Health Technology Assessment (HTA)

HTA Protocol

Title	**Tumour treating fields (TTFields) therapy for patients with glioblastoma multiforme**
Author/Affiliation	**Tim Kanters, Ingelin Kvamme, Stavros Anagnostopoulos, Irene Santi** **From Institute for Medical Technology Assessment, Erasmus University of Rotterdam** **Anouk Oordt** **From Epi-C (Epidemiology-Consultancy)** **Eveline Bunge** **Parttime systematic reviewer**
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Executive summary

Glioblastoma multiforme (GBM) is an aggressive type of brain cancer which corresponds to grade 4 of the World Health Organisation (WHO) classification of primary brain tumours. GBM is 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 represents the standard of care for patients with newly diagnosed GBM. Tumour treating fields (TTFields) are an additional treatment option in combination with temozolomide maintenance chemotherapy starting 4–7 weeks after radiochemotherapy. TTFields aim to prevent cell division by producing alternating electric fields and thus may inhibit the growth of the tumour. Four transducer arrays, which are placed on the patients shaved head, deliver low-intensity, intermediate-frequency alternating fields. Patients are instructed to wear the treatment modality as long as possible in order to maximise treatment effect.

TTFields are temporarily covered by the mandatory health insurance awaiting additional evidence collection. Whether the medical technology qualifies for statutory health insurance coverage is reconsidered in 2024. A Health Technology Assessment (HTA) report was requested to assist policy decision-making. In this HTA protocol, a primary and secondary research question and the operational key questions covering the HTA domains of efficacy/effectiveness/safety, budget impact/cost-effectiveness, ethical/legal/social/organisational issues are formulated and the methodological approach to conduct the HTA is described.

For the clinical review, a systematic literature search of the PubMed (MEDLINE), Embase.com, and Cochrane Library databases will be conducted adhering to international methodological standards. First, the databases will be searched for randomised controlled trials (RCT) and in case less than two RCTs are found, an additional systematic literature search for comparative non-randomised studies will be conducted. Search strings will be compiled for the GBM population and the intervention TTFields, without other search limits. Studies will be selected by applying pre-specified exclusion criteria during the selection process. Included studies will be critically appraised and extracted. The options for clinically relevant data merging/stratification and calculation of pooled estimates by meta-analysis will be explored after data-extraction.

For the economic evaluation, systematic literature searches of economic databases, such as PubMed (MEDLINE), Embase.com, Cochrane Library, Cost Effectiveness Analysis (CEA) registry, Tufts Medical Centre Cost-Effectiveness Analysis Registry, and National Health Service Economic

Evaluation Database (NHS EDD) will identify existing economic studies that are directly applicable to the research questions. The approach will be finalised during the HTA phase. The analysis will utilise up-to-date Swiss-specific cost and clinical inputs that are most applicable to the Swiss context. Finally, a budget impact analysis will be conducted.

For the evaluation of ethical, legal, social, and organisational domains, relevant issues will be identified from the studies included in the clinical evaluation. In addition, targeted non-systematic searches will be conducted to identify grey literature related to these domains; key issues will be summarised narratively.

Table of contents

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
CNS	Central Nervous System
DARTH	Decision Analysis in R for Technologies in Health
DNA	Deoxyribonucleic acid
EAE	Effectiveness, appropriateness, and economic efficiency
EANO	European Association of Neuro-Oncology
ELSO	Ethical, legal, social, and organisational
FDA	Food and Drug Administration
FOPH	Federal Office of Public Health
GBM	Glioblastoma multiforme
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IDH	Isocitrate dehydrogenase
INE	Insulated transducer array
KPS	Karnofsky-Performance-Status
LYs	Life years
MGMT	O^6-methylguanine DNA methyltransferase
MIGEL	Mittel und Gegenständeliste (Swiss Devices and Items List)
MRI	Magnetic resonance imaging
ndGBM	Newly diagnosed glioblastoma multiforme
NHS EED	National Health Service Economic Evaluation Database

