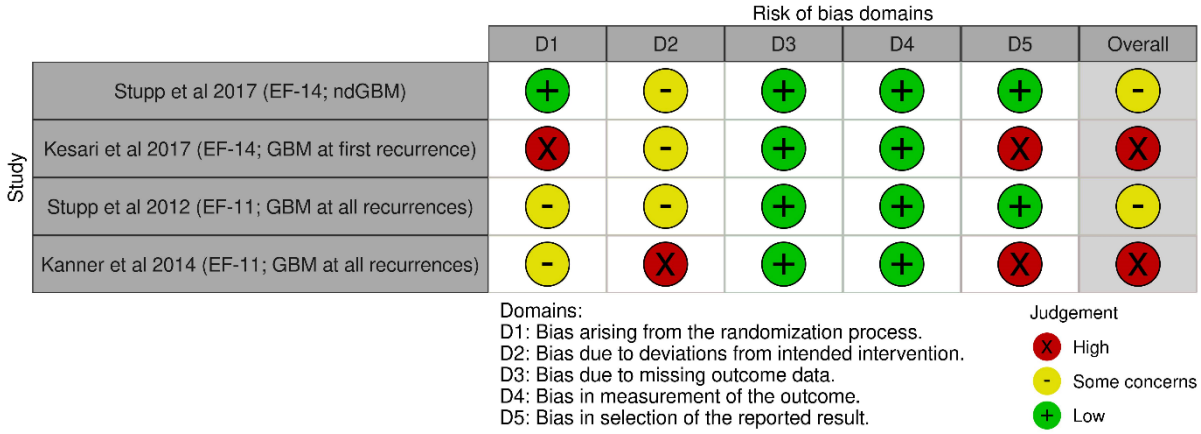
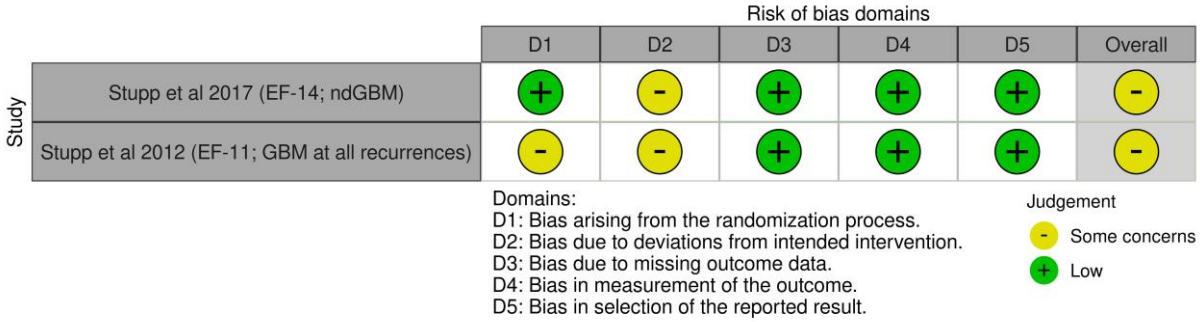


Table 6. Risk of bias RCTs assessed with the RoB 2 tool – Outcome PFS



7.2.3.1.2 ***Health-related quality of life***

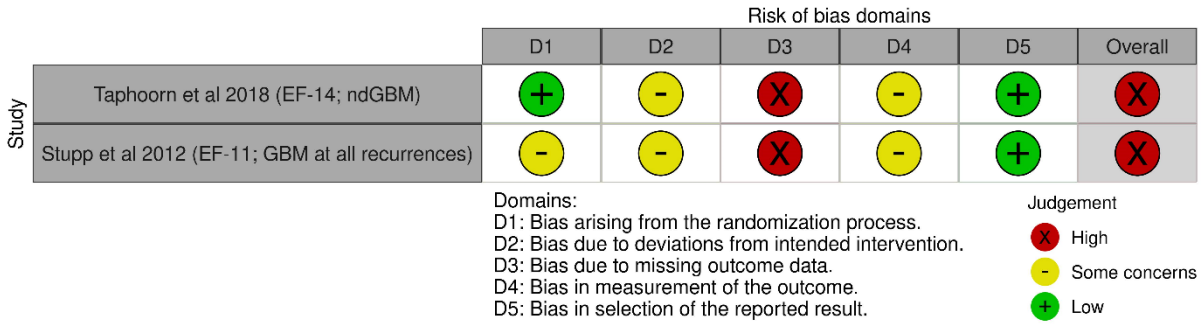
ndGBM

The overall risk of bias was high for the outcome HRQoL of the EF-14 trial (***Table 7***). [32] This bias was caused by missing outcome data. At 12 months of follow-up HRQoL was reported for 139 of the 437 patients (32%) in the TTFields plus TMZ arm and for 58 of the 202 patients (29%) in the TMZ arm. Low adherence to longitudinal HRQoL assessments is a common problem in cancer clinical trials, no reasons were reported for the missing data. Lack of blinding might have caused bias in the assessment of the subjective outcome HRQoL.

GBM at all recurrences

For the outcome HRQoL reported in the EF-11 trial the overall risk of bias was high, caused by missing outcome data (***Table 7***). [34] HRQoL was reported in 36 of the 120 patients (30%) in the intervention arm and in 27 of the 117 patients (23%) in the control arm at 3 months of follow-up. No reasons were reported for the missing data. Data was reported in figure only, without reporting quantitative data and p-values. Lack of blinding might have caused bias in the assessment of the subjective outcome HRQoL.

Table 7. Risk of bias RCTs assessed with the RoB 2 tool – Outcome HRQoL



7.2.3.1.3 ***Serious adverse events***

ndGBM

The overall risk of bias was some concerns for the outcome serious adverse events reported in the EF-14 trial (***Table 8***). [31] In addition to the risk of bias issues described for the survival outcomes, lack of blinding might have caused bias in the assessment of the outcome serious adverse events.

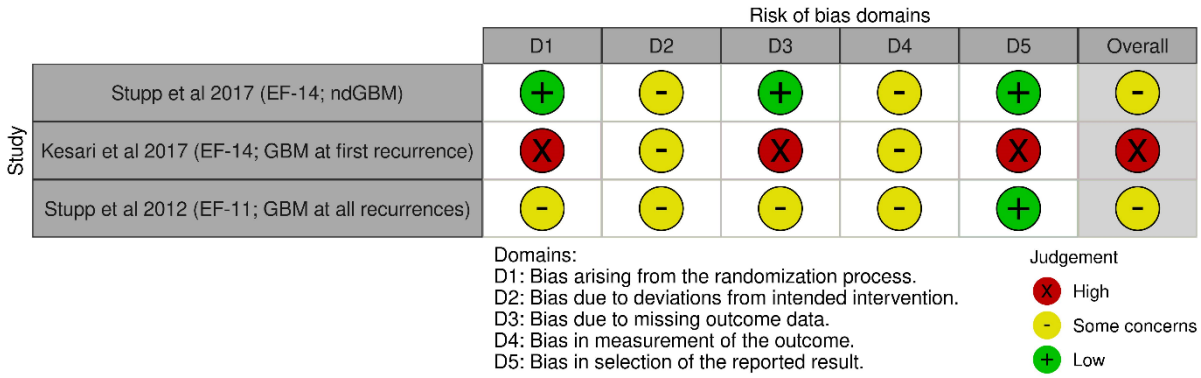
GBM at first recurrence

In the post-hoc analysis of the EF-14 trial the overall risk of bias was high for the outcome serious adverse events (***Table 8***). [33] In the TTFields plus chemotherapy arm the number of patients with ≥1 grade 3-4 severe adverse event was higher than in the chemotherapy arm, however no p-value was reported for this difference. Lack of blinding might have caused bias in the assessment of the outcome serious adverse events. These risk of bias issues are in addition to the risk of bias described for the survival outcomes.

GBM at all recurrences

In the EF-11 trial the overall risk of bias was some concerns for the outcome serious adverse events (***Table 8***). [34] For this outcome 2 additional issues might have impacted the risk of bias. Due to withdrawal of consent (without further specification of the reasons), safety data was reported for 116 of the 120 patients (97%) in the TTFields arm and only for 91 of the 117 patients (78%) in the chemotherapy arm. In addition, lack of blinding might have caused bias in the assessment of the outcome serious adverse events.

Table 8. Risk of bias RCTs assessed with the RoB 2 tool – Outcome SAEs



7.2.3.2 Comparative non-randomised studies

The risk of bias of the 2 included comparative non-randomised studies reporting survival data for patients with ndGBM treated with TTFields plus TMZ versus TMZ alone was assessed with the ROBINS-I tool. [27] Seven domains of bias were assessed: bias due to confounding, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. The summary figures of the risk of bias are enclosed in ***Appendix 14.1.3***.

*7.2.3.2.1 **Survival outcomes***

ndGBM

Overall, both single-centre retrospective cohort studies had a serious risk of bias for the outcome overall survival (***Table 9***) and in addition Chen et al 2022 had a serious risk of bias for the outcome progression-free survival (***Table 10***). [36,37] The studies applied analysis methods to control for confounding factors. Bias due to selection of participants was rated as serious, since no information was reported on the enrolment, total number of eligible patients during the study period, the number of excluded patients and reasons for exclusion. Chen et al 2022 did not report on day zero for the survival measurements and

whether there were differences between participants. Liu et al 2020 applied a Cox proportional hazard model to adjust for the variation in starting with TTFields after ending radiochemotherapy. No information was reported on deviations from intended interventions and missing data. Overall survival is an objective outcome and it was not described by Chen et al 2022 how progression was assessed.

Table 9. Risk of bias comparative non-randomised studies assessed with the ROBINS-I tool – Outcome OS

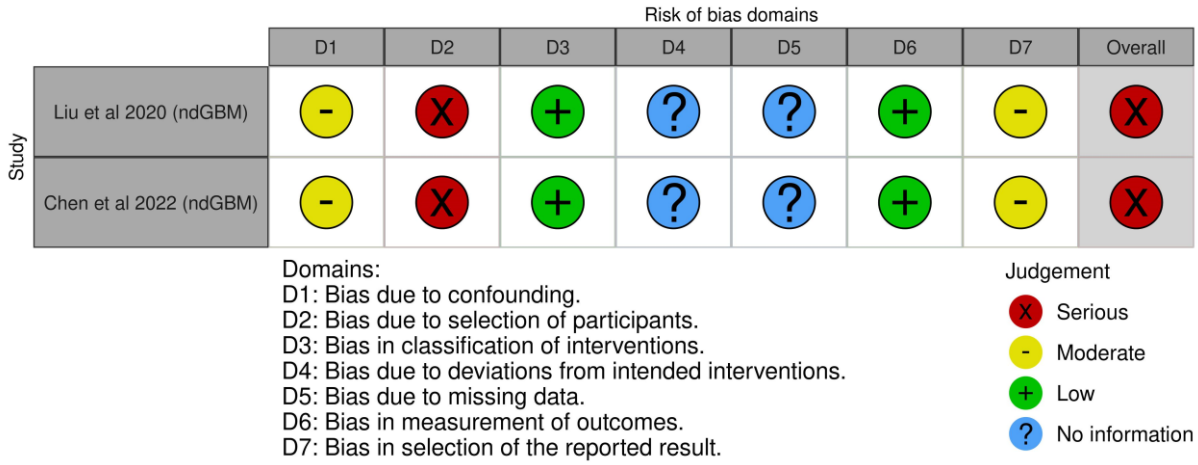
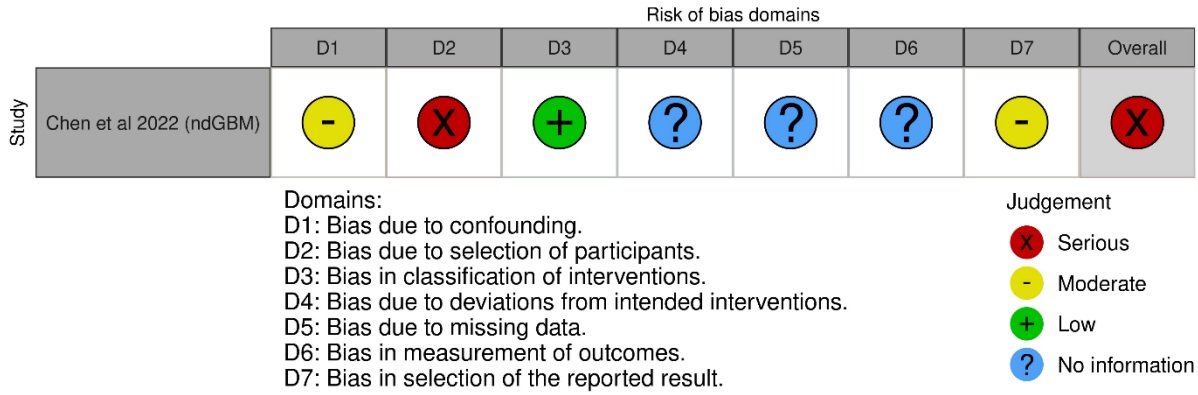


Table 10. Risk of bias comparative non-randomised studies assessed with the ROBINS-I tool – Outcome PFS



7.2.4 Findings efficacy

7.2.4.1 Overall survival and progression-free survival

ndGBM

After a median follow-up of 40 months in the EF-14 trial, the addition of TTFields to TMZ compared with TMZ alone in patients with ndGBM resulted in a statistically significant longer median overall survival of 20.9 months versus 16.0 months from randomisation (hazard ratio for death 0.63; 95% CI 0.53-0.76; p<0.001) (***Table 11****;* ***Table 19***). [31] Also a statistically significant longer median progression-free survival was found after a median follow-up of 40 months in the TTFields plus TMZ arm versus the TMZ alone arm of respectively 6.7 months versus 4.0 months from randomisation (hazard ratio for progression 0.63; 95% CI 0.52-0.76; p<0.001).

GBM at first recurrence

In the post-hoc analysis of the EF-14 trial in patients with GBM at first recurrence, the median overall survival was statistically significant longer in the TTFields plus chemotherapy group (11.8 months from progression) versus the chemotherapy group (9.2 months from progression), with a hazard ratio for death of 0.70 (95% CI 0.48-1.00; p=0.049) (***Table 11****;*

Table 20). [33] No data was reported on the outcome progression-free survival.

GBM at all recurrences

In the EF-11 trial no statistically significant results were found for the outcomes overall survival and progression-free survival. [34] Median overall survival was 6.6 versus 6.0 months from randomisation (hazard ratio for death 0.86; 95% CI 0.66-1.12; p=0.27) and progression-free survival was 2.2 versus 2.1 months from randomisation (hazard ratio for progression 0.81; 95% CI 0.60-1.09; p=0.16), respectively for patients in the TTFields group and chemotherapy group (***Table 11****;* ***Table 21***). In the unplanned post-hoc analysis in the mITT population median overall survival was statistically significant higher in patients receiving at least one course of TTFields therapy versus chemotherapy: 7.8 versus 6.0 months from randomisation (hazard ratio for death 0.69; 95% CI 0.52-0.92; p=0.0093) (***Table 11****;* ***Table 21***). [35] Progression-free survival was not analysed in the post-hoc analysis.

7.2.4.2 Health-related quality of life

ndGBM

HRQoL was evaluated in the EF-14 trial with the European Organisation for Research and Treatment of Cancer (EORTC) core quality-of-life questionnaire (QLQ-C30) and brain module questionnaire (QLQ-BN20) at baseline and every 3 months for up to 12 months. [32] At 12 months of follow-up HRQoL was

reported for 139 of the 437 patients (32%) in the TTFields plus TMZ arm and for 58 of the 202 patients (29%) in the TMZ arm. No statistically significant or clinically relevant differences were found for the HRQoL domains global health scale, cognitive, emotional, physical, role and social functioning (***Table 12***; ***Table 19***), and for the symptom scales pain and weakness of legs (***Table 13***; ***Table 19***),). A statistically significant difference in favour of TMZ was reported for itchy skin at 3, 6 and 9 months of follow-up and this was only clinically relevant at 3 months of follow-up (i.e. a difference of ≥10 points on a scale ranging from 0-100). Indications of spread were provided graphically in the article of Taphoorn et al 2018, but that the graphs were of insufficient quality to allow data approximation.

GBM at first recurrence

For the population GBM at first recurrence no data was reported on the outcome HRQoL.

GBM at all recurrences

In the EF-11 trial, HRQoL was assessed at baseline and at 3 months follow-up with the EORTC QLQ C-30 questionnaire in 36 of the 120 patients (30%) in the TTFields arm and in 27 of the 117 patients (23%) in the chemotherapy arm. [34] Data was reported in figures only without reporting p-values. At 3 months of follow-up no difference was reported for the HRQoL domains global health scale and social functioning. The domains cognitive, emotional and role functioning seemed in favour of TTFields and the domain physical functioning seemed in favour of chemotherapy (***Table 14***; ***Table 21***).

Table 11. Efficacy results: overall survival and progression-free survival

Reference Study name	Intervention Comparator	Sample size analysed	Follow-up (median)	Median time from initial diagnosis to randomisation	OS median (95% CI)	OS HR (95% CI)	p-value	PFS median (95% CI)	PFS HR (95% CI)	p-value	Overall risk of bias
ndGBM											
Stupp et al 2017 [31] EF-14	TTFields + TMZ	466	40 months	3.8 months	20.9 (19.3-22.7) months from randomisation	0.63 (0.53-0.76)	<0.001	6.7 (6.1-8.1) months from randomisation	0.63 (0.52-0.76)	<0.001	Some Concerns
	TMZ	229		3.7 months	16.0 (14.0-18.4) months from randomisation			4.0 (3.8-4.4) months from randomisation			
GBM at first recurrence											
Kesari et al 2017 [33] EF-14 – post-hoc analysis	TTFields + chemotherapy	144	13 months	NR	11.8 (NR) months from first progression	0.70 (0.48-1.00)	0.049	NR	NR	NR	High
	Chemotherapy	60		NR	9.2 (NR) months from first progression			NR			
GBM at all recurrences											
Stupp et al 2012 [34] EF-11	TTFields	120	39 months	11.8 months	6.6 (NR) months from randomisation	0.86 (0.66-1.12)	0.27	2.2 (NR) months from randomisation	0.81 (0.60-1.09)	0.16	Some Concerns
	Chemotherapy	117		11.4 months	6.0 (NR) months from randomisation			2.1 (NR) months from randomisation			
Kanner et al 2014 [35] EF-11 – post-hoc analysis	TTFields	93	NR	NR	7.8 (NR) months from randomisation	0.69 (0.52-0.92)	0.0093	NR	NR	NR	High
	Chemotherapy	117		11.4 months	6.0 (NR) months from randomisation			NR			

Abbreviations

CI = confidence interval, ndGBM = newly diagnosed glioblastoma, NR = not reported, OS = overall survival, PFS = progression-free survival, TMZ = temozolomide, TTFields = tumour treating fields.

Table 12. Efficacy results: health-related quality of life – functioning scales in patients with ndGBM

Reference Study name	Inter-vention Com-parator		Sample size ana-lysed	EORTC QLQ-C30[a]												Overall risk of bias
				Global Health Scale	p-value	Cognitive functioning	p-value	Emotional functioning	p-value	Physical functioning	p-value	Role functioning	p-value	Social functioning	p-value	
ndGBM																
Taphoorn et al 2018 [32] EF-14 – secondary analysis	TTFields + TMZ	0 months: mean score (SD)	437	69.0 (21.0)	0.16	76.7 (23.4)	0.89	77.4 (21.4)	0.17	83.5 (20.1)	0.50	74.5 (28.9)	0.49	73.9 (27.6)	0.55	High
		3 months: mean change[b]	305	-2.6	0.77	-2.3	0.72	+1.4	0.37	-3.7	0.87	-6.1	0.06	-4.0	0.054	
		6 months: mean change[b]	244	-2.5	0.47	-4.1	0.66	-0.1	0.73	-5.8	0.48	-6.1	0.15	-2.5	0.18	
		9 months: mean change[b]	156	-0.7	0.60	-2.1	0.72	+0.8	0.72	-4.0	0.17	-0.8	0.18	-0.6	0.21	
		12 months: mean change[b]	139	-4.0	0.86	-8.0	0.33	-1.1	0.94	-6.6	0.74	-2.3	0.18	-3.4	0.38	
	TMZ	0 months: mean score	202	66.4 (22.0)		76.5 (24.0)		79.7 (18.6)		82.3 (20.7)		72.8 (31.6)		72.4 (28.9)		
		3 months: mean change[b]	126	-1.6		-4.3		-2.8		-3.3		0.0		+1.7		
		6 months: mean change[b]	107	+0.9		-2.5		-3.5		-2.8		-0.3		+3.1		
		9 months: mean change[b]	78	-1.7		-3.1		-1.4		-8.2		-5.7		+2.9		
		12 months: mean change[b]	58	-1.2		-2.9		-0.6		-4.8		-7.6		+1.2		

Abbreviations

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core quality of life questionnaire, SD = standard deviation, TMZ = temozolomide, TTFields = tumour treating fields.

Notes

a = Scales ranging from 0 to 100, with a higher score representing a higher level of functioning. Differences of ≥10 points were classified as the minimum clinically meaningful change in any HRQoL scale/item. The minus sign in mean change score indicates a deterioration of the quality of life scale/item within a trial arm; the plus sign in mean change score indicates an improvement of the quality of life scale/item within a trial arm; between-group changes from baseline were not reported, only p-values were provided.
b = Mean change from baseline score

Table 13. Efficacy results: health-related quality of life – symptom scales in patients with ndGBM

Reference Study name	Intervention Comparator		Sample size analysed	EORTC QLQ-BN20[a]						Overall risk of bias
				Pain	p-value	Itchy skin	p-value	Weakness of legs	p-value	
ndGBM										
Taphoorn et al 2018 [32] EF-14 – secondary analysis	TTFields + TMZ	0 months: mean score (SD)	437	10.0 (16.8)	0.41	14.8 (24.8)	0.39	15.8 (25.5)	0.61	High
		3 months: mean change from baseline score	305	-1.8	0.11	-10.4 [b.c]	0.005	-0.5	0.42	
		6 months: mean change from baseline score	244	-1.7	0.65	-8.1 [b]	0.008	+1.2	0.79	
		9 months: mean change from baseline score	156	+0.6	0.13	-5.3 [b]	0.04	+2.5	0.38	
		12 months: mean change from baseline score	139	-3.3	0.63	-4.6	0.66	-1.3	0.70	
	TMZ	0 months: mean score	202	11.2 (17.4)		16.7 (24.5)		14.6 (25.7)		
		3 months: mean change from baseline score	126	-3.6		+2.3		-4.3		
		6 months: mean change from baseline score	107	+0.2		+4.2		-0.3		
		9 months: mean change from baseline score	78	-3.9		+5.2		-3.2		
		12 months: mean change from baseline score	58	-4.8		+1.9		-4.8		

Abbreviations
EORTC QLQ-BN20 = European Organisation for Research and Treatment of Cancer Quality of life questionnaire for brain cancer, SD = standard deviation, TMZ = temozolomide, TTFields = tumour treating fields.

Notes

a = Scales ranging from 0 to 100, with a higher score representing a lower level of symptoms. Differences of ≥10 points were classified as the minimum clinically meaningful change in any HRQoL scale/item. The minus sign in mean change score indicates a deterioration of the quality of life symptom scale (i.e. increase in symptoms) within a trial arm; the plus sign in mean change score indicates an improvement of the quality of life symptom scale (i.e. decrease in symptoms) within a trial arm; between-group changes from baseline were not reported, only p-values were provided.

b = Statistically significant change in symptom scale ($p<0.05$).

c = Clinically relevant change in symptom scale (≥10-point change from baseline).

Table 14. Efficacy results: health-related quality of life – functioning scales in patients with GBM at all recurrences

Reference Study name	Intervention Comparator	Sample size analysed	EORTC QLQ-C30 (change from baseline to 3 months) Global Health Scale	p-value	Cognitive functioning	p-value	Emotional functioning	p-value	Physical functioning	p-value	Role functioning	p-value	Social functioning	p-value	Overall risk of bias
GBM at all recurrences															
Stupp et al 2012 [34] EF-11	TTFields	36	Figure only: no difference	NR	Figure only: in favour	NR	Figure only: in favour	NR	Figure only: not in favour	NR	Figure only: in favour	NR	Figure only: no difference	NR	High
	Chemotherapy	27	Figure only: no difference		Figure only: not in favour		Figure only: not in favour		Figure only: in favour		Figure only: not in favour		Figure only: no difference		

Abbreviations

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core quality of life questionnaire, NR = not reported, TTFields = tumour treating fields.