NOS	Not otherwise specified
OECD	Organisation for Economic Co-operation and Development
OKP	Obligatorischen 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 multiforme
RoB 2	Revised Cochrane Risk of Bias tool for randomised trials
ROBINS-I	Risk of Bias in Non-randomised Studies – of Interventions
SF-36	Short-form 36
SoC	Standard of care
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 Protocol

Based on a preliminary screening of the literature the objective of the health technology assessment (HTA) protocol is to formulate the research question, to define the population, intervention, comparator, outcomes (PICO) and describe the methodology to conduct a systematic literature search, extract, analyse and synthesise the data in the HTA report on the topic. Key questions are defined, addressing the main HTA domains, i.e. efficacy/effectiveness/safety, budget impact/cost-effectiveness and ethical/legal/social/organisational issues.

1 Policy question and context

Glioblastoma multiforme (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, and maintenance chemotherapy. Treatment at recurrence is varied; the majority of recurrent GBM (rGBM) patients receive systemic treatment, mostly lomustine or less frequently rechallenge with temozolomide (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. [3] According to Roth and colleagues, patients who received radiotherapy or alkylating chemotherapy prior to recurrence should be placed on a different therapeutic modality. [4]

Since the U.S. Food and Drug Administration (FDA) approved the therapy in 2011, tumour treating fields (TTFields) are an additional treatment option for patients with GBM. TTFields are a non-invasive, outpatient treatment option for patients with GBM and are used in combination with maintenance TMZ treatment. [4] 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 two 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 will include evidence for a potential policy investment of expanding TTFields to rGBM patients. For the latter, the economic effectiveness evidence will be 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 will not include sensitivity analyses.

2 Research question

The HTA report will answer two 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 to maintenance chemotherapy alone?

In addition, the HTA report will answer the secondary question - in the treatment of ndGBM and rGBM adult patients after 1st progression in Switzerland, what is the efficacy, effectiveness, and safety, as well as cost-effectiveness and budget impact of TTFields alone or in combination with second-line systemic therapy (physician's choice chemotherapy) compared to second-line systemic therapy (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 (GBM). [7] Currently, the term glioblastoma is the most commonly used, however the term GBM can be found in relevant literature and therefore is also included in the current study. The 2021 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 characterized biology and prognosis. [8] One of the major changes between WHO CNS5 and WHO CNS4 consists of the restriction of the diagnosis of glioblastoma only to tumors that are *IDH* wild type, while previously glioblastomas were divided into (1) glioblastoma, isocitrate dehydrogenase (IDH)-wildtype; (2) glioblastoma, IDH-mutant; and (3) glioblastoma, not otherwise specified (NOS). [7,8] For the purpose of this protocol and the following HTA report, GBM will be used, covering both glioblastoma and glioblastoma multiforme, in line with the terminology used in the pre-scoping report.

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 to the most recent WHO definitions. Although GBM has a global incidence between 3.19 and 4.17 per 100,000 people, it 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 temozolomide in addition to adjuvant 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 symptoms like focal neurological deficit and cognitive impairments as well as dizziness, headaches, nausea, lethargy, seizures, hemiparesis, and stroke-like symptoms. [10,16,17]

GBM is diagnosed through magnetic resonance imaging (MRI) in combination with a contrast-enhancing agent. [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. 3-4 weeks after surgical resection, radiotherapy and chemotherapy are started for the 6 subsequent weeks. In general, following the Stupp protocol, patients receive radiotherapy 5 times per week and chemotherapy daily. After radiotherapy is completed, chemotherapy is given at a higher dosage for 5 days during a 28-day cycle. [11,15]

TTFields can be provided as an additional treatment option for patients with GBM used in combination with maintenance chemotherapy treatment. In a randomized, open-label trial, TTFields in addition to maintenance TMZ in ndGBM patients prolonged progression-free survival (PFS) and overall survival (OS), 6.7 and 20.9 months respectively, when compared with standard treatment alone, 4 and 16 months respectively. The estimated hazard rate was 0.63 (95% CI, 0.52-0.76) for the TTFields-temozolomide group and 0.63 (95% CI, 0.53-0.76; $P < .001$) in the temozolomide-alone group. [19]