7.2.4.3 Compliance and drop-out due to non-adherence

ndGBM

In the EF-14 trial 75% of the patients with ndGBM used the TTFields device for at least 75% of the time during the first 3 months of treatment. [31] Only 2 patients (0.4%) in the TTFields plus TMZ arm and none of the patients in the TMZ arm dropped out due to non-adherence during the study (***Table 15***).

GBM at first recurrence

For the population GBM at first recurrence no data was reported on the outcomes compliance and drop-out due to non-adherence.

GBM at all recurrences

Median compliance with TTFields treatment in patients with GBM at all recurrences was 86% (range 41-98%) of the time in each treatment month. [34] In the TTFields group 27 patients (23%) discontinued treatment early, often within a few days, due to non-compliance or inability to handle the device. In the chemotherapy group one patient (0.9%) dropped out due to non-adherence (***Table 15***).

Table 15. Efficacy results: compliance and drop-out due to non-adherence

Reference **Study name**	**Intervention** **Comparator**	**Sample size analysed**	**Compliance (%)**	**Drop-out due to non-adherence (n (%))**
ndGBM				
Stupp et al 2017 [31] EF-14	TTFields + TMZ	466	75% of the patients used device ≥75% of the time during first 3 months of treatment	2 (0.4%)
	TMZ	229	NR	0 (0%)
GBM at all recurrences				
Stupp et al 2012 [34] EF-11	TTFields	120	median 86% (range 41-98%) of the time in each treatment month	27 (22.5%)
	Chemotherapy	117	NR	1 (0.9%)

Abbreviations
NR = not reported, TMZ = temozolomide, TTFields = tumour treating fields.

7.2.5 Findings effectiveness

7.2.5.1 Overall survival and progression-free survival

ndGBM

Liu et al 2020 did not find statistically significant survival benefits for patients with ndGBM treated with TTFields plus TMZ compared with patients treated with TMZ alone. [36] The hazard ratio for death was 0.93 (95% CI 0.58-1.47; p=0.741), median survival in months was not reported (***Table 16***; ***Table 19***).

In the retrospective cohort study of Chen et al 2022 statistically significant results were reported for overall survival and progression-free survival in favour of the patients with ndGBM treated with TTFields plus TMZ compared with patients treated with TMZ alone. [37] After applying propensity score-matching and inverse probability treatment weighting analysis, treatment with TTFields plus TMZ was associated with a statistically significant lower risk of death with a hazard ratio for death of 0.19 (95% CI 0.09-0.41; p<0.001) and a statistically significant lower risk of progression with a hazard ratio for progression of 0.35 (95% CI 0.14-0.91; p=0.031) compared with treatment with TMZ alone (***Table 16***; ***Table 19***). Median survival in months was not reported.

GBM at first recurrence

For the population GBM at first recurrence no comparative non-randomised studies were found.

GBM at all recurrences

For the population GBM at all recurrences no comparative non-randomised studies were found.

Table 16. Effectiveness results: overall survival and progression-free survival

Reference	Intervention / Comparator	Sample size	Follow-up (median; range)	OS HR (95% CI)	p-value	PFS HR (95% CI)	p-value	Overall risk of bias
ndGBM								
Liu et al 2020 [36]	TTFields + TMZ	37	42 (29-58) months	0.93 (0.58-1.47)	0.741	NR	NR	Serious
	TMZ	67						
Chen et al 2022 [37]	TTFields + TMZ	49	NR	0.19 (0.09-0.41)	<0.001	0.35 (0.14-0.91)	0.031	Serious
	TMZ	87						

Abbreviations

CI = confidence interval, ndGBM = newly diagnosed glioblastoma, NR = not reported, OS = overall survival, PFS = progression-free survival, TMZ = temozolomide, TTFields = tumour treating fields.

7.2.5.2 Health-related quality of life

ndGBM

For the ndGBM population no data was reported on the outcome HRQoL.

GBM at first recurrence

For the population GBM at first recurrence no comparative non-randomised studies were found.

GBM at all recurrences

For the population GBM at all recurrences no comparative non-randomised studies were found.

7.2.5.3 Compliance and drop-out due to non-adherence

ndGBM

Chen et al 2022 assessed patient compliance monthly as the average percentage of each day the TTFields treatment was conducted out of each 24 hour period. [37] The median compliance was 87% in patients with ndGBM treated with TTFields during the recommended therapy period (***Table 17***); the median duration of TTfields therapy was 10.6 months. Liu et al 2020 did not report compliance data. In the retrospective cohort studies no information was reported on the outcome drop-out due to non-adherence.

GBM at first recurrence

For the population GBM at first recurrence no comparative non-randomised studies were found.

GBM at all recurrences

For the population GBM at all recurrences no comparative non-randomised studies were found.

Table 17. Effectiveness results: compliance and drop-out due to non-adherence

Reference	Intervention Comparator	Sample size	Compliance (%)	Drop-out due to non-adherence (n (%))
ndGBM				
Chen et al 2022 [37]	TTFields + TMZ	49	median 87%	NR
	TMZ	87	NR	NR

Abbreviations
NR = not reported, TMZ = temozolomide, TTFields = tumour treating fields.

7.2.6 Findings safety

7.2.6.1 Serious adverse events

The serious adverse events in the included RCTs were graded as severe adverse events, grade 3-4. Grade 3 adverse events are defined as: severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily living. [38] Grade 4 adverse events are defined as: life-threatening consequences; urgent intervention indicated. [38]

ndGBM

In the EF-14 trial in patients with ndGBM, the addition of TTFields to TMZ was not associated with severe adverse events (p=0.58). At least one severe adverse event grade 3-4 was reported in 48% of the patients treated with TTFields plus TMZ and in 44% of the patients treated with TMZ alone (***Table 18***; ***Table 19***). [31]

The included non-randomised comparative studies did not report data for the ndGBM population on the outcome serious adverse events.

GBM at first recurrence

In 49% of the patients with GBM at first recurrence treated with TTFields plus chemotherapy at least one grade 3-4 severe adverse event occurred compared with 33% of the patients in the chemotherapy arm (***Table 18*;**

Table 20). [33] No p-value was reported. The authors highlighted that TTFields showed no grade 3-4 device-related severe adverse events.

GBM at all recurrences

In patients with GBM at all recurrences a statistically significant (p=0.022) lower occurrence of at least one severe adverse event grade 3-4 was reported in patients in the TTFields arm (6%) versus the chemotherapy arm (16%) (***Table 18***; ***Table 21***). [34] Typical systemic side-effects of chemotherapy were not observed in the patients treated with TTFields.

Table 18. Safety results: serious adverse events

Reference **Study name**	**Intervention** **Comparator**	**Sample size analysed (safety)**	**≥1 severe adverse event (grade 3-4)**	**p-value**	**Overall risk of bias**
ndGBM					
Stupp et al 2017 [31] EF-14	TTFields + TMZ	456	48%	0.58	Some concerns
	TMZ	229	44%		
GBM at first recurrence					
Kesari et al 2017 [33] EF-14 – post-hoc analysis	TTFields + chemotherapy	144	49%	NR	High
	Chemotherapy	60	33%		
GBM at all recurrences					
Stupp et al 2012 [34] EF-11	TTFields	116	6%	0.022	Some concerns
	Chemotherapy	91	16%		

Abbreviations
ndGBM = newly diagnosed glioblastoma, NR = not reported, TMZ = temozolomide, TTFields = tumour treating fields.

7.2.6.2 Drop-out due to serious adverse events

None of the included studies reported data on the outcome drop-out due to serious adverse events.

7.2.7 GRADE Summary of Findings Table

Table 19. GRADE summary of findings table for patients with ndGBM

Population: Patients with ndGBM
Intervention: TTFields + TMZ
Comparison: TMZ

Outcomes	Absolute effect (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	TMZ	**TTFields + TMZ**			
Efficacy					
Overall survival measured from randomisation follow-up: median 40 months	median 16.0 months [a] (14.0-18.4)	median 20.9 months [a] (19.3-22.7)	**HR 0.63** (0.53 to 0.76) [death]	695 (1 RCT [31])	⨁⨁⨁◯ Moderate [b]
Progression-free survival measured from randomisation follow-up: median 40 months	median 4.0 months [c] (3.8-4.4)	median 6.7 months [c] (6.1-8.1)	**HR 0.63** (0.52 to 0.76) [progression]	695 (1 RCT [31])	⨁⨁⨁◯ Moderate [b]
HRQoL assessed with: EORTC QLQ-C30 & EORTC QLQ-BN20 follow-up: 12 months	No satistically significant or clinically relevant differences for HRQoL domains global health scale, cognitive, emotional, physical, role and social functioning, and symptom scales pain and weakness of legs. Statistically significant difference in favour of TMZ for itchy skin at 3, 6, 9 months; only clinically relevant at 3 months			197 [d] (1 RCT [32])	⨁⨁◯◯ Low [e]
Effectiveness					
Overall survivial follow-up: median 42 months	NR	NR	**HR 0.93** (0.58 to 1.47) [death]	104 (1 non-randomised study [36])	⨁◯◯◯ Very low [e,f]
Overall survival follow-up: NR	NR	NR	**HR 0.19** (0.09 to 0.41) [death]	136 (1 non-randomised study [37])	⨁⨁◯◯ Low [e]
Progression-free survival follow-up: NR	NR	NR	**HR 0.35** (0.14 to 0.91) [progression]	136 (1 non-randomised study [37])	⨁⨁◯◯ Low [e]
HRQoL		NR			
Safety					
Serious adverse events (≥1 severe adverse event (grade 3-4)) follow-up: median 40 months	441 per 1.000[g]	481 per 1.000 (401 to 573)	**RR 1.09** (0.91 to 1.30) [h]	685 (1 RCT [31])	⨁⨁◯◯ Low [b,f]
Drop-out due to serious adverse events		NR			

Abbreviations
CI = confidence interval, EORTC = European Organisation for Research and Treatment of Cancer, HR = hazard Ratio, NR = not reported, RCT = randomised controlled trial, RR = risk ratio, QLQ-C30 = core quality of life questionnaire, QLQ-BN20 = quality of life questionnaire for brain cancer.
Notes
a = Median overall survival in months as reported per study arm in the RCT.
b = Certainty of evidence downgraded due to serious risk of bias (see ***Chapter 7.2.3.1***).
c = Median progression-free survival in months as reported per study arm in the RCT.
d = Sample size at 12 months for the HRQoL assessment. The sample size in the intervention group declined from 437 at 0 months to 139 at 12 months. The sample size in the comparator group declined from 202 at 0 months to 58 at 12 months.
e = Certainty of evidence downgraded due to very serious risk of bias (see ***Chapter 7.2.3.2***).
f = Certainty of evidence downgraded due to serious imprecision (wide 95% confidence interval including the null effect).
g = Based on the risk in the control group of this RCT.
h = Not reported in the article; calculated by the researchers of this HTA.

Table 20. GRADE summary of findings table for patients with GBM at first recurrence

Population: Patients with GBM at first recurrence
Intervention: TTFields + chemotherapy
Comparison: Chemotherapy

Outcomes	Absolute effect (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Chemotherapy	**TTFields + chemotherapy**			
Efficacy					
Overall survival measured from first progression follow-up: median 13 months	median 9.2 months [a] (NR)	median 11.8 months [a] (NR)	**HR 0.70** (0.48 to 1.00) [death] [b]	204 (1 RCT – post-hoc analysis [33])	⨁⨁◯◯ Low [c]
Progression-free survival	NR				
HRQoL	NR				
Effectiveness					
NR					
Safety					
Serious adverse events (≥1 severe adverse event (grade 3-4)) follow-up: median 13 months	333 per 1.000 [d]	493 per 1.000 (332 to 730)	**RR 1.48** (0.997 to 2.19) [e]	204 (1 RCT – post-hoc analysis [33])	⨁◯◯◯ Very low [c,f]
Drop-out due to serious adverse events		NR			

Abbreviations
CI = confidence interval, HR = hazard Ratio, NR = not reported, RCT = randomised controlled trial, RR = risk ratio.
Notes
a = Median overall survival in months as reported per study arm in the RCT.
b = p-value is 0.049.
c = Certainty of evidence downgraded due to very serious risk of bias (see ***Chapter 7.2.3.1***).
d = Based on the risk in the control group of this RCT.
e = Not reported in the article; calculated by the researchers of this HTA.
f = Certainty of evidence downgraded due to serious imprecision (wide 95% confidence interval including the null effect).

Table 21. GRADE summary of findings table for patients with GBM at all recurrences

Population: Patients with GBM at all recurrences
Intervention: TTFields
Comparison: Chemotherapy

Outcomes	Absolute effect (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Chemotherapy	**TTFields**			
Efficacy					
Overall survival (ITT population) measured from randomisation follow-up: median 39 months	median 6.0 months [a] (NR)	median 6.6 months [a] (NR)	**HR 0.86** (0.66 to 1.12) [death]	237 (1 RCT [34])	⨁⨁◯◯ Low [b,c]
Overall survival (mITT population) measured from randomisation follow-up: NR	median 6.0 months [a] (NR)	median 7.8 months [a] (NR)	**HR 0.69** (0.52 to 0.92) [death]	210 (1 RCT – post-hoc analysis [35])	⨁⨁◯◯ Low [d]
Progression-free survival (ITT population) measured from randomisation follow-up: median 39 months	median 2.1 months [e] (NR)	median 2.2 months [e] (NR)	**HR 0.81** (0.60 to 1.09) [progression]	237 (1 RCT [34])	⨁⨁◯◯ Low [b,c]
HRQoL assessed with: EORTC QLQ-C30 follow-up: 3 months	There seemed no difference for the HRQoL domains global health scale and social functioning; the domains cognitive, emotional and role functioning seemed in favour of TTFields; the domain physical functioning seemed in favour of chemotherapy[f]			63 (1 RCT [34])	⨁◯◯◯ Very low [d,f]
Effectiveness					
NR					
Safety					
Serious adverse events (≥1 severe adverse event (grade 3-4)) follow-up: median 39 months	165 per 1.000 [g]	61 per 1.000 (26 to 142)	**RR 0.37** (0.16 to 0.86) [h]	207 (1 RCT [34])	⨁⨁⨁◯ Moderate [b]
Drop-out due to serious adverse events		NR			

Abbreviations
CI = confidence interval, EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer core quality of life questionnaire, HR = hazard Ratio, ITT = intention-to-treat, mITT = modified intention-to-treat, NR = not reported, RCT = randomised controlled trial, RR = risk ratio.

Notes
a = Median overall survival in months as reported per study arm in the RCT.
b = Certainty of evidence downgraded due to serious risk of bias (see ***Chapter 7.2.3.1***)
c = Certainty of evidence downgraded due to serious imprecision (wide 95% confidence interval including the null effect)
d = Certainty of evidence downgraded due to very serious risk of bias (see ***Chapter 7.2.3.1***)
e = Median progression-free survival in months as reported per study arm in the RCT.
f = Data in figure only, no quantitative data reported, no p-values reported.
g = Based on the risk in the control group of this RCT.
h = Not reported in the article; calculated by the researchers of this HTA.

8 Costs, cost-effectiveness and budget impact

Summary statement costs, cost-effectiveness and budget impact

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Three cost-effectiveness studies on TTFields for patients with ndGBM were included: two from a French healthcare payer perspective using different model structures (a partitioned survival model and a Markov model) and one from a US healthcare payer perspective. While the first 2 studies concluded that TTFields were not cost-effective, the latter concluded the opposite, under local cost-effectiveness thresholds. The results of the cost-effectiveness analyses conducted for Switzerland showed that treatment with TTFields plus TMZ resulted in higher costs, but also additional benefit compared with treatment only with TMZ, with an ICER of CHF 555,465 per QALY gained for the ndGBM population. Scenario analyses and sensitivity analyses showed the robustness of the results. At a hypothetical willingness to pay threshold of CHF 200,000, none of the PSA iterations would be considered cost-effective. An ICER of CHF 6,552,337 per QALY gained was estimated for the rGBM at first recurrence population as the additional benefit was smaller and the estimated costs higher. Finally, according to the budget impact analysis, reimbursement of TTFields in Switzerland can result in additional expenses of CHF 31 million over the span of 5 years, for the ndGBM population. Expanding reimbursement to the rGBM population is associated to a budget impact of CHF 49 million over the span of 5 years.

8.1 Methodology costs, cost-effectiveness and budget impact

8.1.1 Databases and search strategy

The cost-effectiveness systematic literature search followed the principles of the systematic literature search for the clinical evaluation outlined in ***Chapter 7.1***, with reviews performed in duplicate by 2 independent researchers and Rayyan software (Rayyan Systems Inc., USA) was used for the selection of the articles. PubMed (MEDLINE), Cochrane library, and Embase.com databases were searched for peer-reviewed scientific literature. In addition, the economic databases Cost Effectiveness Analysis (CEA) Registry, Tufts Medical Centre Cost-Effectiveness Analysis Registry, and National Health Service Economic Evaluation Database (NHS EED), were searched. The searches were built using the PICO framework (see ***Chapter 5***). In PubMed (MEDLINE), Cochrane library, and Embase.com, the search terms of the efficacy, effectiveness, and safety literature search were combined with cost-effectiveness search terms. The details of the search strategy are presented in ***Appendix 14.2.***

All articles retrieved from PubMed (MEDLINE), Cochrane library, Embase.com, NHS EED and the CEA registry databases, and relevant references were reviewed in a similar manner to the systematic approach described in ***Chapter 7.1.2***, including firstly screening title and abstract and subsequently full-text screening. In the first step, the major topics of the articles were assessed based on relevancy and articles that seemed to contain relevant data for the HTA objectives were selected for the full-text screening. Subsequently, the articles screened in full-text were assessed for inclusion based on pre-specified eligibility criteria defined in the HTA protocol (***Table 22***). The process of selection and inclusion and exclusion of articles was recorded in Microsoft Excel and Endnote version 20. The selection procedure applied during the full-text screening phase is reported in a PRISMA flow diagram and primary reasons for exclusion per excluded article are listed in a table, like in the clinical evaluation approach.

8.1.2 Study selection

The inclusion and exclusion criteria that were applied during the selection processes are listed in ***Table 22.***

Table 22. Inclusion and exclusion criteria for economic evaluation studies

	Inclusion	**Exclusion**
Period publication	All	None
Language of publication	English, French, German, Italian	All other languages
Country of study	Worldwide	None
Study design/type	Economic evaluations - Cost-utility analysis - Cost-effectiveness analysis - Cost-minimisation analysis - Cost-benefit analysis Budget impact analysis Costing studies	- Resource use measurement - Non-pertinent publication types (e.g. letter, comment, expert opinion, editorial, abstract only, conference presentation, book chapter)
Study population	- Adult patients with ndGBM (WHO Grade IV) after tumour resection/biopsy and radiochemotherapy - Adult patients with rGBM (WHO Grade IV) after tumour resection/biopsy and radiochemotherapy	- Animal studies - Patients age <18 years - Patients without tumour resection and radiochemotherapy - Mixed study population of patients with ndGBM and rGBM, without stratification of the results
Study intervention	TTFields either in combination with maintenance chemotherapy/second-line	TTFields in addition to other therapies than maintenance

	systemic therapy (i.e. physician's choice chemotherapy) or alone	chemotherapy/second-line systemic therapy (i.e. physician's choice chemo-therapy)
Study comparator	Maintenance chemotherapy/second-line systemic therapy (i.e. physician's choice chemotherapy)	- Other comparators - No comparator
Study outcomes	- Cost-effectiveness a. Healthcare costs (total and incremental) b. Incremental cost-effectiveness ratio (ICER) and incremental and total costs, quality-adjusted life years (QALYs) and life years (LYs) - Budget impact	- Inadequate data (e.g. missing relevant data or unexplained important errors in patient flow) - Studies with duplicate data (study with the largest sample size or most extended follow-up was included for data extraction of the results) - Unclear follow-up duration - Other outcomes

Abbreviations

HRQoL = health-related quality of life, LYs = life years, ndGBM = newly diagnosed glioblastoma, QALY = quality-adjusted life years, RCTs = randomised controlled trials, rGBM = recurrent glioblastoma, TTFields = tumour treating fields, WHO = World Health Organisation.

8.1.3 Assessment of quality of evidence

The identified studies from the systematic literature search for cost-effectiveness were subjected to a critical appraisal using the Consolidated health Economic Evaluation Reporting Standards (CHEERs) [39] checklist and the Consensus Health Economic Criteria (CHEC) [40] checklist as recommended by the current guidelines. [41] The CHEERS and CHEC are 24-item and 19-item checklists, respectively, with clear questions about the economic evaluation that gives insight into the general quality of the study.

8.1.4 Methodology data extraction, analysis and synthesis of health economic data

The following relevant data from the included articles found in the peer-reviewed literature were summarised using a data-extraction spreadsheet in Excel:

- First author, year
- Country
- Type of study
- Study perspective
- Study funding
- Study population
    - Sample size (n)
    - Mean age and age range
    - Proportion men/women
- Intervention
- Comparator
- Outcome measures
- Total/Incremental costs and QALYs
- Model used (Yes/No)
    - Type of model
    - Health states
    - Time horizon
- Primary sources for the resource use/cost inputs
- Primary sources for the HRQoL inputs

Data synthesis was done using descriptive comparisons of the study question, methods, and results. Summary tables present key information described above. The incremental cost-effectiveness ratios are presented and the reliability (internal validity) and relevance (generalisability) of the estimates was

explored applying the appraisal tools described in ***Chapter 7.2.2.2.*** The analytical approaches used in the studies will be compared and their robustness will be discussed.

8.1.5 Economic model

8.1.5.1 Target population

The population encompasses adult patients with GBM grade 4 after tumour resection/biopsy and radiochemotherapy. The primary analysis included ndGBM patients only. The secondary analysis included rGBM patients at first recurrence.

8.1.5.2 Setting and location

The analysis was performed from the Swiss healthcare setting. This means that, where possible, relevant input parameters were based on data from Switzerland.

8.1.5.3 Study perspective

The analysis was performed from a healthcare payer perspective. Costs of healthcare services covered by the Swiss mandatory health insurance were analysed, irrespective of the actual payer (mandatory health insurer, other social insurer, government (federal government, cantons, communities), out-of-pocket). The analysis did not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs, since the healthcare payer perspective is adopted in Switzerland.

8.1.5.4 Intervention(s)

The intervention is:

- For the primary analysis: TTFields plus TMZ maintenance chemotherapy or TTFields alone after maintenance chemotherapy has stopped;
- For the secondary analysis: TTFields alone or in combination with second-line systemic therapy (i.e. physician’s choice chemotherapy)

8.1.5.5 Comparator(s)

The comparison for the intervention is:

- For the primary analysis: TMZ maintenance chemotherapy
- For the secondary analysis: second-line systemic therapy (i.e. physician’s choice chemotherapy)

8.1.5.6 Time horizon

A lifetime time horizon was used in the base case analysis. In a lifetime time horizon, the model runs until all patients in the model have died. In this specific model, virtually all patients have died after 10 years.

8.1.5.7 Discount rate

In the base case analysis, costs and effects were discounted at 3.0%.

8.1.5.8 Health outcomes

Health outcomes are reported in average life years (LYs) and average quality-adjusted life years (QALYs).

8.1.5.9 Currency, price data, and conversion

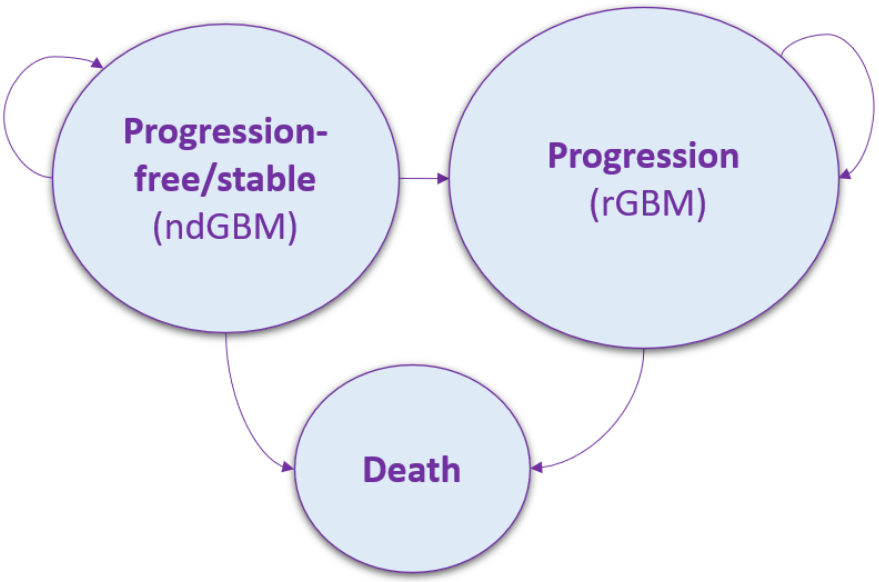
Costs are reported in Swiss Franc (CHF) adjusted for inflation to current price levels using inflation rates from the Swiss Federal Statistical Office, which were accessed from the Organisation for Economic Co-operation and Development (OECD) website (https://data.oecd.org, accessed May 15th, 2023).