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) 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 re-operation, re-exposure to chemotherapy or re-

irradiation, and palliative care (second-line systemic therapy). [20] Roth and colleagues described that the treatment of rGBM in Switzerland is less standardised than the treatment of ndGBM. While re-exposure to TMZ was more frequent in the past, lomustine is now increasingly being considered SoC. [17,21] Bevacizumab is also considered a useful option to reduce clinical symptoms burden in rGBM. Roth and colleagues suggests rGBM patients who were initially only treated with radiotherapy or alkylating chemotherapy should receive a different therapeutic modality than previously treated with. [4] ***Figure 1*** 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 EANO guidelines and reviewer feedback. [17]

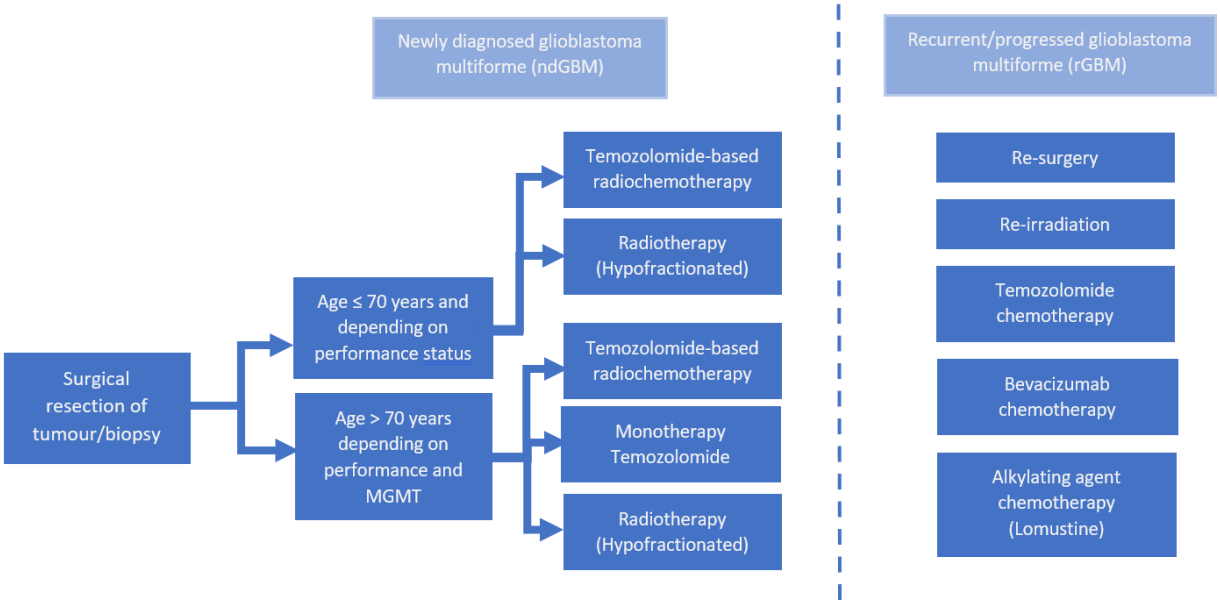

Figure 1. Treatment pathway glioblastoma multiforme (GBM), newly diagnosed and recurrent

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). [22] In this protocol, progression and recurrence are therefore used interchangeably as considered in the Cochrane review by McBain et al. [20]

4 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. TTFields are hypothesised to function through different mechanisms of action, including by disturbing cell mitosis, delaying DNA repair enhancing autophagy, inhibiting

cell metabolism and angiogenesis, and limiting cancer cell migration. 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 change 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. Further, the patient or caretakers are required to recharge the batteries and turning the device off and on. The device can be carried in a bag, thus allowing patients to partake in normal daily life. 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 recurrent glioblastomas
- 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 9.3***). 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 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 multiforme (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 Methodology

The general methodology for the HTA will consist of one systematic review for the clinical evaluation (***Section 7.1***), one systematic review for the economic evaluation (***Section 7.2***), and non-systematic reviews for the ethical, legal, social and organisational domains of the HTA (***Section 7.2.5***). The proposed methodology for the health economic and budget-impact modelling is outlined in ***Section 7.2.3*** and ***Section 7.2.4***.