8.1.5.10 Model structure

The model is a partitioned survival model, with 3 states: progression-free/stable disease, progression and dead. In the base case analysis, treatment is stopped when patients progress to the progression state. The model was programmed in MS Excel.

The conceptual model is illustrated in ***Figure 6.*** In the model, all patients start in the progression-free/stable health state. Once patients experience progression, they transition to the progression health state. After progression, patients cannot return to the progression-free/stable health state. Death is possible in both progression-free/stable and progression health states. A one-month cycle length was used.

Figure 6. Model structure TTFields in GBM



Abbreviations
ndGBM = newly diagnosed glioblastoma, rGBM = recurrent glioblastoma

8.1.5.11 Input parameters

The model input parameters on clinical outcomes and utilities were informed from the results of the data extraction of the systematic literature search of efficacy, effectiveness, and safety and pragmatic literature searches. Costs were based on databases available at the Federal Office of Public Health (FOPH) or pragmatic literature searches. Clinical experts were consulted whenever data was unavailable from the literature. An overview of the input parameters is provided in ***Table 23***. ***Appendix 14.3*** provides an extended table of input parameters, including information on values used in one-way sensitivity analyses (OWSA) and distributions used in probabilistic sensitivity analysis (PSA).

Table 23. Input parameters cost-effectiveness model

Input parameter	Base case value	Source
Baseline characteristics		
Baseline age in years, mean (sd)	56 (5.6)	Stupp et al 2017 [31]
Proportion of women, %	31	Stupp et al 2017 [31]
Survival (coefficients log-normal model)		
TMZ OS Mean log, mean (sd)	2.7671 (0.062)	Estimated using Stupp et al 2017 [31]
TMZ OS sd log, mean (sd)	0.9095 (0.0497)	Estimated using Stupp et al 2017 [31]
TMZ PFS Meanlog, mean (sd)	1.5784 (0.0679)	Estimated using Stupp et al 2017 [31]
TMZ PFS sd log, mean (sd)	0.9641 (0.0549)	Estimated using Stupp et al 2017 [31]
TTF OS Mean log, mean (sd)	2.9880 (0.0421)	Estimated using Stupp et al 2017 [31]
TTF OS sd log, mean (sd)	0.8489 (0.0345)	Estimated using Stupp et al 2017 [31]
TTF PFS Mean log, mean (sd)	1.9072 (0.0453)	Estimated using Stupp et al 2017 [31]
TTF PFS sd log, mean (sd)	0.9034 (0.0366)	Estimated using Stupp et al 2017 [31]
Utilities [a]		
Progression-free/stable, mean (sd)	0.874 (0.087)	Palmer et al 2022 [42]
Progression, mean (sd)	0.724 (0.072)	Palmer et al 2022 [42]
Costs		
TTFields rental cost per month	CHF 14,320.00	FOPH, MiGeL
TMZ acquisition cost per 28 days, mean (sd) [b]	CHF 557.21 (55.72)	FOPH, Präparate Spezialitätenliste
Progression-free/stable disease costs per month, mean (sd)	CHF 1,095.71 (111.37)	Calculated from Panje et al 2019 [43]
Progressed disease costs per month, mean (sd)	CHF 2,975.89 (302.48)	Panje et al 2019 [43]

Abbreviations

FOPH = Federal Office of Public Health, MiGeL = Mittel und Gegenständeliste, OS = overall survival, PFS = progression-free survival, sd = standard deviation, TMZ = temozolomide, TTFields = tumour treating fields.

Notes

a = Utility values were assumed to be dependent on health state only. The intervention was not assumed to affect utility values directly. b = Based on 150mg/m^2 dose, assumed body surface area of 2.0 m^2.

8.1.5.12 Baseline characteristics

The baseline age and men/women distribution were based on the population characteristics from the TTFields arm in the EF-14 trial. [31] Baseline age was 56.0 years and 31% of patients were women. Standard deviation of age was not provided in the EF-14 trial, and was assumed 10% of the mean.

8.1.5.13 Efficacy inputs

The efficacy inputs were derived from the systematic review of efficacy, effectiveness, and safety. In particular, for the primary research question, the efficacy inputs were derived from the Kaplan-Meier curves from the EF-14 trial, using the method described by Hoyle and Henley 2011. [31,44] Progression-free survival (PFS) and overall survival (OS) were estimated using survival functions, using the flexsurvreg package in R. [45] The following standard parametric distributions were used: exponential, Weibull, log-normal, log-logistic, Gompertz and Gamma distributions. The log-logistic and Gompertz distributions were tested but did not converge. The log-normal distribution showed the best goodness of fit (based on Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC)) for OS and PFS for TTFields plus TMZ arm and PFS for the TMZ only arm (***Table 24***). The best fit for TMZ OS was the Gamma distribution, closely followed by the log-normal distribution. To keep the same parametric distribution for each arm and for both PFS and OS, the log-normal distribution was used for TMZ OS as well. [46] ***Table 24*** provides the AIC and BIC for the different distributions. The Kaplan-Meier curves and estimated survival curves are presented in ***Appendix 0***.

Table 24. Goodness of fit statistics for different parametric distributions ndGBM model

	TMZ OS		TMZ PFS		TTF + TMZ OS		TTF + TMZ PFS	
Distribution	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	1389.697	1393.148	963.7015	967.1264	2659.00	2663.13	2020.046	2024.155
Weibull	1367.262	1374.164	965.6886	972.5385	2592.61	2600.872	2005.321	2013.539
Log-normal	1372.455	1379.358	913.8116	920.6615	2583.816	2592.079	1948.597	1956.815
Gamma	1364.415	1371.317	963.6613	970.5112	2584.095	2592.358	1992.148	2000.366

Abbreviations

AIC = Akaike's Information Criterion, BIC = Bayesian Information Criterion, OS = overall survival, PFS = progression-free survival, TMZ = temozolomide, TTF = tumour treating fields.

For the secondary research question, only OS for rGBM at first recurrence was modelled and the efficacy inputs were derived from the Kaplan-Meier curves reported in the post-hoc analyses by Kesari et al 2017. [33] The same parametric survival functions used for the primary research question were tested. The Gamma distribution showed to have the best fit for the TMZ only arm, and the log-normal distribution had the best fit for the TTFields plus TMZ arm. [46] To keep the same parametric distribution for each arm, the log-normal distribution was used for TMZ OS as well, since the log-normal distribution more closely resembled the outcomes of the Kesari et al 2017 analysis than the Gamma distribution.

8.1.5.14 Adverse events

The EF-14 trial reported no significant differences in systemic adverse events rates between the treatment arms.[47] Therefore, adverse events were not included in the base case analyses.

8.1.5.15 Background mortality

The background mortality was based on the most recent Swiss lifetables derived from the Human Mortality Database. [48] Given the high mortality in the GBM population relative to the general population, background mortality had no effect on the outcomes.

8.1.5.16 Utilities

Of the 3 cost-effectiveness studies that were identified in the systematic review of cost-effectiveness, only the Guzauskas et al 2019 study used utility values to calculate QALYs in their base case analysis. [49] This study used utility values for GBM from Garside et al 2007, which were developed for a cost-utility analysis of carmustine implants and TMZ in a population of GBM patients in the UK. [50] The utility values were not obtained in a population of patients with GBM, but instead were obtained from GBM health state ratings of 36 members of the NHS Value of Health Panel. In the Guzauskas et al 2019 model the base case utility value was 0.85 for stable disease and 0.73 for progressed disease.[49]

In addition to the cost-effectiveness studies, 2 publications were found that reported on quality of life estimates for GBM patients using TTFields. [42,51] However, both publications were published as abstracts only, implying that description of methodology is limited and the publications were not subject to extensive peer review before publication. Both publications reported on the same study, with Palmer et al 2022 presenting the final estimates. [42] Palmer et al 2022 obtained utility values using the EQ-5D in a sample of 2,815 newly diagnosed and progressed GBM patients using TTFields. The French tariff was used to calculate utility scores. The final analysis included 1,036 responses. The mean utility value for patients prior to disease progression was 0.874 and after disease progression 0.724. Palmer et al 2022 did not report standard deviations of utility values; standard deviations were assumed 10% of the mean.

Using utilities obtained from EQ-5D data measured directly in patients is preferred over alternative methods to determine quality of life. [52] Although the study by Palmer et al 2022 was not published as a scientific manuscript, the methodology used for obtaining utility data is preferred over the methodology used to inform utility values in the Garside et al 2007 study. [50] Utility values described by Palmer et al 2022 were therefore used in the base case analysis. The utility estimates from Garside et al 2007 were used in a scenario analysis.

The utility decrement from progression as observed by Palmer et al 2022 was 0.150 (0.874 - 0.724 = 0.150). This utility decrement might underestimate the impact of progression. Therefore, in addition to the base case analysis, a scenario analysis was performed in which a larger utility decrement from progression was modelled. For this scenario, the utility decrement from progression as observed by Palmer et al 2022 was doubled. In this scenario analysis, the utility value for progressed disease was set at 0.574 (the utility value prior to progression was unchanged in this scenario, and equal to 0.874).

Disutilities from adverse events were not available in the literature. In the Guzauskas et al 2019 model, disutilities were not included because of the low frequency of adverse events in both treatment arms.[49] In the EF-14 trial in patients with ndGBM, the addition of TTFields to TMZ was not associated with severe adverse events. [47] Palmer et al 2022 did not report on adverse events disutilities. [42] Any disutility from adverse events might already be incorporated in the reported mean health state utility values for stable disease and progressed disease. Adverse events disutilities were not included in the base case analysis, but were included in a scenario analysis, to assess the impact of excluding adverse events disutilities. Since no information on adverse events disutilities was available, a disutility value of 0.10 was assumed. This value was multiplied by the occurrence of severe adverse events in both treatment arms (i.e. 48% for TTFields plus TMZ and 44% for TMZ alone).

8.1.5.17 Resource use and costs

8.1.5.17.1 Monthly rental costs of TTFields

TTFields are rented per month. The monthly rental costs of TTFields were based on the cost of reimbursement for self-application listed in the Swiss Devices and Items List (Mittel und Gegenständeliste) – MiGEL provided by the FOPH. The price represents a cost cap (Höchstvergütungsbetrag). In the base case analysis, TTFields was only used while patients were in the progression-free state.

8.1.5.17.2 Acquisition costs of TMZ

Standard maintenance TMZ dose was 150-200 mg/m^2 per day for 5 days, every 28 days for 6 treatment cycles. [47] The average dose during the EF-14 trial was not reported. Therefore, a dose of 150 m/m^2 was

used in line with Guzauskas et al 2019. [49] The average body surface area (BSA) of patients was not reported in the trial either. To calculate the TMZ dose, a BSA of 2.0 m^2 was assumed. [53]

The acquisition costs of TMZ were based on the Präparate Spezialitätenliste by the FOPH. The *Publikumspreis* including *Mehrwertsteuer* was used to determine the costs of TMZ. TMZ is available in different dosages and packages and available from different suppliers. The least costly option was used in the analyses.

After progression, patients can receive different treatments, including bevacizumab, with different treatment costs. Acquisition costs of TMZ were therefore only used for progression-free patients. Treatment costs after progression are included in the healthcare cost estimates (section 8.1.5.17.3).

8.1.5.17.3 Healthcare costs

Of the 3 cost-effectiveness studies that were identified in the systematic review of cost-effectiveness, only the Bernard-Arnoux et al 2016 study provides a detailed breakdown of healthcare costs. [54] Apart from costs associated to treatment (TMZ and TTFields), costs components were assumed equal across treatment arms. Costs were calculated for the Swiss setting in 2022 values using purchasing power parities (OECD data [55]) and inflation correction (World Bank data [56]). ***Table 25*** provides a breakdown of monthly costs used in the model used for progression-free/stable disease. The model uses a cost of CHF 2,427.50 per month for patients in the progression-free/stable disease state.

Table 25. Breakdown of monthly costs inputs reported in Bernard-Arnoux et al 2016 [54] converted to 2022 CHF progression-free/stable disease, excluding treatment costs

Type of cost	Monthly costs (CHF)
Hospital stays (including long-term care, home care, and rehabilitation)	1,795.27
Transports	499.13
Imaging	79.23
Medical visits	39.61
Biologic exams	14.26
Total costs	2,427.50

Abbreviations
CHF = Swiss franc.

Bernard-Arnoux et al 2016 used the same monthly costs for the progressed state, except that patients in the progressed state also receive chemotherapy after recurrence. [54] Conversed to 2022 Swiss values,

this was associated to an additional monthly cost of CHF 617.97. This additional cost was accrued from month 1 onwards in the TMZ alone arm and from month 3 onwards in the TTFields plus TMZ arm.

The study by Bernard-Arnoux et al 2016 provided healthcare costs but did not provide details on the healthcare utilisation of patients. [54] Therefore, Swiss unit costs could not be applied to the observed (French) healthcare utilisation. Instead, costs were converted using purchasing power parities. Using these converted costs would potentially introduce a deviation from actual Swiss costs, since purchasing power parities do not adequately reflect international price differences of healthcare specifically.

In addition to the cost-effectiveness studies, Panje et al 2019 reported costs for rGBM patients in 8 Swiss centers. [43] The study provided the sources from which unit costs were derived but did not provide details on the healthcare utilisation of patients. Therefore, current unit costs could not be attached to the observed healthcare utilisation. Instead, inflation correction was used to update the estimates to current prices. Monthly estimates were derived by assuming the life expectancy of patients was similar to patients in the comparator arm in the EF-11 trial (i.e. 6 months). [34] Monthly costs for rGBM patients were hence estimated to be CHF 2,975.89, including chemotherapy treatment costs. The study only provided costs for the recurrent population; costs for progression-free patients were not provided. Bernard-Arnoux et al 2016 found that 1) treatment-related costs for rGBM patients were approximately 46% of total costs and 2) non-treatment costs for progression-free patients were approximately 80% of costs for progressed patients. [54] Therefore, total costs were reduced by 46% to exclude treatment-related costs (assuming the same proportion as observed by Bernard-Arnoux et al 2016). Non-treatment cost for progression-free patients were assumed to be 80% of costs for progressed patients (again, assuming the same proportion as observed by Bernard-Arnoux et al 2016). As such, monthly costs for progression-free GBM patients were estimated to be CHF 1,095.71.

Although different assumptions had to be made, the estimates from Panje et al 2019 were considered most appropriate, since the study was performed in the Swiss setting. [43] The estimates from Bernard-Arnoux et al 2016 were used in a scenario analysis. [54]

Since Swiss specific data was limited, 2 clinical experts were asked to estimate the healthcare use of GBM patients. The estimate provided were multiplied with Swiss-specific unit costs. Monthly costs for were estimated to be CHF 1,451.18 CHF 2,646.42, for progression-free and progressed patients, respectively. Since the data was obtained through expert elicitation, these estimates were considered to be of inferior quality compared with published studies using observed data. The estimates from the expert elicitation exercise were therefore used in a scenario analysis. The assumption that non-treatment costs for progression-free patients were approximately 80% of costs for progressed patients was tested in a scenario analysis; in which costs in the progression-free state were 25% of costs for progressed patients. Finally, a scenario analysis was run in which the difference in health state costs

between progression-free and progressed patients was increased. In this scenario, the health state costs of progressed patients were multiplied with a factor of 1.5. This scenario would account for the possibility that the costs based on the Panje et al 2022 paper were underestimating actual costs, for instance because expensive treatments in the progressed state were not correctly accounted for.

8.1.5.18 Analytical methods

8.1.5.18.1 Base case analysis

The base case analysis was conducted using the settings for the input parameters and assumptions as described in the previous chapters. The secondary analysis was modelled with discount rate 3% and other base case assumptions.

8.1.5.18.2 Scenario analyses

Structural uncertainty was explored in several scenario analyses. ***Table 26*** shows the different scenario analyses, compared with the base case analysis.

Table 26. Scenario analyses

	Base case	Scenario
Model settings		
Discount rate	3%	- 0% (i.e. no discounting) - 5%
Time horizon	Lifetime (10 years)	- 2 years - 5 years
Population		
Population	ndGBM patients	rGBM patients
Health state transitions		
Parametric survival functions	Log-normal distribution	- Exponential distribution - Weibull distribution - Gamma distribution
Utilities		
Health state utility values	Palmer et al 2022 [42]	- Garside et al 2007 [50] - Utility decrement from progression doubled
Adverse events disutilities	Excluded	Included
Costs		

Health state costs	Panje et al 2019 [43]	- Bernard-Arnoux et al 2016 [54] - Clinical expert input - Healthcare costs progression-free state 25% of healthcare costs in progression state - Healthcare costs progression state multiplied by factor 1.5

Abbreviations
ndGBM = new diagnosed glioblastoma, rGBM = recurrent glioblastoma.

8.1.5.18.3 One-way sensitivity analyses (OWSA)

Parameter uncertainty was first tested using OWSA where model parameters are systematically and independently varied over range of 10% increase/decrease of the parameter value used in the base case. Uncertainty around survival estimates was based on the 95% confidence interval of the estimates. The incremental cost-effectiveness ratio (ICER) was recorded at the upper and lower limits to produce a tornado diagram. The OWSA were run for the ndGBM population. ***Appendix 14.3*** provides the values used in one-way sensitivity analyses (OWSA).

In addition, the effect of hypothetical price discounts on the monthly rental costs of TTFields was assessed.

8.1.5.18.4 Probabilistic sensitivity analysis (PSA)

Joint parameter uncertainty was explored through PSA where all parameters to which probability distributions are assigned are varied jointly. The distributions that were applied in the PSA are provided in ***Appendix 14.3***. Cholesky decomposition matrices were used to account for dependencies of survival coefficients. Monte Carlo simulations were performed (with 1,000 iterations), and the results were recorded. Results were plotted on the cost-effectiveness plane (CE plane). From these results, a cost-effectiveness acceptability curve (CEAC) was produced. The PSA was run for the ndGBM population.

8.1.5.19 Model assumptions

Table 27 lists the assumptions used in the cost-effectiveness model.

Table 27. Model assumptions

Model component	Assumption
Patient characteristics	Model baseline patient characteristics are equal to the EF-14 trial
Utility values	French utilities (calculated by Palmer et al 2022) apply to the Swiss situation
Utility values	No additional disutilities from adverse events were modeled
Costs	Cost were assumed equal across treatment arms, except treatment costs

Costs	Life expectancy for patients in the Panje et al 2019 [43] study was assumed equal to that of patients in the comparator arm
Costs	Costs for progression-free patients is equal to 80% of costs for progressed patients

8.1.6 Budget Impact Analysis

A budget impact model (BI) was developed according to the ISPOR principles of good practice guidelines. [57] The analysis was performed from the Swiss healthcare payer perspective.

The BI was assessed separately for the ndGBM and rGBM population. The time horizon of the BI model was restricted to 5 years. Per-patient costs of both treatment strategies (i.e. TTFields plus TMZ and TMZ alone) were informed by the cost-effectiveness model. These costs included all costs from the healthcare payer perspective (i.e. treatment acquisition costs and healthcare costs) but did not include indirect costs due to informal care or productivity losses and additional non-medical costs for patients, such as travel costs. Treatment acquisition costs and healthcare costs (as described for the cost-effectiveness model) were multiplied by the anticipated numbers of people using TTFields in Switzerland. Data from Tarifpool SASIS AG supplied by the FOPH showed that on average 30 patients were using TTFields at any given time in the year in Switzerland. Swiss general population growth was used to predict the growth in patient numbers in later years. No additional growth in patient numbers was modelled. Since TTFields plus TMZ postponed progression and death, and progression-free and progression health states are affected with deviating healthcare costs, this affected the budget impact as well. Time to progression and death were used to estimate the numbers of patients that had experienced progression.

The BI was calculated as the difference between the total 5-year costs of both treatment strategies for the total population. The costs were reported in Swiss Francs (CHF).

For the ndGBM population, scenario analyses with 20% increase/decrease of patient numbers were run to show the impact of patient numbers on the budget impact estimates. In addition, a scenario analysis was added in which a yearly growth in the number of patients was modelled (10% per annum), in addition to the growth in patient numbers due to general population growth.

8.2 Results costs, cost-effectiveness and budget impact

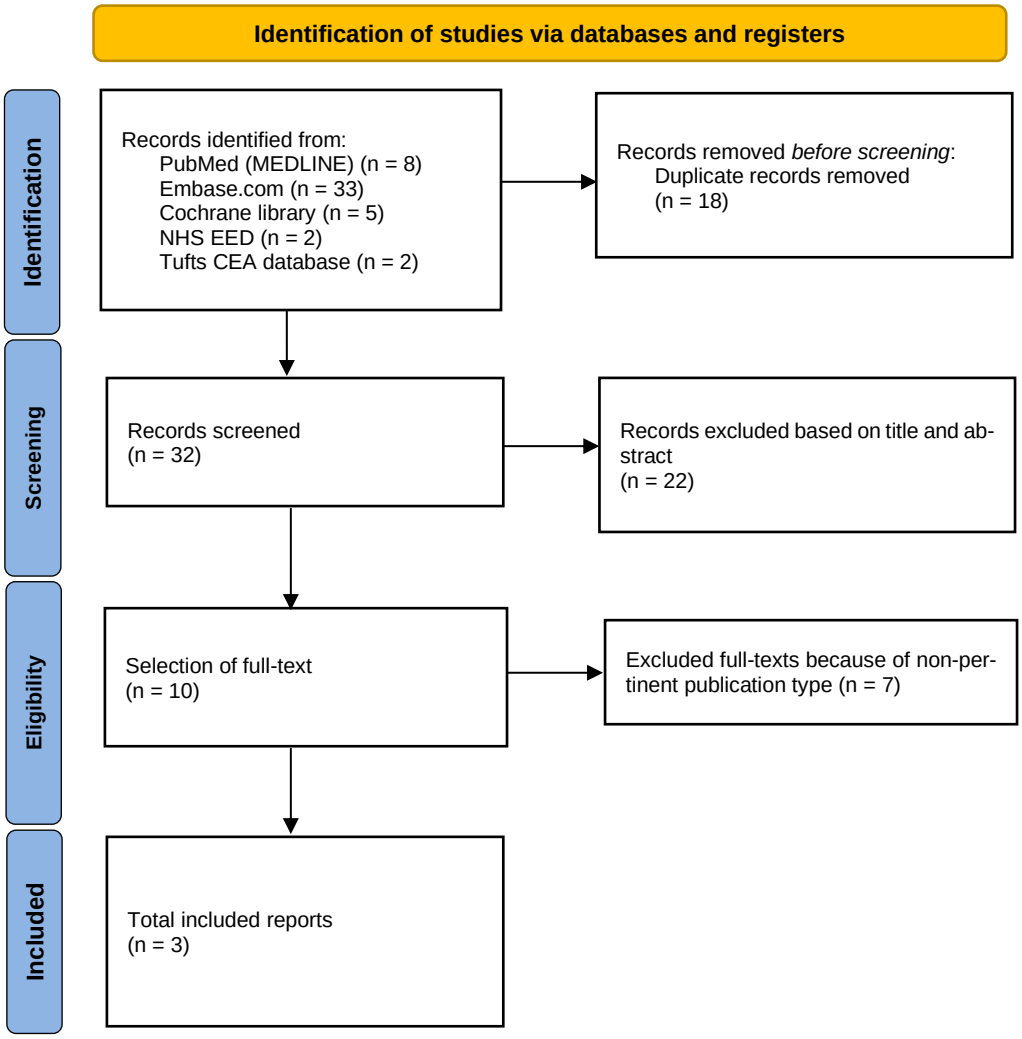
8.2.1 PRISMA flow diagram

In total, 32 unique records were identified in PubMed (MEDLINE) and Embase.com, as well as the NHS EED and other sources, on TTFields for patients with GBM for the cost-effectiveness search. Of those, 22 records were excluded based on their title and abstract, yielding 10 studies to be screened in full-text. After applying the inclusion and exclusion criteria, 7 studies were excluded, leaving the following 3 studies included:

1. 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. Journal of Medical Economics. 2019 Oct 3;22(10):1006–13.
2. 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 Aug;18(8):1129–36.
3. 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 Jul;143(3):605–11.

The reason for excluding the 7 other studies was the publication type (i.e. 5 conference abstracts and 2 editorials). The PRISMA flow diagram is shown in ***Figure 7***.

Figure 7. PRISMA flow diagram [24] of the cost-effectiveness systematic literature search



Abbreviations

NHS EED = National Health Service Economic Evaluation Database, CEA = Cost-Effectiveness Analysis.

Notes

Search date 4 April 2023.

8.2.2 Study characteristics and quality assessment of included studies

In ***Table 28*** the study characteristics of the 3 included cost-effectiveness studies are presented. These studies were all model based studies, using data from the EF-14 trial. [47] The study by Guzauskas et al 2019 was a cost-effectiveness analysis in the United States, using a partitioned survival model. The authors supplemented the EF-14 trial data with data from an observational study to estimate long-term effects. [49] The study of Bernard-Arnoux et al 2016 was a cost-effectiveness study in France, using a Markov model. Connock et al 2019 build upon the work of Bernard-Arnoux et al 2016, but used a partitioned survival model instead of a Markov model. [54,58] Bernard-Arnoux et al 2016 and Connock et al 2019 used the EF-14 trial data only. [54,58] Guzauskas et al 2019 reported utilities, QALYs and a cost per QALY gained estimate. [49] Bernard-Arnoux et al 2016 did not report utilities or QALYs. [54] Connock et al 2019 reported a cost per QALY gained estimate in a scenario analysis. [58]

The completed CHEC and CHEERS checklists for these 3 studies are presented in ***Table 29*** and ***Table 30***. [40,59] All 3 studies performed well on both checklists, however the studies of Bernard-Arnoux et al 2016 and Connock et al 2019 did not report the health outcomes as QALYs therefore also did not report utility values on health states which were elements of interest for this HTA. [54,58] The CHEERS checklist also showed that all 3 studies included adequately almost all information of interest. However the study of Guzauskas et al 2019 was the most detailed one among the three included studies. [49]

Table 28. Overview study characteristics of cost-effectiveness studies

Reference	Country	Patient population	Intervention	Comparator	Type of economic evaluation	Perspective	Time horizon	Discount rates[a]	Outcomes
Guzauskas et al 2019 [49]	USA	A cohort of patients starting treatment at age 56 years, consistent with the EF-14 trial population	TTFields therapy in addition to standard maintenance TMZ	Standard maintenance TMZ alone	Modelling study (Partitioned survival model)	US Payer Perspective	Lifetime horizon	3%	• QALYs • LYG • Costs • ICER (Costs/QALY)
Bernard-Arnoux et al 2016 [54]	France	A cohort of patients with the same characteristics as those in the EF-14 trial	TTFields therapy in addition to standard maintenance TMZ	Standard maintenance TMZ alone	Modelling study (Markov model)	French National Health Insurance	Lifetime horizon	4%	• LYG • Costs ICER (Costs/LYG)
Connock et al 2019 [58]	France	A cohort of patients with the same characteristics as those in the EF-14 trial	TTFields therapy in addition to standard maintenance TMZ	Standard maintenance TMZ alone	Modelling study (Partitioned survival model)	French National Health Insurance	20-year horizon	4%	• LYG • Costs ICER (Costs/LYG)

Abbreviations

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year, LYG = life years gained, TMZ = temozolomide, TTFields = tumour treating fields.

Notes

a = Applied to both costs and outcomes.

Table 29. Critical appraisal of cost-effectiveness studies using the CHEC checklist [60]

			Guzauskas et al 2019 [49]	Bernard-Arnoux et al 2016 [54]	Connock et al 2019 [58]
Study design	**1**	Is the study population clearly described?	✓	✓	✓
	2	Are competing alternatives clearly described?	✓	✓	✓
	3	Is a well-defined research question posed in answerable form?	✓	✓	✓
	4	Is the economic study design appropriate to the stated objective?	✓	✓	✓
	5	Is the chosen time horizon appropriate in order to include relevant costs and consequences?	✓	✓	✓
	6	Is the actual perspective chosen appropriate?	✓	✓	✓
Costs	**7**	Are all important and relevant costs for each alternative identified?	✓	✓	✓
	8	Are all costs measured appropriately in physical units?	✓	✓	✓
	9	Are costs valued appropriately?	✓	✓	✓
Outcomes	**10**	Are all important and relevant outcomes for each alternative identified?	✓	X, no QALYs	X, no QALYs
	11	Are all outcomes measured appropriately?	✓	✓	✓
	12	Are outcomes valued appropriately?	✓	✓	✓
Interpretation and results	**13**	Is an incremental analysis of costs and outcomes of alternatives performed?	✓	✓	✓
	14	Are all future costs and outcomes discounted appropriately?	✓	✓	✓
	15	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	✓	✓	✓
	16	Do the conclusions follow from the data reported?	✓	✓	✓
	17	Does the study discuss the generalisability of the results to other settings and patient/client groups?	X	X	✓
	18	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	X	✓	✓
	19	Are ethical and distributional issues discussed appropriately?	X	X	X

Abbreviations

QALY = quality-adjusted life year.

Table 30. Critical appraisal of cost-effectiveness studies using the CHEERS Checklist 2022 [59]

	Item	Guidance for Reporting	Reported in section		
			Guzauskas et al 2019 [49]	Bernard-Arnoux et al 2016 [54]	Connock et al 2019 [58]
TITLE					
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	(Y) Title, Page 2	(Y) Title, Page 1	(Y) Title, Page 1
ABSTRACT					
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	(Y) Abstract, Page 2	(Y) Abstract, Page 1	(Y) Abstract, Page 1
INTRODUCTION					
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	(Y) Introduction, Fourth paragraph	(Y) Introduction, Third paragraph	(Y) Introduction, Third paragraph until the end
METHODS					
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	(Y) Methods, 'Approach' section	(Y) Methods, 'Model, Population, and Treatment' section	(Y) Methods, 'Model, population, treatment and effectiveness' section
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	(Y) Methods, 'Approach' and 'Clinical trial results' section	(Y) Methods, 'Model, Population, and Treatment' section	(Y) Methods, 'Model, population, treatment and effectiveness' section
Setting and location	6	Provide relevant contextual information that may influence findings.	(Y) Methods, 'Approach' section and 'Epidemiology data' section	(Y) Methods, 'Direct Costs and Effectiveness' section	(Y) Methods, 'Costs' section
Comparators	7	Describe the interventions or strategies being compared and why chosen.	(Y) Methods, 'Approach' section	(Y) Methods, 'Model, Population, and Treatment' section	(Y) Methods, 'Model, population, treatment and effectiveness' section
Perspective	8	State the perspective(s) adopted by the study and why chosen.	(Y) Methods, 'Approach'	(Y) Methods, 'Direct Costs and	(Y) Methods, 'Costs' section

			section	Effectiveness' section	
Time horizon	9	State the time horizon for the study and why appropriate.	(P) Methods, 'Approach' section	(P) Methods, 'Model, Population, and Treatment' section	(P) Methods, 'Model, population, treatment and effectiveness' section
Discount rate	10	Report the discount rate(s) and reason chosen.	(Y) Methods, 'Approach' section	(Y) Methods, 'Analysis' section	(Y) Methods, 'Analysis' section
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	(Y) Methods, 'Analysis' section	(Y) Methods, 'Direct Costs and Effectiveness' section	(P) Methods, 'Analysis' section
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	(Y) Methods	(Y) Methods	(Y) Methods
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	(Y) Methods, 'Quality-of-life parameters' section	(NA)	(NA)
Measurement and valuation of resources and costs	14	Describe how costs were valued.	(Y) Methods, 'Treatment parameters in the model' and 'Adverse event parameters in model' section	(Y) Methods, 'Direct Costs and Effectiveness' section	(Y) Methods, 'Costs' section
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	(P) Methods, 'Treatment parameters in the model' section	(Y) Methods, 'Direct Costs and Effectiveness' section	(Y) Methods, 'Costs' section
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	(Y) Methods, 'Approach' section	(Y) Methods, 'Model, Population, and Treatment' section and Figure 1	(Y) Methods, 'Model, population, treatment and effectiveness' section
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any	(Y) Methods, 'Survival curves' section and Figure 1	(Y) Methods	(Y) Methods

		model used.			
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	(NA)	(NA)	(NA)
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	(NA)	(NA)	(NA)
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	(Y) Methods, 'Analysis' section	(Y) Methods, 'Analysis' section	(Y) Methods, 'Analysis' section
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	(NA)	(NA)	(NA)
RESULTS					
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	(Y) Methods, Table 2	(P) Methods, Table 2	(P) SM7
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	(Y) Results, Second to Fourth paragraph and Table 3	(Y) Results, 'Base case' section	(Y) Results, First to Third paragraph
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	(Y) Results, Fourth and Fifth paragraph and Figure 2	(Y) Results, 'Sensitivity Analysis' section and Figures 2, 3 and 4	(Y) Results, Fourth to last paragraph and Figure 1
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	(NA)	(NA)	(NA)
DISCUSSION					
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	(Y) Discussion	(Y) Discussion	(Y) Discussion
Other relevant information					
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	(Y) End of manuscript	(Y) End of manuscript	(N) Not reported
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	(Y) End of manuscript	(Y) End of manuscript	(Y) End of manuscript

Abbreviations
N = not reported, NA= not applicable, P= partially reported, SM= supplemental material, Y= yes.

8.2.2.1 Evidence table

Table 31 presents the cost-effectiveness outcomes of the 3 included studies. All 3 studies found that TTFields plus TMZ was more effective than TMZ alone, but at higher costs. Even though the studies largely used the same underlying data, the 3 studies found different effects sizes, due to modelling choices. Guzauskas et al 2019 estimated an ICER of $197,336 per QALY gained ($150,452 per LY gained). [49] Bernard-Arnoux et al 2016 estimated an ICER of €596,411 per LY gained. [54] Connock et al 2019 estimated an ICER of €667,173 per QALY gained (€510,273 per LY gained). [58] The differences between the estimates are mainly driven by different techniques and underlying sources used to model survival. In particular, Bernard-Arnoux et al 2016 used a Markov model, whereas Guzauskas et al 2019 and Connock et al 2019 used partitioned survival models. Whereas Bernard-Arnoux et al 2016 and Connock et al 2019 solely used information from the EF-14 trial, Guzauskas et al 2019 used two additional sources to model survival (epidemiological data from the USA for years 5-10 and years 10-15 from Porter et al 2011 and age adjusted general population estimates from year 16 onwards). [61] Connock et al 2019 argues that the approach employed by Guzauskas et al 2019 overestimates survival gains and underestimates costs, resulting in an underestimation of the ICER value. [58] For reasons of comparison, in a scenario analysis Connock et al 2019 replicated the approach used by Guzauskas et al 2019, resulting in an ICER of 347,801 per QALY gained, much closer to the estimate from Guzauskas et al 2019. Another source for discrepancies in model outcomes between Guzauskas et al 2019 and the two French studies were differences in supportive care costs used in the model.

Table 31. Overview outcomes of cost-effectiveness studies

Reference	Costs			QALYs			LYs			ICER (cost/QALY gained)	ICER (cost/LY gained)
	TTFields plus TMZ	TMZ only	Incre-mental	TTFields plus TMZ	TMZ only	Incremen-tal	TTFields plus TMZ	TMZ only	Incremental		
Guzauskas et al 2019 [49]	$231,620[a]	$42,983[a]	$188,637[a]	2.57[a]	1.61[a]	0.96[a]	3.34[a]	1.84[a]	1.25[a]	$197,336[a]	$150,452[a]
Bernard-Arnoux et al 2016 [54]	€243,141[b]	€57,665[b]	€185,476[b] €180,431[a]	-	-	-	1.84[b]	1.5[b]	0.34[b] 0.3[a]	-	€596,411[a]
Connock et al 2019 [58]	€326,543[a]	€67,848[a]	€258,695[a]	-	-	-	2.35[a]	1.84[a]	0.507[a]	€667,173[a,c]	€510,273[a]

Abbreviations

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year, LY = life year, TMZ = temozolomide, TTFields = tumour treating fields.

Notes

a = Discounted. b = Undiscounted. c = Cost per QALY estimates were provided in a scenario analysis; (incremental) QALY estimates were not reported

8.2.3 Findings costs

As described in ***Chapter 8.1.5.17.3***, the included studies did not provide relevant cost data for the Swiss cost-effectiveness and budget impact models. The study by Panje et al 2019 [43] was used as a basis to inform the healthcare costs for the progression-free and progression states. In addition, costs from the Bernard-Arnoux et al 2016 [54] and costs estimated on the basis of clinical expert input were used in scenario analysis of the ndGBM cost-effectiveness model. For the latter, Swiss databases and publicly available sources were used for the unit cost inputs. Clinical experts provided information on which cost categories to be included. ***Table 32*** provides the unit costs used for the scenario analysis based on the volumes obtained from clinical expert opinion.

Table 32. Unit costs used for the scenario analysis based on clinical expert opinion

Cost inputs	Swiss unit cost (CHF)	Source
Outpatient visits [a]	109.08 CHF per visit	TARMED [62]
Hospitalisation	1258.36 CHF per night	Swiss DRG codes [63]
Laboratory	1372.00 CHF per exam	TARMED [62]
MRI	658.15 CHF per MRI	MR-Zentrum Thun [64]
Physiotherapy	48.00 CHF per visit	TARMED [62]
General practitioner	102.73 CHF per visit	TARMED [62]

Abbreviations

CHF = Swiss franc, MRI = magnetic resonance imaging.

Notes

a = Includes neurologist, neuro-oncologist, radiation oncologist, neurosurgeon, psycho-oncologist, specialised nurse, emergency unit, and palliative care.

8.2.4 Findings cost-effectiveness

The base case analysis was conducted using the settings for the input parameters and assumptions as described in the previous sections. ***Table 33*** shows the total costs and QALYs and incremental costs and QALYs of TTFields plus to TMZ compared with TMZ only. TTFields resulted in additional life years and QALYs, at higher costs. The ICER was CHF 555,465 per QALY gained.

Table 33. Costs, QALYs, and corresponding incremental costs and QALYs (ndGBM), discounted

Treatment	Costs (CHF)	LYs	QALYs	Incremental costs (CHF)	Incremen-tal LYs	Incremen-tal QALYs	ICER Cost per QALY gained
TMZ only	57,492	1.892	1.465				
TTFields plus TMZ	208,884	2.228	1.737	151,392	0.336	0.273	555,465

Abbreviations
CHF = Swiss franc, ICER = incremental cost-effectiveness ratio, LYs = life years, QALYs = quality-adjusted life years, TMZ = temozolomide, TTFields = tumour treating fields.

The secondary analysis was conducted for rGBM at first recurrence patients. Apart from the population, all other assumptions and input parameters were equal to the base case. ***Table 34*** shows the total costs and QALYs and incremental costs and QALYs of TTFields plus TMZ compared with TMZ only. TTFields resulted in additional life years and QALYs, at higher costs. The ICER was CHF 6,552,337 per QALY gained. Compared with the base case incremental costs were higher, while incremental QALYs were much lower than in the base case.

Table 34. Costs, QALYs, and corresponding incremental costs and QALYs for secondary analysis (rGBM at first recurrence), discounted

Treatment	Costs (CHF)	LYs	QALYs	Incremen-tal costs (CHF)	Incre-mental LYs	Incre-mental QALYs	ICER Cost per QALY gained
Chemotherapy only	44,237	1.239	0.897				
TTFields plus chemotherapy	266,845	1.286	0.931	222,608	0.047	0.047	6,552,337

Abbreviations
CHF = Swiss franc, ICER = incremental cost-effectiveness ratio, LYs = life years, QALYs = quality-adjusted life years, TTFields = tumour treating fields.

8.2.4.1 Scenario analyses

Fourteen scenario analyses were run, adjusting for different parameters. The results are presented in ***Table 35***.

Since the life expectancy of patients is relatively short, discounting does not have a major impact on the results. Therefore, using alternative discount rates did not have a large impact on the ICER.

When a 2-year time horizon was used, the ICER was much higher than the base case with a lifetime time horizon. After 2 years, only a minority of patients remained in the progression-free state. As such, TTFields treatment is stopped in most patients and incremental costs are similar to the base case scenario. However, using a 2-year time horizon does neglect the incremental QALYs that are gained after 2 years, compared with the base case. Hence, the ICER for this scenario is much higher than in the base case. A time horizon of 5 years did not lead to substantial differences compared with the base case, since the vast majority of patients has died within 5 years.

Different distributions were used to best estimate the OS and PFS of patients, but the use of alternative distributions did not affect the ICERs much.

The sources for utilities and healthcare costs were also varied in the scenario analyses, but neither had a large impact on the ICER. This is explained by the fact that the alternative values were similar to the values used in the base case. When the utility decrement related to progression of disease was doubled, the ICER increased. Since survival after disease progression was higher for patients receiving TTFields plus TMZ compared to patients receiving TMZ alone, a lower utility value for this group implied a reduction in incremental QALYs, and consequently resulting a higher ICER. The effect of including disutilities from adverse events was also small.

Table 35. Outcomes scenario analyses cost-effectiveness

Treatment	Incremental costs (CHF)	Incremental QALYs	ICER Cost per QALY gained (CHF)
Base case	151,392	0.273	555,465
No discounting	154,681	0.293	528,379
5% discount rate	149,427	0.261	572,853
2-year time horizon	129,783	0.132	980,457
5-year time horizon	147,505	0.235	628,095
Exponential distribution	153,531	0.325	472,059
Weibull distribution	144,936	0.240	604,693
Gamma distribution	143,948	0.249	579,088

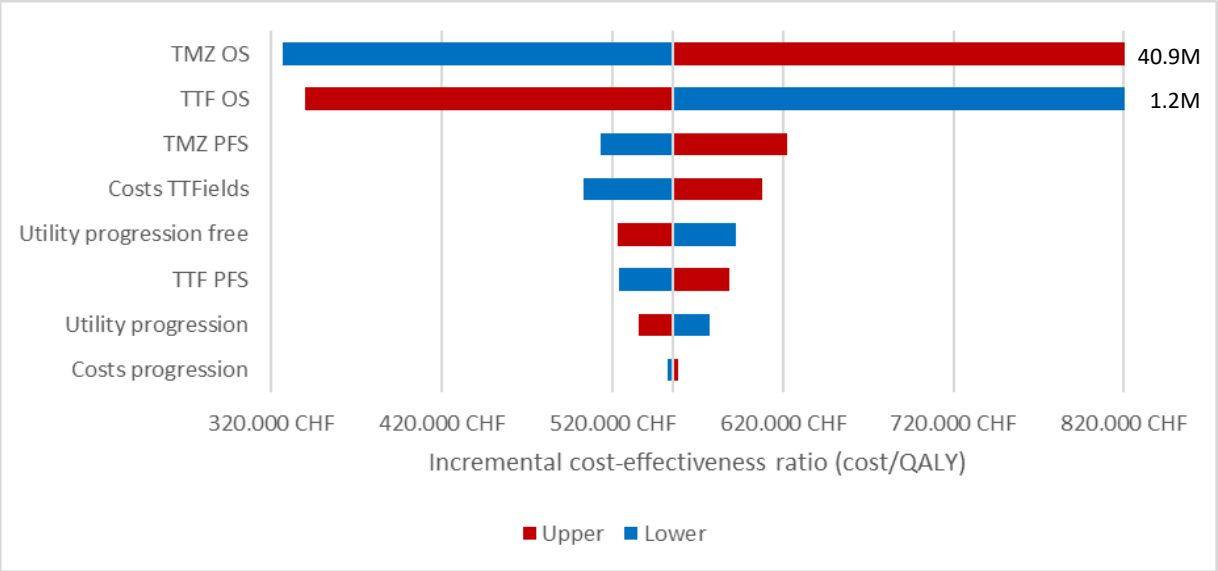
Utilities from Garside et al 2007 [65]	151,392	0.269	563,419
Utility decrement due to progression doubled	151,392	0.251	602,020
Adverse events disutilities included	151,392	0.261	580,862
Healthcare costs from Bernard-Arnoux et al 2016 [54]	159.041	0.273	583.530
Healthcare costs from expert input	151.670	0.273	556.486
Healthcare costs in progression-free state 25% of healthcare costs progression state	150,567	0.273	552,438
Healthcare costs in progression state multiplied by factor 1.5	153,901	0.273	564,670

Abbreviations
CHF = Swiss franc, QALY = quality-adjusted life year, ICER = incremental cost-effectiveness ratio.

8.2.4.2 One-way sensitivity analyses

Figure 8 presents the tornado diagram of the OWSA (for the ndGBM population). The width of the bars represents the potential range of the estimate given the potential variation in each variable with the other variables held constant. As indicated by their order (highest impact on top), the parameters with the largest impact on the ICER were the OS estimates. Using the upper value of the OS estimate for the TMZ only arm would result in a much longer survival for the TMZ only arm, and substantially reduce the survival gain from TTFields plus TMZ compared to TMZ alone. As a result, this would lead to a much higher ICER compared to the base case analysis. Similarly, using the lower value for the TTFields plus TMZ arm would also lead to much smaller survival gains from TTFields plus TMZ compared to TMZ alone, leading to a much higher ICER. The impact of monthly rental costs of TTFields, PFS estimates and utility values (both progression-free and progression states) on the ICER was much smaller. Using a lower value of acquisition costs of TTFields reduces incremental costs, resulting in a more favourable ICER (and vice versa). Since both OS and PFS were estimated to be higher for TTFields plus TMZ compared with TMZ alone, using lower utility values would result in lower QALY gains. This would lead to a less favourable ICER. The costs for the progression-free state and the acquisition costs from TMZ had a relatively small impact on effects. Alternative values for the starting age of the patients and the percentage of women did not affect the ICER at all.

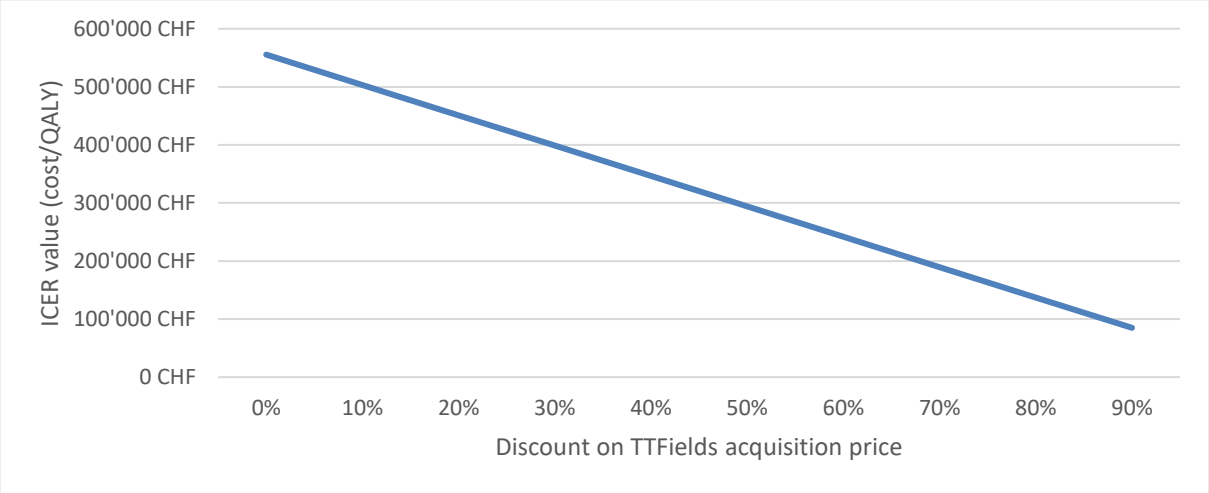
Figure 8. Tornado diagram of One-Way Sensitivity Analysis



Abbreviations

CHF = Swiss franc, OS = overall survival, PFS = progression-free survival, QALY = quality-adjusted life year, TMZ = temozolomide, TTFields = tumour treating fields.

Figure 9. Impact of TTFields price on ICER



Abbreviations

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year, CHF = Swiss franc, TTFields = tumour treating fields.