7.1 Clinical evaluation

A systematic review is a method to identify, appraise and synthesise all the empirical evidence that meets pre-specified eligibility criteria to answer a specific research question. [23] The systematic review methodology described in this HTA protocol is developed in line with the Cochrane Handbook for Systematic Reviews of Interventions (Version 6.3) [23] and 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 will be implemented: (1) a systematic literature search for RCTs; and (2) in case less than two RCTs are found, an additional systematic literature search for comparative non-randomised studies.

The main sources for the systematic review will be peer-reviewed journal articles published in medical journal databases. Systematic literature searches will be conducted in three 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 will be conducted on the websites of ClinicalTrials.gov (https://clinicaltrials.gov) and the European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu).

The search strategy will be developed based on the PICO criteria reported in ***Chapter 5***. Search strings will be compiled for the GBM population (i.e. newly diagnosed or recurrent patients) and the intervention TTFields. No search limits will be applied. Studies will be selected by applying pre-specified exclusion criteria during the selection process (***Table 2***). The syntax of the search strategy will be composed for one medical database, PubMed (MEDLINE), and customised to the other databases. The details of the search strategies are outlined in ***Appendix 9.1***.

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

7.1.2 Study selection

Relevant articles will be selected by a systematic approach by two independent researchers. Firstly, the major topics of the articles will be assessed on relevancy to the objectives by the title and abstract. Articles that seem to contain relevant data for the objectives will be selected for full-text screening. Articles without relevancy to the objectives will be excluded, without documenting the reason for exclusion. Secondly, the articles will be assessed in full-text based on the pre-specified eligibility criteria. Articles will be included in the systematic review if they fulfil the inclusion criteria; the remaining articles will be excluded and the primary reason for exclusion will be listed.

The search results will be screened against the pre-specified eligibility criteria, based on elements of the article, study design and PICO (***Table 2***). If relevant additional criteria emerge during the study selection this table will be complemented in close collaboration with the Federal Office of Public Health (FOPH). To avoid steering the study selection, the FOPH will be blinded for the study details and results during this process. The final list of applied inclusion and exclusion criteria will be presented in the HTA report.

To provide insight in the details of the selection process, a PRISMA flow chart with the results of the study selection and a table with the primary reasons for exclusion by each excluded article at full-text review will be composed and included in the HTA report.

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 - 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
Intervention	TTFields either in combination with maintenance chemotherapy/second-line systemic therapy (physician's choice chemotherapy) or alone	- TTFields in addition to other therapies than maintenance chemotherapy/second-line systemic therapy (physician's choice chemotherapy)
Comparator	Maintenance chemotherapy/second-line systemic therapy (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 will be included for data extraction of the results[a]) - Unclear follow-up duration - Other outcomes

Abbreviations:

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

Notes:

a = Studies with interim results will be included as additional input on the study methodology, but the interim results will not be extracted.

7.1.3 Data extraction

Relevant data from the included studies found in the medical journal databases will be independently extracted by one researcher into a standardised data-extraction spreadsheet in Microsoft Excel. This spreadsheet will include:

- bibliographic reference
- study characteristics (study design, 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)
- intervention (dose density and duration of TTFields; type, dose, and duration of maintenance chemotherapy/second-line systemic therapy (physician's choice chemotherapy))
- comparator (type, dose, and duration of maintenance chemotherapy/ second-line systemic therapy (physician's choice chemotherapy))
- outcomes (overall survival, progression-free survival, HRQoL, adverse events, compliance/adherence)
- additional comments (study limitations or issues that will need to be considered not identifiable from other extracted data).

Details of ongoing RCTs found in ClinicalTrials.gov and the European Union Clinical Trials Register will be extracted and summarised in a table in Microsoft Word:

- study identifier
- status (e.g. recruiting, not yet recruiting)
- country
- study period
- enrolment (estimated, actual)
- population (ndGBM, rGBM)
- intervention (dose density and duration of TTFields; type, dose, and duration of maintenance chemotherapy/second-line systemic therapy (physician's choice chemotherapy))
- comparator (type, dose, and duration of maintenance chemotherapy/second-line systemic therapy (physician's choice chemotherapy))

- outcomes (overall survival, progression-free survival, HRQoL, adverse events, compliance/adherence).