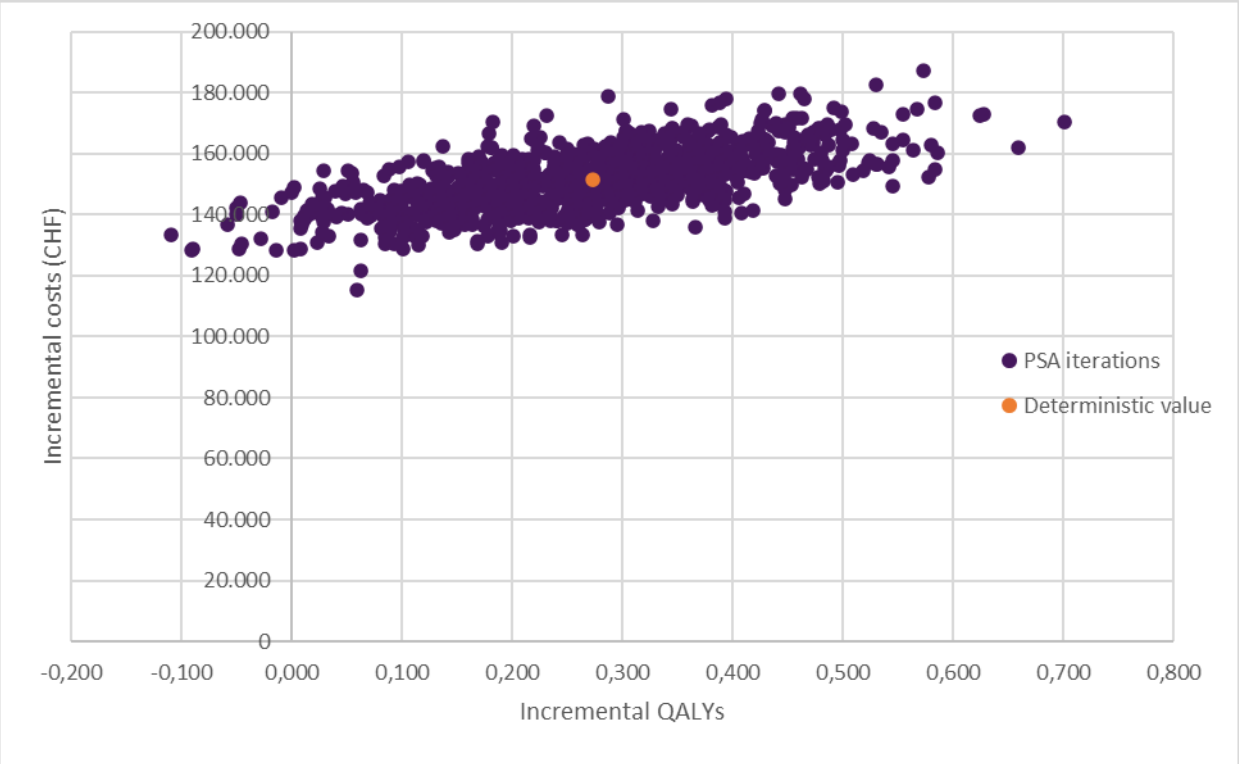
Figure 9 provides plots of the ICER values against the hypothetical discount on the acquisition price of TTFields for the ndGBM population. Higher hypothetical price discounts result in lower ICER values. At a hypothetical price, discount of 90% results in an ICER of approximately CHF 85,000 per QALY gained.

8.2.4.3 Probabilistic sensitivity analysis

Cost-effectiveness planes (CE-planes) and cost-effectiveness acceptability curves (CEAC) for the ndGBM population are presented in ***Figure 10*** and ***Figure 11***. The PSA presents findings similar to

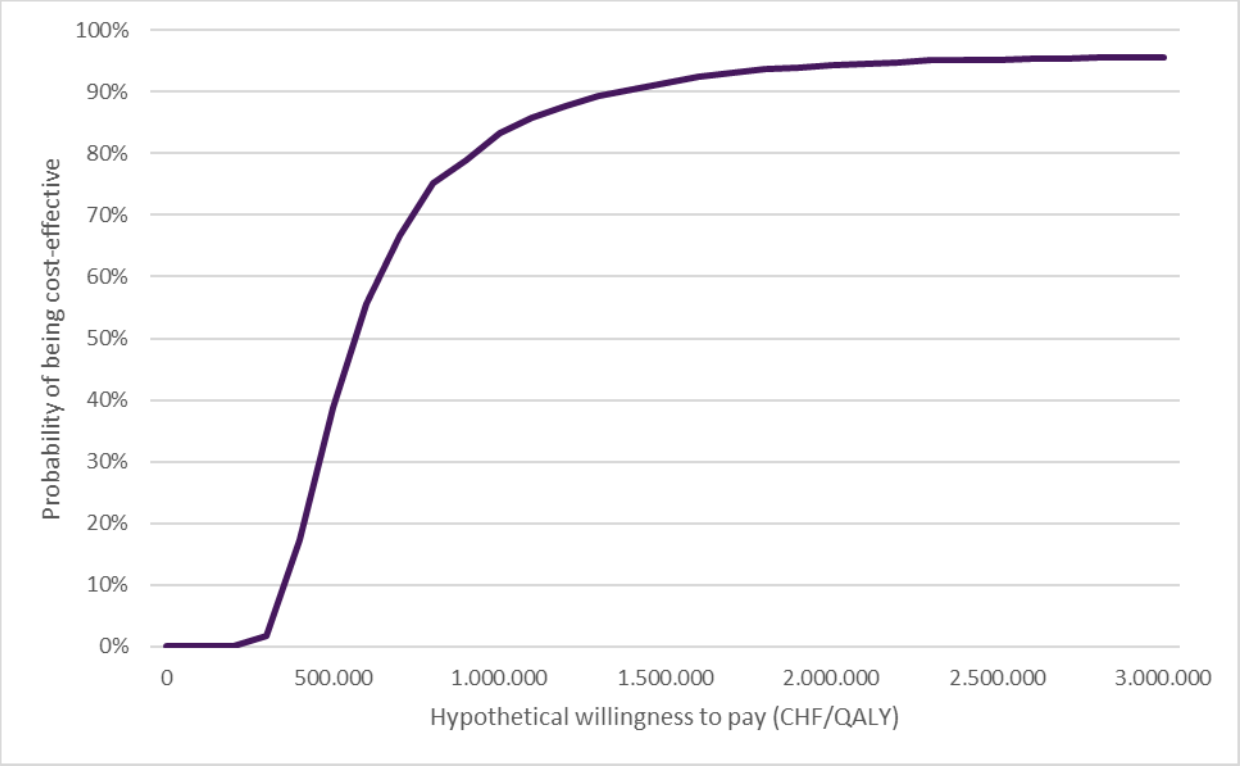
those of the deterministic analyses. All PSA iterations are located in the top section of the CE-plane, meaning the costs are higher for TTFields plus TMZ compared with TMZ alone. Virtually all iterations (99%) are in the north-east quadrant of the CE-plane, meaning that TTFields plus TMZ is more effective and more costly than TMZ alone. Reviewing the CEAC in ***Figure 11***, the probability of TTFields plus TMZ being optimal is 50% at a hypothetical willingness to pay threshold of approximately CHF 550,000. At a hypothetical willingness to pay threshold of CHF 200,000, none of the PSA iterations would be considered cost-effective.

Figure 10. Cost-effectiveness plane



Abbreviations
CHF = Swiss franc, PSA = probabillistic sensiticity analysis, QALY = quality-adjusted life year.

Figure 11. Cost-effectiveness acceptability curve



Abbreviations
CHF = Swiss franc, QALY = quality-adjusted life year.

8.2.5 Findings budget impact

The budget impact of TTFields plus TMZ for ndGBM over a period of 5 years is presented in ***Table 36***. Data provided by the FOPH showed that, in the period between December 2021 and March 2023, on average 30 patients were using TTFields. Over a 5-year period, this number slightly increased due to general population growth in the TTFields plus TMZ arm. In contrast, the number of patients in the TMZ only arm decreased, since survival for TMZ only was worse compared to TTFields plus TMZ. As a result, the yearly budget impact related to TMZ only decreased over time (yearly budget impact estimates are provided in ***Appendix 14.5***).

The reimbursement of TTFields is associated with a budget impact of CHF 30.5 million over a period of 5 years. The budget impact is mainly associated to the rental costs of TTFields. Since TTFields plus TMZ was expected to improve survival, patients receive TMZ and supportive healthcare for a longer period, compared with TMZ alone.

Scenario analyses showed that a 20% increase of number of patients would lead to a budget impact of CHF 38.2 million; an additional budget impact of 25.2% compared to the base case analysis. A 20% decrease in the number of patients would lead to a budget impact of CHF 22.6 million, a decrease in the budget of 25.8%. When a yearly additional growth in patients with 10% was modelled, this resulted in a budget impact of CHF 41.3 million.

Table 36. Budget impact analysis results (CHF) for ndGBM, 5-year period

Treatment	TTFields plus TMZ	TMZ only	Budget impact
Total costs 2024-2028	39,004,766	8,499,349	30,505,416
Costs of TMZ treatment	1,023,038	481,429	541,608
Costs of TTFields	26,291,520	0	26,291,520
Healthcare costs	11,690,208	8,017,920	3,672,288

Abbreviations
TMZ = temozolomide, TTFields = tumour treating fields.

Table 37 presents the budget impact over a period of 5 years of reimbursing TTFields plus chemotherapy to the rGBM population (secondary research question). The reimbursement of TTFields in the rGBM population is associated with a budget impact of CHF 49 million over a period of 5 years. The budget impact is predominantly associated to the rental costs of TTFields. Yearly budget impact estimates are provided in ***Appendix 14.5***.

Table 37. Budget impact analysis results (CHF) for rGBM, 5-year period

Treatment	TTFields plus chem-otherapy	Chemotherapy only	Budget impact
Total costs 2024-2028	58,529,664	9,677,952	48,851,712
Costs of TTFields	48,458,880	0	48,458,880
Healthcare costs	10,070,784	9,677,952	392,832

Abbreviations

TMZ = temozolomide, TTFields = tumour treating fields.

9 Ethical, legal, social and organisational issues

Summary statement ethical, legal, social and organisational issues

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A total of 16 articles were identified from the systematic reviews and pragmatic searches. Findings in the ethical domain address physician recommendations and patient perspectives on treatment challenges. Additionally, patient's socioeconomic status, conflicts of interest for academic centers, and the high cost of TTFields are identified as potential barriers to patient access to treatment with TTFields. Discrepancies regarding TTFields treatment in international clinical practice guidelines exist. No legal issues were identified from the systematic searches. In the social domain, it is discussed that the use of TTFields in GBM patients is heavily reliant on social support, necessitating the involvement of caregivers in both the physician's and patient's decision-making process. Compliance to the treatment of both patients and caregivers is emphasized in order for optimal benefits of the treatment to be achieved. Finally, the expanding role of oncology nurses is highlighted, as they play a pivotal role in guiding patients and caregivers through the initiation and adherence to TTFields therapy.

9.1 Methodology ethical, legal, social and organisational issues

9.1.1 Databases and search strategy

Titles of interest for the ethical, legal, social and organisational (ELSO) domains were gathered from the systematic literature searches for efficacy, effectiveness, and safety and for cost-effectiveness, and relevant websites were further searched for grey literature. The majority of articles relevant for the ELSO aspects of TTFields were derived from the systematic literature searches, while additional relevant results were identified through searches on the websites of Embase.com, Cochrane Library, Pubmed (MEDLINE), and the Erasmus University Rotterdam library.

9.1.2 Other sources

Not applicable.

9.1.3 Assessment of quality of evidence

Not applicable.

9.1.4 Methodology data extraction, analysis and synthesis of the domains ethical, legal, social and organisational issues

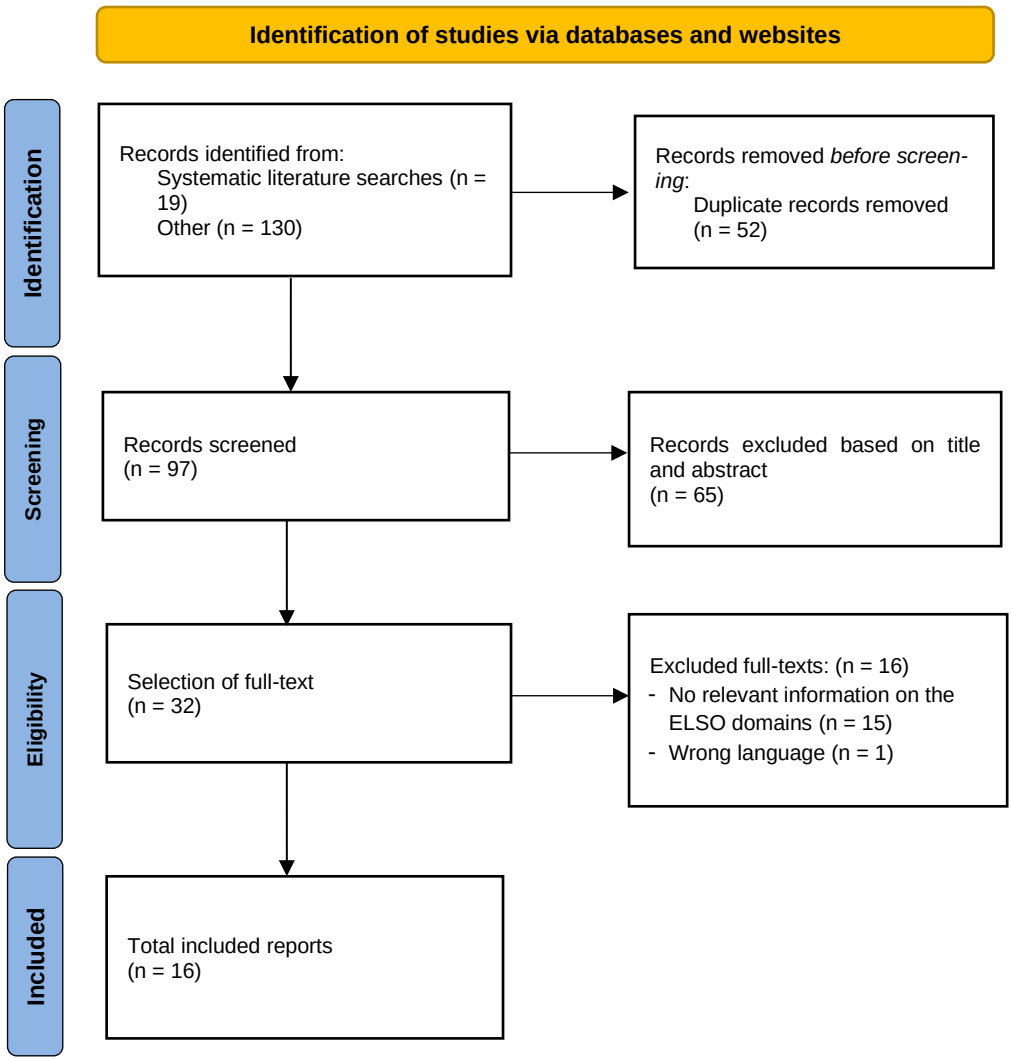
The summary of the findings related to the ELSO domains was provided narratively. No statistical tests were applied to the literature search output of these domains.

9.2 Results ethical, legal, social and organisational issues

9.2.1 PRISMA flow diagram

The results of the literature search on ELSO domains are summarised in ***Figure 12***. In total, 97 unique records were identified for the systematic literature search and other sources with the search on 28 April 2023. Of those, 65 records were excluded based on title and abstract, leaving 32 articles for review in full-text. A total of 16 articles were included in the systematic review. For most excluded articles, the reason for exclusion was that no relevant information on either the ethical, legal, social, or organisational domains was identified in the full-text review.

Figure 12. PRISMA flow diagram [24] of the literature search for the ELSO domains



Abbreviations

ELSO = ethical, legal, social and organisational.

Notes

Search date 28 April 2023.

9.2.2 Study characteristics and risk of bias of included studies

Not applicable.

9.2.3 Evidence table

Not applicable.

9.2.4 Findings ethical issues

In this section, the ethical issues concerning how factors, such as the treating physician's criteria for suggesting the device, inequalities in patients' access to treatment, health status and the pricing of the device, can play a key role in patients' access to TTFields treatment are discussed.

Physician's criteria

One of the key factors in patients' access to TTFields treatment is the treating physician's opinion, which entails both their recommendation on the treatment and their judgment on eligibility. In the study by Kumthekar et al 2021 conducted in the USA, patients were interviewed about the factors that shaped their decision to receive TTFields treatment. [66] Out of the 40 enrolled patients, 33 (82.5%) chose to receive TTFields treatment and 7 (17.5%) did not. Among the patients that received TTFields treatment, 69.7% reported that their treating physician recommended it and 6.1% reported that their physician recommended against it, while in the group that did not receive TTFields 14.3% and 28.6% were advised in favor of and against TTFields, respectively. When asked about the key factors that lead to choosing TTFields, patients mentioned the potential life extension and physician's opinion. Even though the sample size is quite limited, this study suggests that the physician plays an important role in the decision-making process of the patients.

However, the physician's role as a mediator between the treatment and the patient can limit the patient's access to TTFields. A UK study by Brodbelt et al 2018, where 3 centers were offered TTFields for trialing, observed that in one center all the oncologists refused to support the use of the device. [67] As a result, patients of this center were not approached to receive TTFields. However, the physicians' decision to reject TTFields all together might not reflect the patients' decision have they had the choice, as patients of the other 2 centers that were offered TTFields expressed that they were grateful to receive it. Physicians' reluctance to offer TTFields as a treatment option was also shown in a survey conducted by Davis 2019 at a neuro-oncology meeting that involved clinicians, scientists as well charity members in the UK. [68] The results showed that 7 out of 8 clinicians did not discuss TTFields with their patients even if the National Institute for Health and Care Excellence (NICE) guidelines did not state "Do not discuss". The most common reasons for physicians for not discussing the TTFields option with their patients were "not available", "very expensive" and "don't know enough".

Patient's perspective

In the 2019 study by Onken et al, the use of TTFields was evaluated using patient-reported outcomes. [69] The results showed that the most frequently restricting aspects of the TTFields device were the duration of the therapy for 74% percent of the patients, the size and the weight for 66% and 70% respectively, and the changing time and placing of the transducer arrays for 66%. Additionally, 63% of the patients

experienced difficulties in the exercise of their hobbies and work, 71% in taking care of their body, and 64% in sexuality and relationship matters, however approximately 70% of the patients reported that they would reuse the device if needed and would recommend it to others.

Patient's and caregiver's burden

Patients and caregivers are instructed to replace the transducer arrays, to shave the scalp, and reapply the new transducer arrays at least every 4 days. Some patients require this procedure to be done more frequently depending on their individual hair growth, sweating rate, activity levels and the weather. The used transducers and other disposable parts of the system are returned to be handled properly. [70]

Inequality in patients' access to treatment

A study by Rivera Perla et al 2022 in the USA found that socioeconomic factors also seem to affect patient access to adequate treatment for GBM. [71] In particular, the study found that disadvantaged patients (based on their neighborhood of residence) had a decreased access to treatments such as chemotherapy, radiation (that belongs to the standard of care), but also TTFields, and clinical trial participation. Identified potential reasons for these differences were high out-of-pocket costs, lack of social support and lack of transportation.

Generalisability of EF-14 trial

The EF-14 trial may not be fully representative of the ndGBM population in Switzerland. In particular, the trial only included people with ndGBM with successful completion of chemoradiotherapy and stable disease. The paper by Wick 2016 explains that there are certain subpopulations within this proportion of ndGBM patients e.g. elderly people that received shorter courses of chemoradiotherapy, patients for whom progression may not be excluded at the first or second MRI after chemoradiation, or patients who had an interruption of TMZ due to toxicity, and would be excluded. [72] Overall, decisions related to what the standard of care consists of are to be made by the guideline committees and the healthcare policy makers, and since there are relevant groups of patients who would not be able to receive TTFields with the current trial data, it is appropriate that additional studies are conducted in order to conclude that TTFields are part of the standard of care. [72]

Discrepancies in guidelines

Discrepancies regarding the TTFields treatment in clinical practice guidelines and standard operational practices (SOPs) can lead to legal implications. Lawson McLean et al 2019 reviewed TTFields guidelines for GBM in European countries and North America. [73] A large variation was reported between guidelines formulated by the National Comprehensive Cancer Network (NCCN - USA), NICE (UK),

German Society for Neurology, German Society for Haematology and Medical Oncology, EANO and European Society for Medical Oncology (ESMO), while some had not been updated while the McLean et al 2019 study was conducted since the results of the EF-14 trial. This variation potentially affects patient outcomes (in particular, OS and PFS), quality of care and safety.

In the UK, the NICE guidelines advise against TTFields, because (indirect) health economic evidence showed that TTFields are not considered a cost-effective use of NHS resources. [74] A survey conducted by Davis 2019 showed that most physicians do not discuss about TTFields during the consultation with their patients. However, the majority of non-clinicians that were included in the survey reported that TTFields should at least be discussed with all patients. [68]

Institutional barriers

In the 2022 study by Ballo et al the issue of institutional barriers regarding TTFields was also discussed. [75] Academic centers conducting non-TTFields research may see TTFields usage by patients as a disruption to their protocols, creating a conflict of interest between funding and patient well-being. To tackle these barriers, patient advocacy and collaboration with academic centers are essential to design robust clinical trials. To address this promptly, TTFields use should not be a general reason for excluding patients from protocol enrolment, although there might be other reasons, such as lack of safety data or research design issues, why TTFields use interferes with protocol enrolment.

Price of TTFields

Finally, another reason that is preventing TTFields from being part of the standard of care is its price. One of the most prominent issues when TTFields are discussed is affordability, as it is a highly priced medical technology. Zhang and Knisely in their 2016 paper describe that with the current price, all developing and most developed countries would not be able to routinely offer TTFields. [76]As a result, the only possible discussed solutions are to either only target patients who will benefit the most or make the treatment more affordable.

Compliance to treatment

The TTFields device itself is designed to assist the patient, caregiver, and healthcare team achieve optimal device wear time. Every month, a patient-specific compliance report is generated in order to monitor the percentage of active TTFields delivered over a 24-hour period. The purpose of the report is to assist patients and caregivers identify issues with adherence so that strategies can be adopted to optimise treatment duration and clinical response.[70]

9.2.5 Findings legal issues

No relevant legal issues were identified.

9.2.6 Findings social issues

In this section the social issues that are related to the caregiver's role in TTFields treatment, patients' experiences and patients' self-information are discussed.

Importance of social support and caregiver's role

The diagnosis of GBM profoundly affects the patients' life and has a significant impact on their family and friends. The suitability of TTFields therapy for GBM patients depends on their social, cognitive and physical conditions. Patients with impairments and limited daily support may face challenges in achieving the recommended treatment adherence goals, affecting the potential clinical benefits. Ideally, every patient should have at least one support person to assist with device alarms, adverse events, and array maintenance during TTFields treatment. [70,77]

It is crucial for both patients and caregivers to receive education about TTFields to ensure successful treatment. A basic understanding of the mechanism of action and the importance of meeting treatment goals are essential. Caregivers need to diligently assess the skin for any signs of redness or irritation during each array change, promptly reporting any observed changes to the healthcare team, especially when TTFields are combined with radiotherapy which often leads to increased skin toxicity. [78,79] They should also consult the personalised array layout map provided at the beginning of treatment. [78] Training is provided before starting TTFields, covering system care, alarm management, addressing skin irritation and emphasising on adherence throughout the follow-up period. [70]

Additionally, a few studies have identified social support as a factor that not only affects patients' decision on initiating TTFields but also their adherence levels to the treatment scheme. [75,80,81] In the Nguyen et al study the considerations of 3 patients in their decision-making process of initiating treatment with TTFields were described. [80] One patient who lived independently agreed to receive TTFields but only in a hospital setting, would have declined treatment at home due to living alone and having no caregiver. In a study by Onken et al 2018, where 58 out of 175 patients were found eligible for TTFields treatment, 37 of these 58 patients decided not to be treated with TTFields. [81] Main reasons for their decision were having to shave their heads, the visibility of the device and the interference with their daily and social life (50%), while 17% reported lack of social/family support as one of the reasons.

Ballo et al 2022 performed a retrospective analysis of factors that affected TTFields usage. [75] The recommendation of TTFields as part of the standard treatment for primary GBM was strongly advocated to 91 patients, but only 59 patients (65%) actually initiated TTFields, as some patients refused. The study identified 3 distinct patient groups: one group immediately declined TTFields, another group was enthusiastic and wanted to start without waiting for the prescribed break, and a third group desired to start but

faced challenges committing fully to the therapy. No specific patient, tumour or treatment-related characteristics were found to correlate with TTFields usage; however, it was observed that those who initiated TTFields tended to be slightly younger. Individual healthcare providers and communication skills were not included as confounders in the analysis as all care team members emphasised the importance of TTFields to the patients. Therefore, factors such as home environment and social support that were not investigated in this analysis, are believed to influence decision-making.

Lack of social support can also affect the patient's adherence to the treatment guidelines. Compliance is a crucial factor for improved patient outcomes when using the intervention with a recommendation of over 75% by the manufacturer, while a subgroup analysis of the EF-14 trial showed that patients with compliance >90% had increased median and 5-year survival rates. [82,83] When studying the variables of the 5 dimensions of adherence as defined by the WHO (social, economic, medical condition, therapy-related and patient behaviours) [84] in a patient population that received TTFields, Pandey et al 2016 found that 2 out of 7 patients who complied less than 75% of the time attributed non-compliance to the lack of caregiver support. [85] Without commitment of both patient and caregiver compliance rates decrease which potentially results in decreased quality of life of both patient and caregiver, because of the perceived burden of the device and reduced benefits of the treatment. [78]

Due to the necessity for social support during TTFields treatment, physicians also use its presence in the patient's life as an eligibility criterion for their introduction to the treatment. In a study by Onken et al 2018, it was observed that physicians discussed TTFields with only 57 out of the 175 of their patients that were diagnosed with GBM. [81] The main reason reported was comorbidities, which among others included conditions like depression, while other reasons were the patient's residence and the patient's lack of social support.

Patient self-information trends

Internet-based healthcare research is becoming more important for cancer patients' self-information, and search engine query databases are valuable tools to understand population-level behaviours and awareness. The study by Byun et al 2021 used search engine query data to gauge population-level awareness of TTFields. [86] Data from Google Trends retrieved between January 2007 and January 2021 in the USA showed that the trade name "Optune®" for GBM treatment significantly increased in search volume from 2014, thus suggesting a growing interest in TTFields both over time, and when compared with baseline searches for disease pathologies.

Even though the internet is not the main source of information about TTFields for all patients, it is a valuable tool. In an observational study conducted by Onken et al in 2019 in 2 centres, 81% of patients learned about TTFields treatment from their treating physician while the remaining 11% found

information online or through patient platforms. [69] The decision for TTFields treatment was driven by the desire to actively combat the tumour (100%), the perceived additional benefit of TTFields to standard therapy (73.3%), the novel therapeutic concept (76.6%), and the treating physician's recommendation (96%).

9.2.7 Findings organisational issues

In this section organisational issues relating to the changing role of oncology nurses related to the treatment specification of TTFields are addressed.

Nurse's role in education and compliance

The increasing use of TTFields in cancer treatment necessitates the expansion of the role of oncology nurses in administering this emerging therapy and educating patients and caregivers, which can potentially lead to additional workload. In the paper by Benson 2018, nurses are described as educators, navigators, and advocates, that guide patients through the decision-making process, initiation of TTFields therapy, and coping with daily challenges to optimise treatment outcomes. [70] Oncology nurses are expected to play a vital role in coaching patients and caregivers to achieve the adherence goal of using the device at least 18 hours per day. [70,83]

Additionally, assessing the patient's status and cognitive function is crucial for device usage. Oncology nurses can provide various resources to address device challenges in combination with the nCompass Program, the device manufacturer's 24/7 support program. However, managing medical symptoms related to the device remains the responsibility of the healthcare team. Nurses can refer patients to support programs involving one-on-one interactions with current device users, fostering open communication between patients and healthcare providers regarding device usage. [78]

10 Additional issues

10.1 Guideline recommendations

Lawson McLean et al 2019 reviewed clinical practice guidelines for GBM in North America and Europe. They found that guidelines from the NCCN (USA), NICE (UK), EANO and ESMO, showed a large variation. The results of the EF-14 trial had not been incorporated in many guidelines during the conduct of the study by Lawson McLean et al 2019. [73]

The NCCN added TTFields to its guidelines for patients with ndGBM, following maximal safe resection and completion of radiation therapy in 2020. The addition was based on the 5-year survival results from the EF-14 trial. In the NCCN guideline, TTFields treatment is intended to be used for 18 hours a day for at least 4 weeks. The NCCN guideline also warn that the most common side effect is skin irritation. The NCCN panel was divided about recommending TTFields for patients with rGBM, due to lack of clear efficacy data. [87]

In the UK, the NICE published its current guidelines on brain tumours (primary) and brain metastases in patients over 16 years old in 2018 (most recent update 2021, search date 24 August 2023). The NICE clinical guidelines recommended that TTFields should not be offered as part of management of a newly diagnosed grade IV glioma (GBM) or as part of management of recurrent high-grade glioma. because (indirect) health economic evidence showed that TTFields are not considered a cost-effective use of NHS resources. [88]

The current guidelines for the diagnosis and management of adult patients with diffuse gliomas provided by EANO were published in 2020 (search date 24 August 2023). The guidelines mention TTFields among the specific recommendations for IDH-wild-type GBM but do not specifically recommend the use of TTFields. Specifically, controversies about the EF-14 trial and the cost-effectiveness of TTFields are brought forwards, and the guidelines mention that TTFields are not widely available in Europe. [17] The guidelines advocate against the use of TTFields in patients beyond confirmed progression.

In the 2021 combined guidelines by Deutsche Gesellschaft fur Hamatologie und Medizinische Onkologie e.V. (DGHO), Swiss Society of Medical Oncology (SSMO), Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie (ÖGHO), and Schweizerische Gesellschaft fur Hämatologie (SGH-SSH) for Germany, Austria and Switzerland, respectively, TTFields are included for GBM treatment in adults. [89] Addtionally, in Sweden, following the 2017 HTA conducted by TLV, TTFields are included in the country's national reimbursement system for the treatment of ndGBM. [90,91] In France, TTFields for patients with ndGBM received a favourable opinion by CNEDiMTS (Commission Nationale d'Evaluation des Dispositifs Médicaux et des Technologies de Santé) after the 2021 HTA by HAS (Haute Autorité de santé) and are also nationally reimbursed. [92]

10.2 Ongoing clinical trials

No ongoing RCTs were found for the intervention TTFields – either in combination with chemotherapy or alone after maintenance chemotherapy has stopped – compared with maintenance chemotherapy in adult patients with ndGBM or rGBM (search date 25 April 2023).

11 Discussion

The present HTA evaluated the efficacy, effectiveness, safety, cost-effectiveness and budget impact of TTFields plus TMZ compared with TMZ alone in patients with ndGBM, TTFields plus chemotherapy compared with chemotherapy alone in patients with GBM at first recurrence, and TTFields treatment alone compared with chemotherapy in patients with GBM at all recurrences. In this section, the main strengths, limitations and evidence gaps of this HTA are discussed.

A rigorous systematic review methodology, adhering to international methodological standards, was applied to identify, critically appraise, analyse, and summarise pertinent evidence on the predefined outcomes of interest in order to minimise bias. Two systematic literature searches were conducted to search for RCTs and comparative non-randomised studies on TTFields in patients with GBM. The evidence base was limited. Only 5 articles, reporting data on 2 RCTs, and 2 retrospective cohort studies were included in the clinical review. No ongoing RCTs were found in line with our PICO. A limitation of the studies reporting data on the RCTs is that these were conducted by the same research group and funded by Novocure Ltd., the device manufacturer of TTFields. Two out of five studies were based on unplanned post-hoc analyses. In the EF-14 trial, 51% of the patients with ndGBM in the intervention arm continued TTFields treatment after the first recurrence until second recurrence. The population with GBM at all recurrences in the EF-11 trial was a mixed population with 12% at first recurrence, 47% at second recurrence, and 41% at third or greater recurrence. The sample size of the retrospective cohort studies was relatively small. Studies conducted in patients with ndGBM compared TTFields with TMZ, though in patients with rGBM TTFields were compared with chemotherapy. Chemotherapy was a mix of chemotherapy and targeted therapy agents, given as single agent or in combination. Due to the low number of studies and the difference between the study populations, it was not possible to calculate pooled estimates for the outcomes reported in the RCTs. Effectiveness data for overall survival of the 2 single-centre retrospective cohort studies was not pooled in light of the discrepancy between these results.

Overall, the evidence base for TTFields in GBM was limited, consisting only of one RCT in ndGBM and one RCT in rGBM with a certainty of evidence for the reported outcomes ranging from very low to

moderate. This could relate to the issue that once a new therapy is established and the results have been implemented into guidelines, it might become unethical to conduct additional RCTs in which patients with a short life expectancy are randomly assigned to treatment strategies that are considered inferior. [93]

A systematic literature search for the costs, cost-effectiveness and budget impact was conducted to identify studies with relevant information on inputs and outcomes, following the same rigorous methodology as the clinical systematic review. Of the 10 studies that were identified for the full-text review, only 3 were found in line with the predefined criteria. A common limitation was that none of the included cost-effectiveness studies were conducted with the scope of the Swiss setting. Additionally, of the 3 cost-effectiveness studies only one reported health outcomes in QALYs, while the other 2 only reported Lys.

The cost-effectiveness model structure was similar to previously published models that investigated the cost-effectiveness of TTFields in ndGBM. Similar to the models published by Guzauskas et al 2019 and Connock et al 2019, a partitioned survival model was developed, to adequately represent the nature of the disease, without a constraint of constant transition probabilities of a Markov model. [49,58] Connock et al 2019 identified the drawbacks of the model presented by Guzauskas et al 2019, which leads to an overoptimistic ICER value. [58] This critique has been reiterated in the HTA submission to HAS in France. [92] The cost-effectiveness model in the current HTA was therefore in line with the methodology employed in the Connock et al 2019 study. [58] Limitations of the model are related to data availability. Individual patient data (IPD) was not available, which necessitated deriving the efficacy inputs from the published Kaplan-Meier curves. The lack of IPD also denies the opportunity to remove ndGBM patients who are treated with TTFields after progression, as indicated by Stupp et al 2017, or rGBM patients who were not treated with TTFields before progression, as indicated by Kesari et al 2017. [31,33] In addition, the Kesari et al 2017 study was an unplanned post-hoc analysis of the EF-14 trial, facing methodological issues related to confounding due to heterogeneity of prior treatment history and local practice. Swiss-specific data on healthcare costs was only available for the rGBM population and had to be estimated for the progression-free patients. [43] Still, scenario analyses showed that using alternative cost estimates from a French study, or estimated on the basis of expert input did not affect results. The RCTs did not provide estimates on quality of life and utlties that could be used to inform the cost-effectiveness model. EQ-5D based utilities were only available from a conference abstract describing a French study. [94] An alternative source determined utilities on ratings by 36 members of the NHS Value of Health Panel. [65] However, scenario analyses showed that using these alternative utility values did not alter the results.

Since TTFields are currently reimbursed, for ndGBM patients the number of patients using TTFields from Tarifpool SASIS AG were deemed representative of future use of TTFields in ndGBM patients. However, given the scientific debate about this intervention, new insights could affect the numbers of

users in the future. Additional limitations of the budget impact model concern the assumptions made to estimate the numbers of progressed patients. For the ELSO domains, no exclusion criteria were used in terms of study types, therefore abstracts and editorials were also included in the findings, allowing for a broader perspective. However, since these study types are not peer-reviewed and the information presented in these studies is limited, it is difficult to assess the quality of the information and the validity is uncertain.

12 Conclusions

The clinical evidence is based on 1 RCT and 2 retrospective cohort studies in patients with ndGBM, 1 RCT in patients with GBM at all recurrences (i.e. 88% at ≥2nd recurrence), and 2 unplanned post-hoc analyses of these RCTs. In patients with ndGBM, treatment with TTFields plus TMZ compared with TMZ alone is probably efficacious in terms of survival (1 RCT; moderate certainty evidence), may result in little or no difference in severe adverse events (1 RCT; low certainty evidence), and may have little or no effect on HRQoL except for itchy skin (1 RCT; low certainty evidence). Two single-centre retrospective cohort studies in patients with ndGBM showed inconclusive results for the effectiveness of TTFields plus TMZ compared with TMZ alone. In patients with GBM at first recurrence, treatment with TTFields plus chemotherapy compared with chemotherapy alone may be efficacious in terms of survival (1 RCT – post-hoc analysis; low certainty evidence) and may result in little or no difference in severe adverse events but the evidence is very uncertain (1 RCT – post-hoc analysis; very low certainty evidence). In patients with GBM at all recurrences, TTFields treatment alone compared with chemotherapy may result in little or no difference in efficacy in terms of survival (1 RCT; low certainty evidence), probably shows less severe adverse events than chemotherapy (1 RCT; moderate certainty evidence), and may show little or no difference in HRQoL but the evidence is very uncertain (1 RCT; very low certainty evidence).

From a health economic perspective, TTFields plus TMZ in ndGBM is likely to improve survival and QALYs and to increase costs compared to TMZ alone. For patients with GBM at first recurrence, incremental costs are higher and incremental QALYs are lower than for patients with ndGBM. The budget impact analyses showed that the budgetary impact of TTFields is mainly driven by the rental costs of TTFields. Finally, the use of TTFields is associated with important ethical, social and organisational issues.

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14 Appendices

14.1 Systematic review clinical evaluation

14.1.1 Search strategy for the clinical evaluation systematic literature search

Table 1S. 1. PubMed (MEDLINE)

Population	"Glioblastoma"[Mesh] OR glioblastoma*[tiab] OR glyoblastoma*[tiab] OR GBM[tiab] OR ndGBM[tiab] OR rGBM[tiab]
Intervention	tumortreating field*[tiab] OR tumor-treating field*[tiab] OR tumourtreating field*[tiab] OR tumour-treating field*[tiab] OR TTfield*[tiab] OR TTF[tiab] OR TTFs[tiab] OR alternating electric field*[tiab] OR alternating electrical field*[tiab] OR mild electric field*[tiab] OR mild electrical field*[tiab] OR novocure*[tiab] OR optune[tiab] OR EFE-G100[tiab] OR novoTTF*[tiab] OR novo-TTF*[tiab] OR EF11[tiab] OR EF-11[tiab] OR EF14[tiab] OR EF-14[tiab]
Comparator	No search string
Outcomes	No search string

Table 1S. 2. Embase.com

Population	Glioblastoma/exp OR glioblastoma*:ti,ab OR glyoblastoma*:ti,ab OR GBM:ti,ab OR ndGBM:ti,ab OR rGBM:ti,ab
Intervention	'tumortreating field*':ti,ab OR 'tumor-treating field*':ti,ab OR 'tumourtreating field*':ti,ab OR 'tumour-treating field*':ti,ab OR TTfield*:ti,ab OR TTF:ti,ab OR TTFs:ti,ab OR 'alternating electric field*':ti,ab OR 'alternating electrical field*':ti,ab OR 'mild electric field*':ti,ab OR 'mild electrical field*':ti,ab OR novocure*:ti,ab OR optune:ti,ab OR EFE-G100:ti,ab OR novoTTF*:ti,ab OR novo-TTF*:ti,ab OR EF11:ti,ab OR EF-11:ti,ab OR EF14:ti,ab OR EF-14:ti,ab
Comparator	No search string
Outcomes	No search string
Limits	No conference abstracts/select other publication types: ([article]/lim OR [article in press]/lim OR [conference paper]/lim OR [conference review]/lim OR [data papers]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim OR [preprint]/lim)

Table 1S. 3. Cochrane Library

Population	[mh Glioblastoma] OR glioblastoma*:ti,ab OR glyoblastoma*:ti,ab OR GBM:ti,ab OR ndGBM:ti,ab OR rGBM:ti,ab
Intervention	(tumortreating NEXT field*):ti,ab OR (tumor-treating NEXT field*):ti,ab OR (tumourtreating NEXT field*):ti,ab OR (tumour-treating NEXT field*):ti,ab OR TTfield*:ti,ab OR TTF:ti,ab OR TTFs:ti,ab OR ('alternating electric' NEXT field*):ti,ab OR ('alternating electrical' NEXT field*):ti,ab OR ('mild electric' NEXT field*):ti,ab OR ('mild electrical' NEXT field*):ti,ab OR novocure*:ti,ab OR optune:ti,ab OR EFE-G100:ti,ab OR novoTTF*:ti,ab OR novo-TTF*:ti,ab OR EF11:ti,ab OR EF-11:ti,ab OR EF14:ti,ab OR EF-14:ti,ab
Comparator	No search string
Outcomes	No search string

Table 1S. 4. ClinicalTrials.gov and EU Clinical Trials Register

Population	glioblastoma OR glyblastoma OR GBM OR ndGBM OR rGBM
Intervention	TTFields
Comparator	No search string
Outcomes	No search string

14.1.2 Excluded articles during full-text selection

Table 1S. 5. Excluded articles found with the clinical evaluation systematic literature search: RCTs

Reference	Reason for exclusion
Guzauskas G, Salzberg M, Wang B. The estimated long-term survival benefit of adding TTFields to the standard of care for glioblastoma patients. Neuro-oncology. 2017;19:vi6.	Irrelevant publication type (abstract)
Guzauskas GF, Salzberg M, Wang BC. Estimated lifetime survival benefit of tumor treating fields and temozolomide for newly diagnosed glioblastoma patients. CNS Oncol. 2018;7(3):Cns23.	Modelling study
Kesari S, Tran D, Read W, Ahluwalia M, Villano J, Toms S, et al. Tumor treating fields with second line treatment compared to second line treatment alone in patients at first recurrence of glioblastoma-a post hoc analysis of the EF-14 phase 3 clinical trial. Neuro-oncology. 2017;19:vi13.	Irrelevant publication type (abstract)
Kumar V, Harris D, Linendoll N, Mignano J, Moreno-koehler A, Saif N, et al. Compliance and duration of treatment with tumor treating fields (TTFIELDS) in adjuvant treatment for newly diagnosed glioblastomas (GBMS) improves progression-free survival (PFS) and overall survival (OS). Neuro-oncology. 2016;18:vi180.	Irrelevant publication type (abstract)
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.	Systematic review
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.	Systematic review
Mittal S, Klinger NV, Michelhaugh SK, Barger GR, Pannullo SC, Juhász C. Alternating electric tumor treating fields for treatment of glioblastoma: rationale, preclinical, and clinical studies. J Neurosurg. 2018;128(2):414-21.	Systematic review
Ram Z, Wong ET, Gutin PH. Comparing the effect of novottf to bevacizumab in recurrent GBM: a post-HOC sub-analysis of the phase III trial data. Neuro-oncology. 2011;13:iii52.	Irrelevant publication type (abstract)

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.	Out of scope post-hoc analysis (of EF-14 trial)
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.	Systematic review
Shah PP, White T, Khalafallah AM, Romo CG, Price C, Mukherjee D. A systematic review of tumor treating fields therapy for high-grade gliomas. J Neurooncol. 2020;148(3):433-43.	Systematic review
Stupp R, Kanner A, Engelhard H, Heidecke V, Taillibert S, Lieberman FS, et al. A prospective, randomized, open-label, phase III clinical trial of NovoTTF-100A versus best standard of care chemotherapy in patients with recurrent glioblastoma. Journal of clinical oncology. 2010;28(18):950.	Irrelevant publication type (abstract)
Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms SA, et al. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. Jama. 2015;314(23):2535-43.	Interim analysis (of EF-14 trial)
Stupp R, Taillibert S, Kanner A, Kesari S, Toms SA, Barnett GH, et al. Tumor treating fields (TTFields): a novel treatment modality added to standard chemoand radiotherapy in newly diagnosed glioblastoma-First report of the full dataset of the EF14 randomized phase III trial. Journal of clinical oncology. 2015;33(15).	Irrelevant publication type (abstract)
Stupp R, Hegi ME, Idbaih A, Steinberg DM, Lhermitte B, Read W, et al. Tumor treating fields added to standard chemotherapy in newly diagnosed glioblastoma (GBM): final results of a randomized, multicenter, phase III trial. Cancer research. 2017;77(13).	Irrelevant publication type (abstract)
Szasz AM, Arrojo Alvarez EE, Fiorentini G, Herold M, Herold Z, Sarti D, et al. Meta-Analysis of Modulated Electro-Hyperthermia and Tumor Treating Fields in the Treatment of Glioblastomas. Cancers (Basel). 2023;15(3).	Systematic review
Taphoorn MJB, Dirven L, Taillibert S, Honnorat J, Chen T, Sroubek J, et al. Effect of tumor treating fields (TTFields) on health-related quality of life (HRQoL) in newly diagnosed glioblastoma. Results of the EF-14 randomized phase iii trial. Neuro-oncology. 2017;19:vi206.	Irrelevant publication type (abstract)
Wong ET, Ram Z, Gutin PH. Updated survival data of the phase III clinical trial of NovoTTF-100A versus best standard chemotherapy for recurrent glioblastoma. Neuro-oncology. 2011;13:iii87.	Irrelevant publication type (abstract)
Zhu P, Zhu JJ. Tumor treating fields: a novel and effective therapy for glioblastoma: mechanism, efficacy, safety and future	Systematic review

perspectives. Chin Clin Oncol. 2017;6(4):41.	
Zhu JJ, Demireva P, Kanner AA, Pannullo S, Mehdorn M, Avgeropoulos N, et al. Health-related quality of life, cognitive screening, and functional status in a randomized phase III trial (EF-14) of tumor treating fields with temozolomide compared to temozolomide alone in newly diagnosed glioblastoma. J Neurooncol. 2017;135(3):545-52.	Interim analysis (of EF-14 trial)

Table 1S. 6. Excluded articles found with the clinical evaluation systematic literature search: comparative non-randomised studies

Reference	Reason for exclusion
Dono A, Mitra S, Shah M, Takayasu T, Zhu JJ, Tandon N, et al. PTEN mutations predict benefit from tumor treating fields (TTFields) therapy in patients with recurrent glioblastoma. J Neurooncol. 2021;153(1):153-60	No patient characteristics reported for the comparator group and not compared with the characteristics of the intervention group
Krigers A, Pinggera D, Demetz M, Kornberger LM, Kerschbaumer J, Thomé C, et al. The Routine Application of Tumor-Treating Fields in the Treatment of Glioblastoma WHO° IV. Front Neurol. 2022;13:900377.	No comparator
Mrugala MM, Engelhard HH, Dinh Tran D, Kew Y, Cavaliere R, Villano JL, et al. Clinical practice experience with NovoTTF-100A™ system for glioblastoma: The Patient Registry Dataset (PRiDe). Semin Oncol. 2014;41:S4-s13.	Comparator group is from another RCT
Nishikawa R, Yamasaki F, Arakawa Y, Muragaki Y, Narita Y, Tanaka S, et al. Safety and efficacy of tumour-treating fields (TTFields) therapy for newly diagnosed glioblastoma in Japanese patients using the Novo-TTF System: a prospective post-approval study. Jpn J Clin Oncol. 2023.	No comparator
She L, Gong X, Su L, Liu C. Effectiveness and safety of tumor-treating fields therapy for glioblastoma: A single-center study in a Chinese cohort. Front Neurol. 2022;13:1042888.	Part of the ndGBM patients received targeted therapy (not specified) and part of the rGBM patients received re-operation or targeted therapy (i.e. nimotuzumab, bevacizumab or anlotinib)
Vymazal J, Kazda T, Novak T, Slanina P, Sroubek J, Klener J, et al. Eighteen years' experience with tumor treating fields in the treatment of newly diagnosed glioblastoma. Front Oncol. 2022;12:1014455.	Partly duplicate data (15% of the patients treated as part of the EF-14 study)

14.1.3 Summary figures risk of bias of the RCTs

Figure 1S. 1. Summary risk of bias RCTs assessed with the RoB 2 tool – Outcome OS