7.1.4 Analysis of study quality

The included studies will be critically appraised by one researcher using different tools depending on the study design. The quality of RCTs will be assessed with the revised Cochrane Risk of Bias tool for randomised trials (RoB 2). [23,26] RoB 2 is a results-based tool which assesses the bias in an RCT for specific outcomes instead of assessing the risk of bias for the RCT as whole. If applicable, the comparative non-randomised studies will be assessed with the Risk of Bias in Non-randomised Studies - of Interventions (ROBINS-I) tool. [27]

The overall certainty of the evidence on outcome level will be appraised using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. [23,28] 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 involves appraisal of five domains: (1) risk of bias (i.e. study limitations), (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 (i.e. random error), 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 can be classified as high, moderate, low, or very low. The overall certainty of the evidence will be summarised in a GRADE summary of findings table, together with key information concerning the magnitudes of relative and absolute effects of the intervention and the amount of available evidence. [23] GRADEpro GDT software (Evidence Prime Inc., Canada) will be used to construct the summary of findings table for up to a maximum of seven patient-important outcomes.

7.1.5 Data analysis and synthesis of efficacy, effectiveness, and safety outcomes

The extracted data of the included studies in the Microsoft Excel spreadsheet will be summarised in study characteristics tables, risk of bias tables, summary tables, and a GRADE summary of findings table. When possible, forest plots will be created to visualise the results.

Based on the heterogeneity of the study characteristics and data reported in the included studies, the options for clinically relevant data merging/stratification will be explored and if necessary, discussed with a clinical expert. The clinical expert will be blinded for the study results during this process. The details of the applied data merging/stratification will be reported in the methodology section of the HTA report.

Pooled estimates will be calculated by meta-analysis for outcomes reported by at least two studies; if the outcome measures can be combined. If applicable, separate pooled estimates will be calculated for

the outcome data of RCTs and the comparative non-randomised studies. Considering the expected heterogeneity in the data, a random-effects model will be used for the analyses. [23] Heterogeneity will be assessed graphically with forest plots and statistically using the Chi^2 test, the I^2 statistic, and prediction intervals. The analyses will be conducted with the Comprehensive Meta-Analysis (CMA) software (Biostat, USA). For outcomes reported in a minimum of ten studies, the publication bias will be assessed using tests for funnel plot asymmetry. The results of the clinical trial registry search will be used for a narrative description of publication bias.

Outcomes for which it is not possible to calculate pooled estimates will be analysed narratively and presented in summary tables. A range of relative effects from the studies or direction of the effect will be presented.

7.1.6 Quality control

Quality control measures applied during the search strategy:

- An information specialist can be consulted during the development of the search strategy. The search strategy will be checked by a second researcher.

Quality control measures applied during the study selection:

- The titles and abstracts retrieved by the systematic literature searches will be screened in duplicate by two independent researchers. If the two researchers disagree on the relevance of an article, this will be discussed. If the differences remain after discussion, the article will be assessed in full text.
- The screening of full-text articles will be done in duplicate by two independent researchers. Any differences will be resolved by discussion, if needed a third researcher will be consulted.
- Relevant systematic reviews to our research question will be selected during the screening of titles and abstracts. During the full-text screening phase, the reference lists of these systematic reviews will be checked for possibly missed individual articles. Narrative reviews will be excluded directly and not be checked for references. The systematic review itself will be excluded after the reference check, with a documented reason for exclusion in the flow chart, and the additionally found individual articles will be assessed with our pre-specified eligibility criteria.
- The supplementary search technique backward citation chasing will be applied, i.e. by finding other studies cited within the included articles. The additionally found individual studies will be assessed with our pre-specified eligibility criteria.