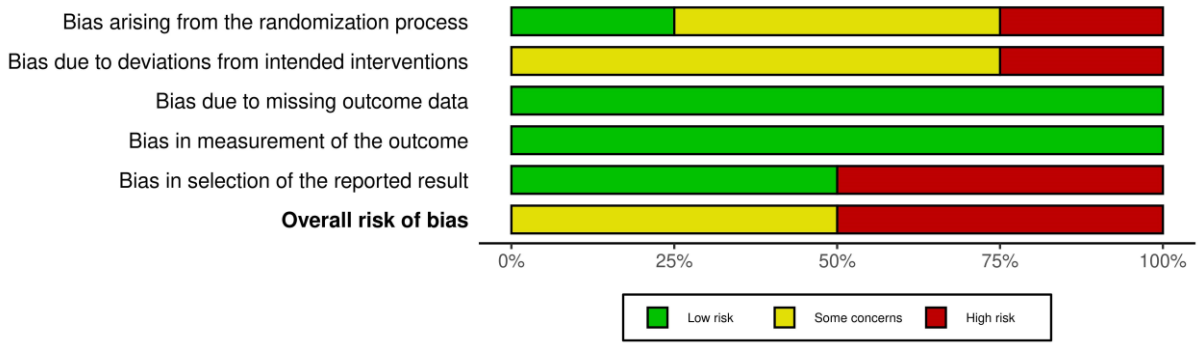


Figure 1S. 2. Summary risk of bias RCTs assessed with the RoB 2 tool – Outcome PFS

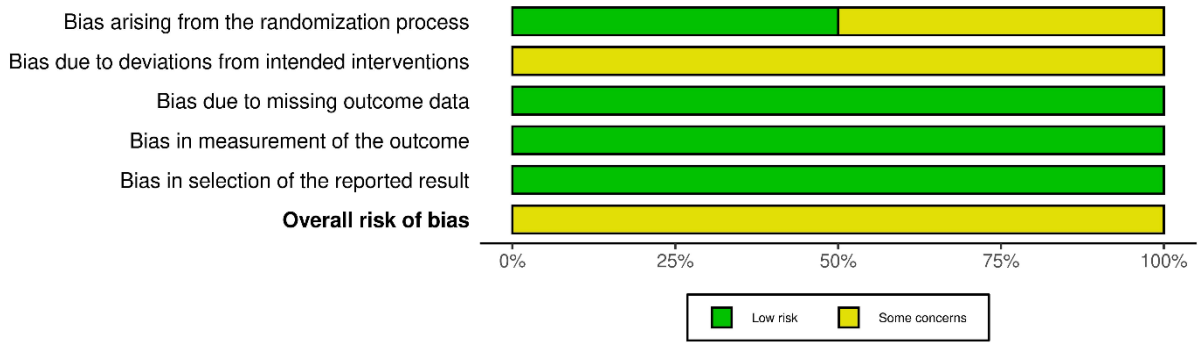


Figure 1S. 3. Summary risk of bias RCTs assessed with the RoB 2 tool – Outcome HRQoL

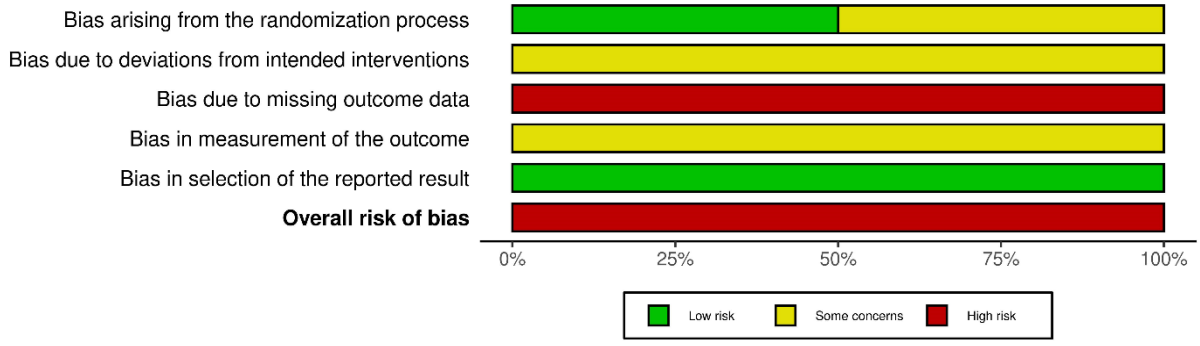
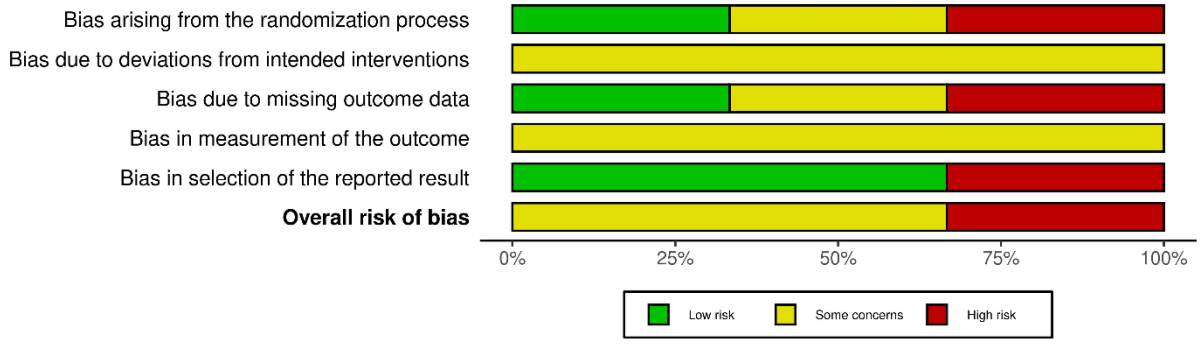


Figure 1S. 4. Summary risk of bias RCTs assessed with the RoB 2 tool – Outcome SAEs



14.1.4 Summary figures risk of bias of the comparative non-randomised studies

Figure 1S. 5. Summary risk of bias comparative non-randomised studies assessed with the ROBINS-I tool – Outcome OS

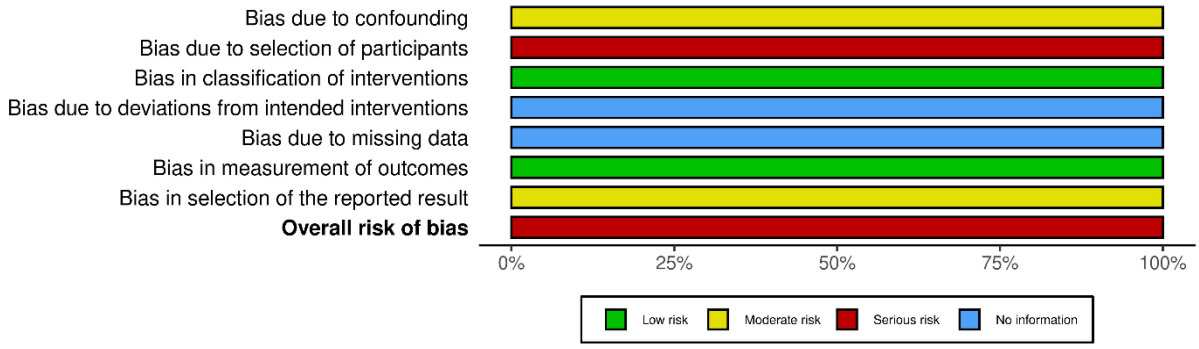
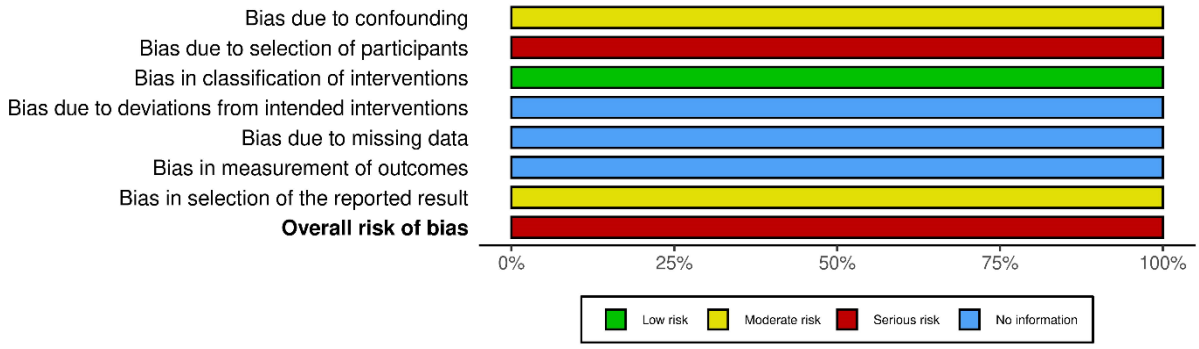


Figure 1S. 6. Summary risk of bias comparative non-randomised studies – Outcome PFS



14.2 Systematic review cost-effectiveness

14.2.1 Search strategy for economic evaluation systematic literature search

Table 2S. 1. PubMed (MEDLINE)

Population	"Glioblastoma"[Mesh] OR glioblastoma*[tiab] OR glyoblastoma*[tiab] OR GBM[tiab] OR ndGBM[tiab] OR rGBM[tiab]
Intervention	tumortreating field*[tiab] OR tumor-treating field*[tiab] OR tumourtreating field*[tiab] OR tumour-treating field*[tiab] OR TTfield*[tiab] OR TTF[tiab] OR TTFs[tiab] OR alternating electric field*[tiab] OR alternating electrical field*[tiab] OR mild electric field*[tiab] OR mild electrical field*[tiab] OR novocure*[tiab] OR optune[tiab] OR EFE-G100[tiab] OR novoTTF*[tiab] OR novo-TTF*[tiab] OR EF11[tiab] OR EF-11[tiab] OR EF14[tiab] OR EF-14[tiab]
Comparison	No search string
Outcomes	No search string
Cost-effectiveness	“Technology Assessment, Biomedical”[Mesh] OR “Cost-Benefit Analysis”[Mesh] OR “Quality-Adjusted Life Years”[Mesh] OR “technology assessment” [tiab] OR “economic evaluation” [tiab] OR “economic value” [tiab] OR “cost-benefit” [tiab] OR “cost-effective” [tiab] OR “cost-effectiveness” [tiab] OR “cost-utility” [tiab] OR “cost-consequence” [tiab] OR “quality-adjusted life year” [tiab] OR “QALY” [tiab]

Notes
The economic search filter used is a customised search filter for economic outcomes, which has been developed together with an information specialist. Existing economic search filters were used as input.

Table 2S. 2. Embase.com and NHS EED

Population	Glioblastoma/exp OR glioblastoma*:ti,ab OR glyoblastoma*:ti,ab OR GBM:ti,ab OR ndGBM:ti,ab OR rGBM:ti,ab
Intervention	'tumortreating field*':ti,ab OR 'tumor-treating field*':ti,ab OR 'tumourtreating field*':ti,ab OR 'tumour-treating field*':ti,ab OR TTfield*:ti,ab OR TTF:ti,ab OR TTFs:ti,ab OR 'alternating electric field*':ti,ab OR 'alternating electrical field*':ti,ab OR 'mild electric field*':ti,ab OR 'mild electrical field*':ti,ab OR novocure*:ti,ab OR optune:ti,ab OR EFE-G100:ti,ab OR novoTTF*:ti,ab OR novo-TTF*:ti,ab OR EF11:ti,ab OR EF-11:ti,ab OR EF14:ti,ab OR EF-14:ti,ab
Comparison	No search string
Outcomes	No search string
Cost-effectiveness	'biomedical technology assessment'/exp OR 'economic evaluation'/exp OR 'quality adjusted life year'/exp OR 'program cost effectiveness'/de OR ((technology NEAR/3 assessment*) OR (economic* NEAR/3 (evaluat* OR value)) OR ((cost OR costs) NEAR/3 (benefit* OR effectiv* OR efficien* OR efficac* OR minim* OR utilit* OR consequen*)) OR (qualit* NEAR/3 adjust* NEAR/3 (life-year* OR lifeyear*)) OR qaly*):ab,ti

Notes
The economic search filter used is a customised search filter for economic outcomes, which has been developed together with an information specialist. Existing economic search filters were used as input.

Table 2S. 3. Cochrane Library

Population	[mh Glioblastoma] OR glioblastoma*:ti,ab OR glyoblastoma*:ti,ab OR GBM:ti,ab OR ndGBM:ti,ab OR rGBM:ti,ab
Intervention	(tumortreating NEXT field*):ti,ab OR (tumor-treating NEXT field*):ti,ab OR (tumourtreating NEXT field*):ti,ab OR (tumour-treating NEXT field*):ti,ab OR TTfield*:ti,ab OR TTF:ti,ab OR

	TTFs:ti,ab OR ('alternating electric' NEXT field*):ti,ab OR ('alternating electrical' NEXT field*):ti,ab OR ('mild electric' NEXT field*):ti,ab OR ('mild electrical' NEXT field*):ti,ab OR novocure*:ti,ab OR optune:ti,ab OR EFE-G100:ti,ab OR novoTTF*:ti,ab OR novo-TTF*:ti,ab OR EF11:ti,ab OR EF-11:ti,ab OR EF14:ti,ab OR EF-14:ti,ab
Comparator	No search string
Outcomes	No search string
Cost-effectiveness	[mh "Technology Assessment, Biomedical"] OR [mh "Cost-Benefit Analysis"] OR [mh "Quality-Adjusted Life Years"] OR "technology assessment":ti,ab OR "economic evaluation":ti,ab OR "economic value":ti,ab OR cost-benefit:ti,ab OR cost-effective:ti,ab OR cost-effectiveness:ti,ab OR cost-utility:ti,ab OR cost-consequence:ti,ab OR "quality-adjusted life year":ti,ab OR QALY:ti,ab

Notes
The economic search filter used is a customised search filter for economic outcomes, which has been developed together with an information specialist. Existing economic search filters were used as input.

Table 2S. 4. Tufts Medical Centre Cost-Effectiveness Analysis Registry and International HTA database

Population	Glioblastoma OR glioblastoma OR glyoblastoma OR GBM OR ndGBM OR rGBM
Intervention	tumortreating field OR tumor-treating field OR tumourtreating field OR tumour-treating field OR TTfield OR TTF OR TTFs OR alternating electric field OR alternating electrical field OR mild electric field OR mild electrical field OR novocure OR optune OR EFE-G100 OR novoTTF OR novo-TTF OR EF11 OR EF-11 OR EF14 OR EF-14
Comparator	No search string
Outcome	No search string

14.2.2 Excluded articles during full-text selection

Table 2S. 5. Excluded studies found with the systematic literature search

Reference	Reason for exclusion
Armoiry X, Auguste P, Dussart C, Guyotat, Connock M. P14.12 The cost-effectiveness of tumor-treating fields therapy in patients with newly diagnosed glioblastoma. Neuro Oncol. 2019 Sep;21(Issue Supplement_3):iii68-iii69.	Non-pertinent publication type; abstract
Guzauskas GF, Pollom E, Leonard F, Stieber VW. Treating Elderly Glioblastoma Patients > 65 Years with TTFields - a Cost-Effectiveness Perspective. International Journal of Radiation Oncology*Biology*Physics. 2019 Sep;105(1):E439–40.	Non-pertinent publication type; abstract
Guzauskas GF, Pollom EL, Stieber VW, Wang BC, Garrison L. Abstract LB-257: Tumor treating fields treatment for patients with newly diagnosed glioblastoma: A cost-effectiveness analysis. Cancer Research. 2018 Jul 1;78(13_Supplement):LB-257-LB-257.	Non-pertinent publication type; abstract
Guzauskas GF, Wang BCM, Kinzel A, Proescholdt C. P01.109 Tumor treating fields treatment for patients with newly diagnosed glioblastoma: a cost-effectiveness analysis for Sweden. Neuro-Oncology.	Non-pertinent publication type; abstract

2018 Sep 19;20(suppl_3):iii256–iii256.	
Guzauskas GF, Wang BCM, Pollom EL, Stieber VW, Kinzel A, Proescholdt C, et al. P01.102 Cost effectiveness of treating glioblastoma patients age 65 years or older with Tumor Treating Fields plus Temozolomide versus Temozolomide alone. Neuro-Oncology. 2018 Sep 19;20(suppl_3):iii254–iii254.	Non-pertinent publication type; abstract
Schiff D, Schrag D. Living in a material world: tumor-treating fields at the top of the charts. Neuro Oncol. 2016 Aug;18(8):1033–4.	Non-pertinent publication type; editorial
Zhang I, Knisely JPS. Tumor treating fields—effective, but at what cost? Translational Cancer Research. 2016 Dec;5(S7):S1349–53.	Non-pertinent publication type; editorial

14.2.3 Mittel- und Gegenständeliste (MiGeL) 1 April 2022

09.04 Geräte zur Erzeugung und Anwendung von Tumortherapiefeldern

Die Tumortherapiefelder sind elektrische Wechselspannungsfelder zur regionalen Behandlung von Tumoren.

Positions-Nr.	*L*	*Bezeichnung*	*Menge / Einheit*	*HVB Selbstanwendung*	*HVB Pflege*	*Gültig ab*	*Rev.*

09.04.01.00.2	L	Tumortherapiefelder (TTFields) zur Behandlung des neu diagnostizierten Glioblastoms, inkl. Keramikgelpads mit Keramikisolatoren für einen Durchschlagspannungswiderstand von mindestens 4'000 Volt, mit Temperatursensoren und Feldgeneratoren zur Regelung der Energie der Isolatoren; inkl. Serviceleistungen und Wartungsarbeiten
		
		Limitation:
		• Indikationen:
		  • Für Versicherte ab 18 Jahren
		  • Karnofsky-Performance-Score von mind. 70
		  • Therapiebeginn: 4-7 Wochen nach Radiochemotherapie
		  • Nur in Kombination mit begleitender Temozolomid-Erhaltungstherapie
		  • Keine Tumorprogression nach der adjuvanten Radiochemotherapie
		• Vergütungsvoraussetzungen:
		  • Vergütungsstopp sobald Tumorprogression
		  • Keine Vergütung beim Einsatz bei Rezidiv-Glioblastom
		  • Nach 3 Monaten (und regelmässig in der weiteren Behandlung) muss der behandelnde Arzt / die behandelnde Ärztin eine Beurteilung der Compliance vornehmen; bei unzweckmässiger Versicherten-Compliance (Tragedauer von mind. 18 Stunden / Tag nicht erfüllt) darf die Therapie nicht mehr vergütet werden
		  • Verschreibung nur durch Fachärzte und Fachärztinnen für medizinische Onkologie
		  • Kostenübernahme nur auf vorgängige besondere Gutsprache des Versicherers, der die Empfehlung des Vertrauensarztes oder der Vertrauensärztin berücksichtigt, danach jährliche Erneuerung der Kostengutsprache.
		• Erstinstruktion und Sicherstellung der Behandlung (inkl. Compliance-Kontrolle) durch Anbieter
		• Max. vergütete Behandlungsdauer: 2 Jahre
			Miete / Monat	14'320.00	13'604.00	01.04.2021
						01.10.2021
							N
							P

Mittel- und Gegenständeliste (MiGeL) vom 1.4.2022

		In Evaluation bis 30.06.2024					

14.3 Cost-effectiveness model input parameters (extended)

Table 3S. 1. Cost-effectiveness model input parameters (extended)

Input parameter	Base case value	Lower value used in OWSA	Upper value used in OWSA	Distribution in PSA	Source
Baseline characteristics					
Baseline age in years, mean (sd)	56 (5.6)	50	56	Normal (μ=56; sd=5.6)	Stupp et al 2017 [31]
Proportion of women, %	31	27.9	34.1	Beta (α=222; β=473)	Stupp et al 2017 [31]
Survival (coefficients log-normal model)					
TMZ OS Mean log, mean (sd)	2.7671 (0.062)	2.6450 [a]	2.8891 [a]	Normal (μ=2.7671; sd=0.062)	Estimated using Stupp et al 2017 [31]
TMZ OS sd log, mean (sd)	0.9095 (0.0497)	0.8172 [a]	1.0123 [a]	Normal (μ=0.9095; sd=0.0497)	Estimated using Stupp et al 2017 [31]
TMZ PFS Meanlog, mean (sd)	1.5784 (0.0679)	1.4454 [a]	1.7114 [a]	Normal (μ=1.5784; sd=0.0679)	Estimated using Stupp et al 2017 [31]
TMZ PFS sd log, mean (sd)	0.9641 (0.0549)	0.8623 [a]	1.0779 [a]	Normal (μ=0.9641; sd=0.0549)	Estimated using Stupp et al 2017 [31]
TTF OS Mean log, mean (sd)	2.9880 (0.0421)	2.9055 [a]	3.0705 [a]	Normal (μ=2.9880; sd=0.0421)	Estimated using Stupp et al 2017 [31]
TTF OS sd log, mean (sd)	0.8489 (0.0345)	0.7840 [a]	0.9192 [a]	Normal (μ=0.8489; sd=0.0345)	Estimated using Stupp et al 2017 [31]
TTF PFS Mean log, mean (sd)	1.9072 (0.0453)	1.8183 [a]	1.9960 [a]	Normal (μ=1.9072; sd=0.0453)	Estimated using Stupp et al 2017 [31]

TTF PFS sd log, mean (sd)	0.9034 (0.0366)	0.8345 [a]	0.9780 [a]	Normal (μ=0.9034; sd=0.0366)	Estimated using Stupp et al 2017 [31]
Utilities [b]					
Progression-free/stable, mean (sd)	0.874 (0.087)	0.7866	0.9614	Beta (α=11.73; β=1.69)	Palmer et al 2022 [42]
Progression, mean (sd)	0.724 (0.072)	0.6516	0.7964	Beta (α=26.88; β=10.25)	Palmer et al 2022 [42]
Costs					
TTFields rental cost per month	CHF 14,320.00	CHF 12,888	CHF 15,752	Not varied in PSA	FOPH, MiGeL
TMZ acquisition cost per 28 days, mean (sd) [c]	CHF 557.21 (55.72)	CHF 501.49	CHF 612.93	Gamma (α=96.79; β=5.57)	FOPH, Präparate Spezialitätenliste
Progression-free/stable disease costs per month, mean (sd)	CHF 1,095.71 (111.37)	CHF 986.14	CHF 1,205.28	Gamma (α=96.79; β=11.32)	Calculated from Panje et al 2019 [43]
Progressed disease costs per month, mean (sd)	CHF 2,975.89 (302.48)	CHF 2,678.30	CHF 3,273.48	Gamma (α=100.00; β=30.75)	Panje et al 2019 [43]

Abbreviations

FOPH = Federal Office of Public Health, MiGeL = Mittel und Gegenständeliste, OS = overall survival, OWSA = one-way sensitivity analyses, PFS = progression-free survival, PSA = probabilistic sensitivity analysis, SD = standard deviation, TMZ = temozolomide, TTFields = tumour treating fields.

Notes

a = Coefficients used for estimating survival (mean log and sd log) are interdependent and are varied simultaneously in the OWSA for each survival model (separate OWSA were run for TTFields OS, TMZ OS, TTFields PFS and TMZ PFS models). b = Utility values were assumed to be dependent on health state only. The intervention was not assumed to affect utility values directly. c = Based on 150mg/m^2 dose, assumed body surface area of 2.0 m^2.

Table 3S. 2. Cost calculations based on clinical expert input, progression-free health state

Healthcare component	Proportion of patients using healthcare component	Quantity if using healthcare component	Unit price	Average costs
Hospitalisation	5%	7 days	1258.36	440.42
General Practitioner	50%	1 visit	102.73	51.36
Laboratory	50%	1 exam	1372.00	686.00
MRI / CT	40%	0.4 scans	658.15	105.30
Physiotherapy	20%	2 visits	48.00	19.20
Neurologist	20%	0.5 visits	109.08	10.91
Neuro-oncologist	30%	0.5 visits	109.08	16.36
Radiation oncologist	20%	4 visits	109.08	87.26
Neurosurgeon	10%	1 visit	109.08	10.91
Emergency unit	10%	1 visit	109.08	10.91
Specialised nurses	5%	0.5 visits	109.08	2.73
Psycho-oncologist	10%	0.5 visits	109.08	5.45
Palliative care	2%	2 visits	109.08	4.36
Total costs per month				1451.18

Table 3S. 3. Cost calculations based on clinical expert input, progression health state

Healthcare component	Proportion of patients using healthcare component	Quantity if using healthcare component	Unit price	Average costs
Hospitalisation	10%	7 days	1258.36	880.85
General Practitioner	50%	2 visits	102.73	102.73
Laboratory	50%	2 exams	1372.00	1372.00
MRI / CT	40%	0.4 scans	658.15	105.30
Physiotherapy	20%	2 visits	48.00	19.20
Neurologist	20%	0.5 visits	109.08	10.91
Neuro-oncologist	30%	0.5 visits	109.08	16.36
Radiation oncologist	10%	4 visits	109.08	43.63
Neurosurgeon	10%	1 visit	109.08	10.91
Emergency unit	15%	1 visit	109.08	16.36
Specialised nurses	5%	0.5 visits	109.08	2.73
Psycho-oncologist	20%	2 visits	109.08	43.63
Palliative care	10%	2 visits	109.08	21.82
Total costs per month				2646.42

14.4 Survival curves ndGBM population

Figure 4S. 1. Kaplan-Meier curve and estimated survival curves for overall survival with TMZ only (ndGBM)

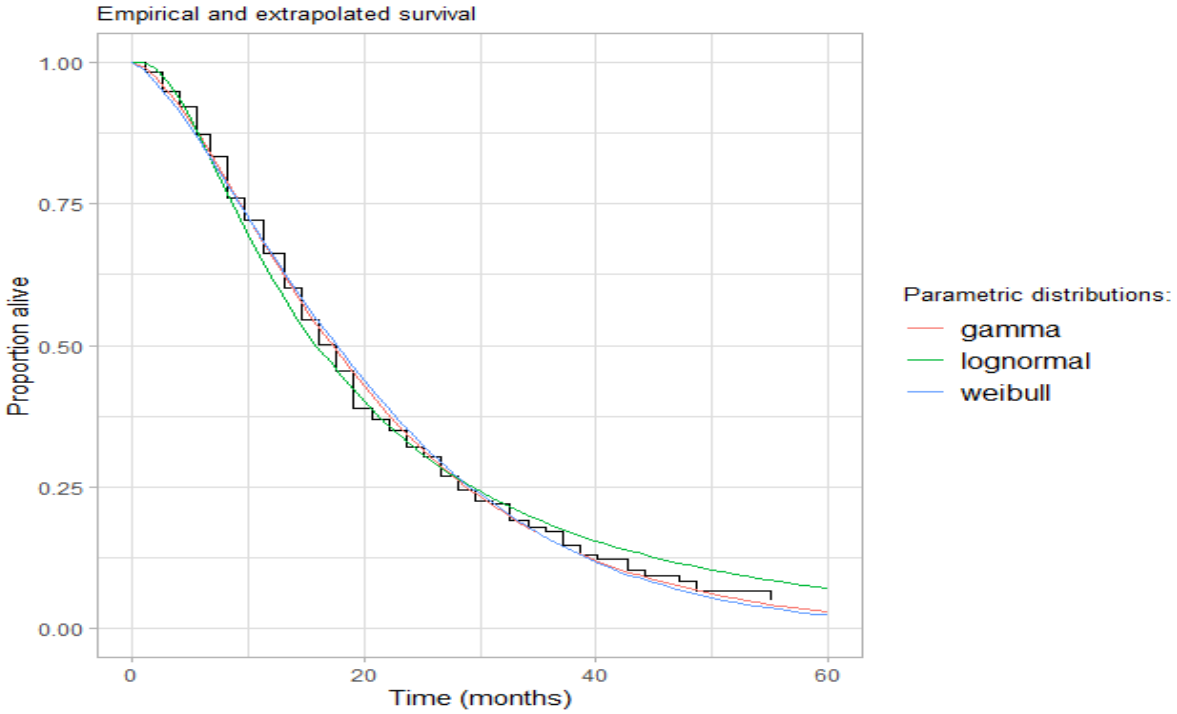


Figure 4S. 2. Kaplan-Meier curve and estimated survival curves for overall survival with TTFields plus TMZ (ndGBM)

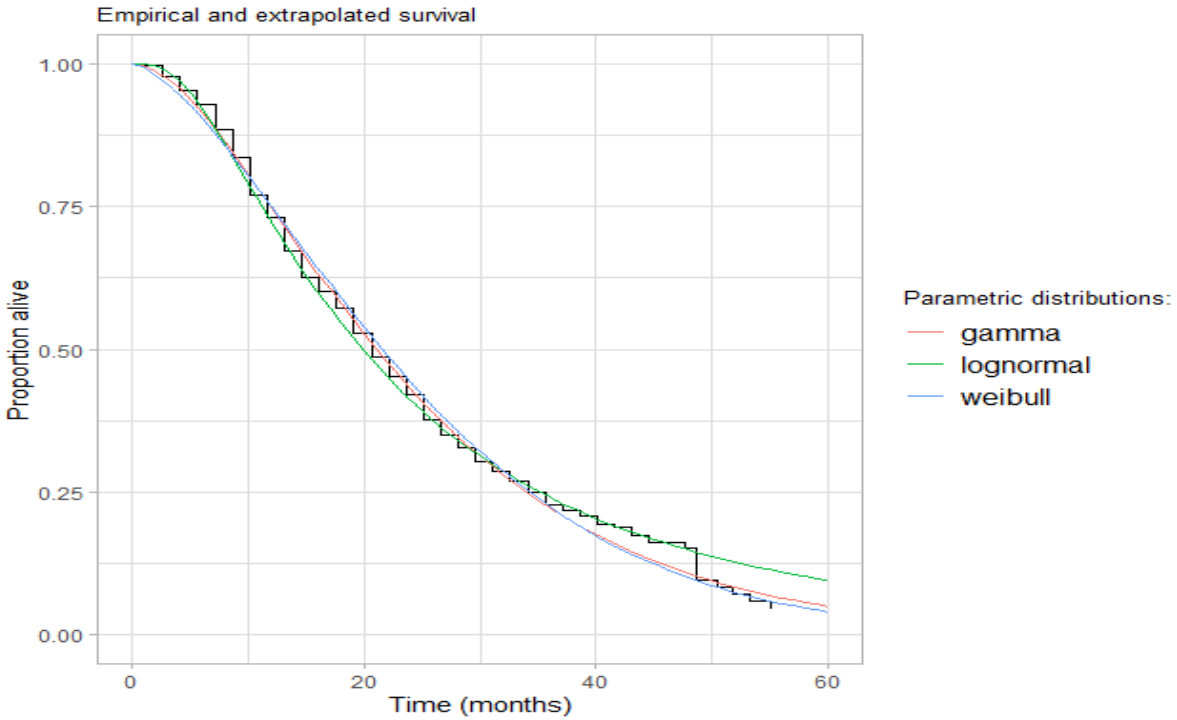


Figure 4S. 3. Kaplan-Meier curve and estimated survival curves for progression-free survival with TMZ only (ndGBM)

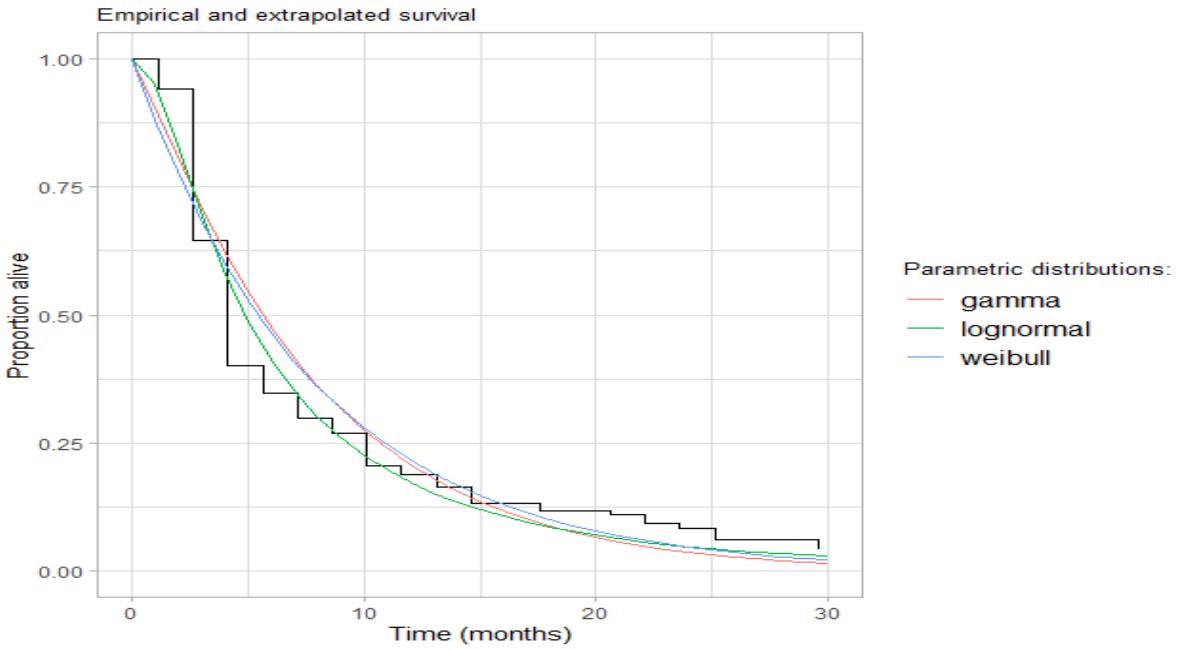


Figure 4S. 4. Kaplan-Meier curve and estimated survival curves for progression-free survival with TTFields plus TMZ (ndGBM)

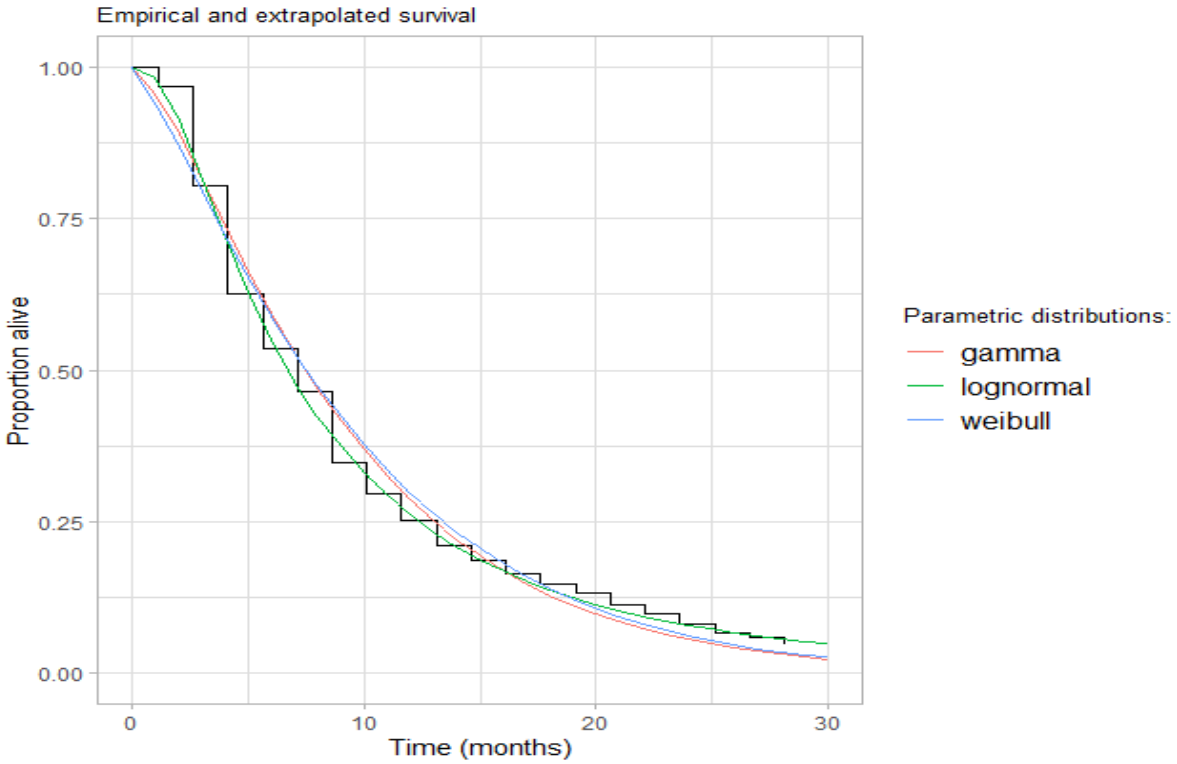


Figure 4S. 5. Extrapolated survival curves for overall survival with TMZ only (ndGBM)

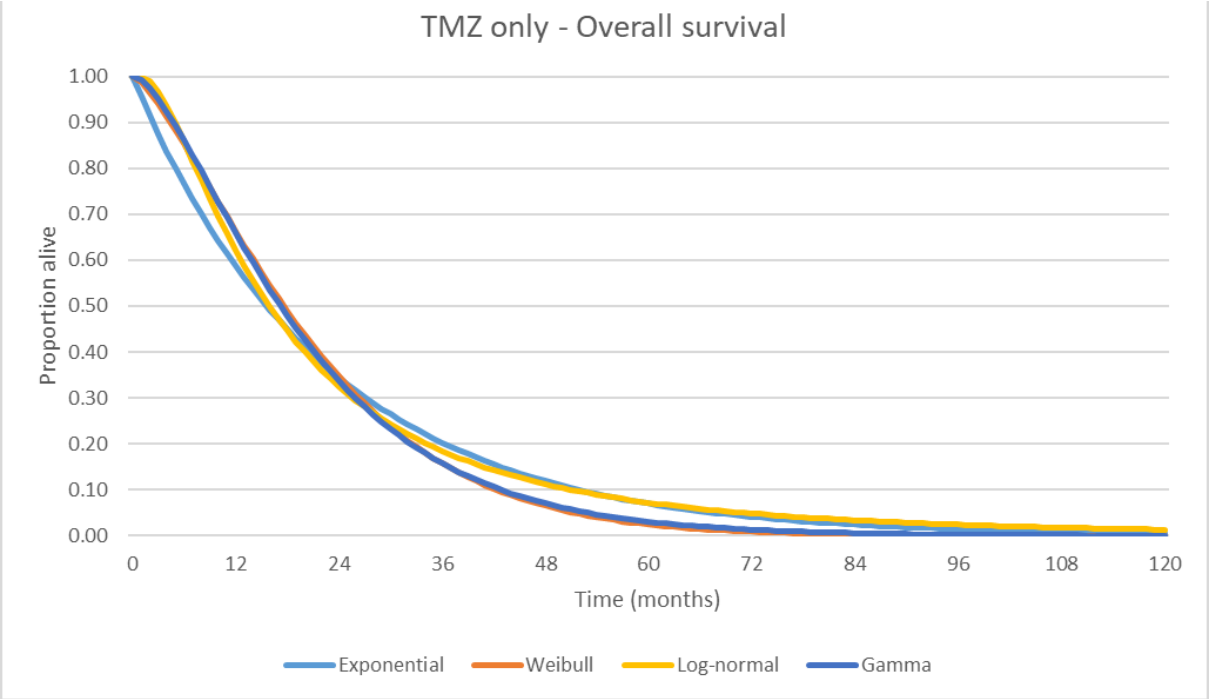


Figure 4S. 6. Extrapolated urvival curves for overall survival with TTFields plus TMZ (ndGBM)

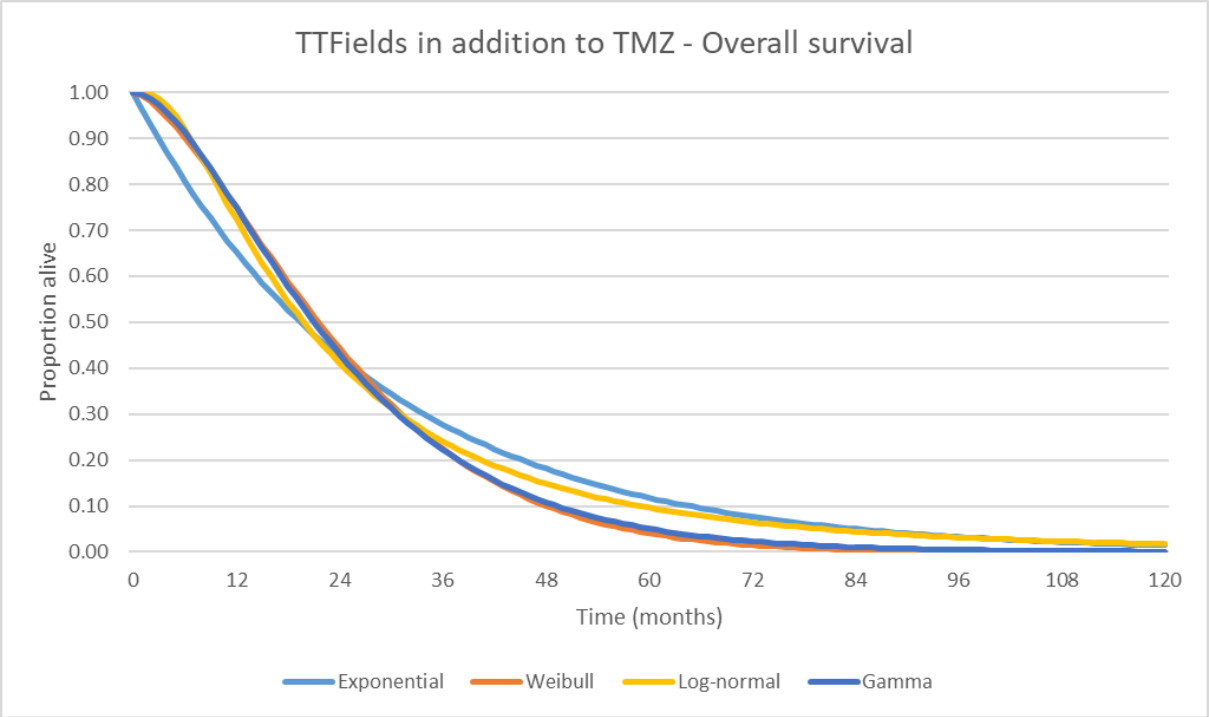


Figure 4S. 7. Extrapolated survival curves for progression-free survival with TMZ only (ndGBM)

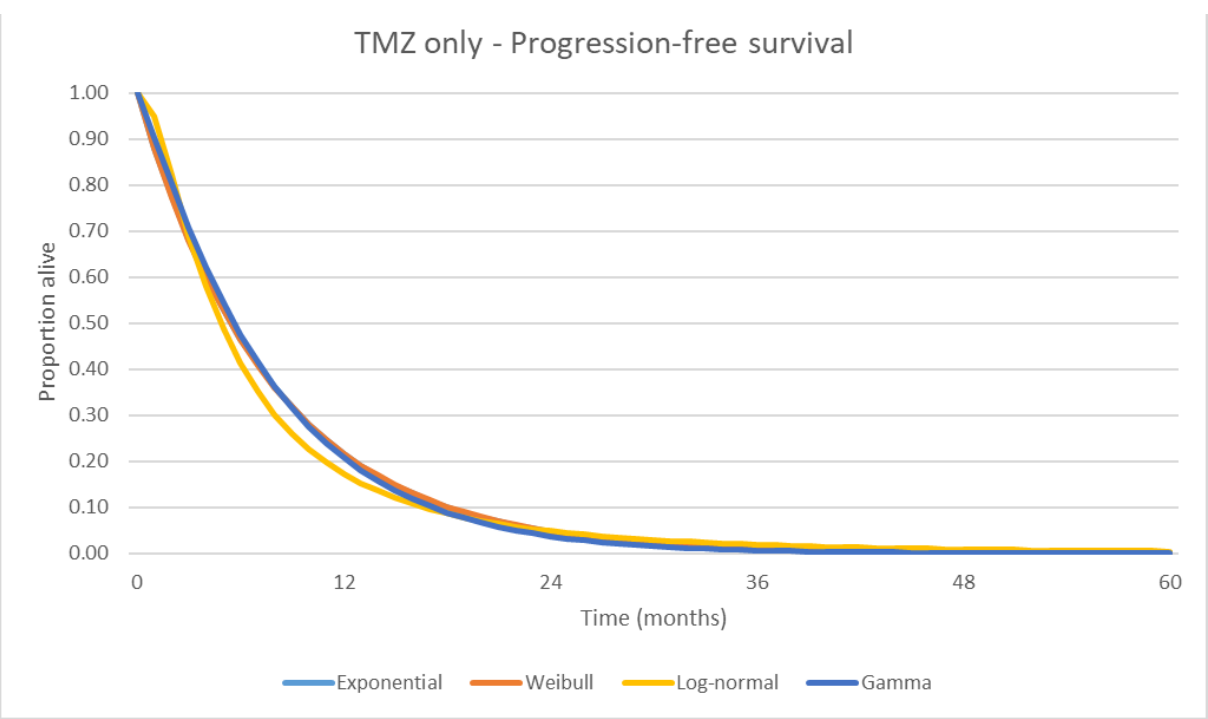
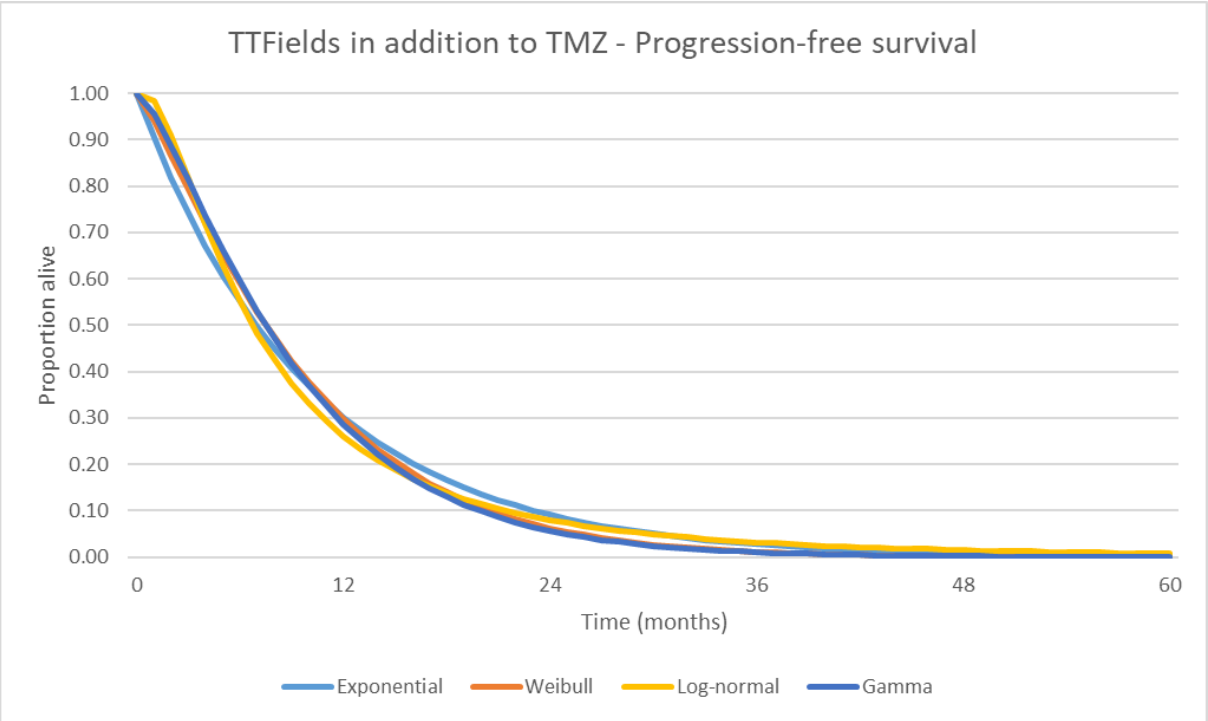


Figure 4S. 8. Extrapolated urvival curves for progression-free survival with TTFields plus TMZ (ndGBM)



14.5 Budget impact per year (2024-2028)

Table 5S. 1. Budget impact estimates per year (ndGBM)

Total costs	**2024**	**2025**	**2026**	**2027**	**2028**	**Total 2024-2028**
TTFields plus TMZ	7.678.804	7.678.804	7.870.482	7.870.482	7.906.194	39.004.766
TMZ only	2.706.142	2.071.269	1.579.245	1.198.321	944.372	8.499.349
Budget impact	4.972.662	5.607.534	6.291.237	6.672.161	6.961.822	30.505.416

Abbreviations
TMZ = temozolomide, TTFields = tumour treating fields.

Table 5S. 2. Budget impact estimates per year (rGBM)

Total costs	**2024**	**2025**	**2026**	**2027**	**2028**	**Total 2024-2028**
TTFields plus chemotherapy	11.622.912	11.622.912	11.622.912	11.830.464	11.830.464	58.529.664
Chemotherapy only	1.928.448	1.928.448	1.928.448	1.928.448	1.964.160	9.677.952
Budget impact	9.694.464	9.694.464	9.694.464	9.902.016	9.866.304	48.851.712

Abbreviations
TTFields = tumour treating fields.