Quality control measures applied during the data extraction, analysis, and synthesis:

- The data extraction Microsoft Excel spreadsheet, critical appraisal of the included studies, data synthesis files, summary tables, and the GRADE summary of findings table will be fully reviewed

by a second researcher. Differences will be resolved by discussion; in case of discrepancy a third researcher will be consulted to reach consensus.

7.2 Economic evaluation

7.2.1 Databases and search strategy

7.2.1.1 Search strategy

The cost-effectiveness systematic literature search follows the principles of the systematic literature search for the clinical evaluation outlined in ***Chapter 7.1***, with reviews performed in duplicate by two independent researchers and Rayyan software (Rayyan Systems Inc., USA) will be used for the selection of the articles. PubMed (MEDLINE), Cochrane library, and Embase.com databases will be searched for peer-reviewed scientific literature. In addition, economic databases, such as the Cost Effectiveness Analysis (CEA) Registry, Tufts Medical Centre Cost-Effectiveness Analysis Registry, and National Health Service Economic Evaluation Database (NHS EED), will be searched. The searches will be 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 will be combined with cost-effectiveness search terms. The details of the search strategy are presented in ***Appendix 9.2***.

7.2.1.2 Selection procedure

All articles retrieved from PubMed (MEDLINE), Cochrane library, Embase.com, NHS EED and the CEA registry databases, and relevant references will be reviewed in a similar manner to the systematic approach described in 7.1.2., including firstly screening title and abstract and subsequently full-text screening. In the first step, the major topics of the articles will be assessed based on relevancy and articles that seem to contain relevant data for the HTA objectives will be selected for the full-text screening. Subsequently, the articles screened in full-text are assessed for inclusion based on pre-specified eligibility criteria defined in the HTA protocol (***Table 3***). Like with the clinical evaluation eligibility criteria, if any relevant additional criteria emerge during the study selection, this table will be complemented in close collaboration with the FOPH, and the same blinding approach will be applied to avoid steering the study selection. The final list of applied inclusion and exclusion criteria will be presented in the HTA report. The process of selection and inclusion and exclusion of articles will be recorded in Microsoft Excel and Endnote version 20. This method will provide transparency regarding all selection steps and assures reproducibility. The selection procedure applied during the full-text screening phase will be reported in a PRISMA flow chart and primary reasons for exclusion per excluded article will be listed in a table, like in the clinical evaluation approach.

7.2.1.3 Inclusion and exclusion criteria

The inclusion and exclusion criteria which will be applied during the selection processes are listed in ***Table 3***.

Table 3 Inclusion and exclusion criteria for economic 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/ Type	Economic evaluations • Cost-utility analysis • Cost-effectiveness analysis • Cost-minimisation analysis • Cost-benefit analysis Budget impact analysis Costing studies	- Resource use measurement
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
Intervention	TTFields either in combination with maintenance chemotherapy/second-line systemic therapy (physician's choice chemotherapy) or alone	- TTFields in addition to other therapies than maintenance chemotherapy/second-line systemic therapy (physician's choice chemotherapy)
Comparator	Maintenance chemotherapy/second-line systemic therapy (physician's choice chemotherapy)	- Other comparators - No comparator
Outcome	Cost-effectiveness a. Health-care costs (total and incremental) b. Incremental cost-effectiveness ratio (ICER) and incremental and total costs, quality-adjusted life years (QALYs) and life years - 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 will be included for data extraction of the results[a]) - Unclear follow-up duration - Other outcomes

Abbreviations:

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

Notes:

a = Studies with interim results will be included as additional input on the study methodology, but the interim results will not be extracted.

7.2.2 Data extraction, analysis, and synthesis

7.2.2.1 Data extraction

The following relevant data from the included articles found in the peer-reviewed literature will be 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
- Primary sources for the resource use/cost inputs
- Primary sources for the HRQoL inputs

7.2.2.2 Critical appraisal

The identified studies from the systematic literature search for cost-effectiveness will be subjected to a critical appraisal using the Consolidated health Economic Evaluation Reporting Standards (CHEERs) [29] checklist and the Consensus Health Economic Criteria (CHEC) checklist [30] as recommended by the current guidelines. [31] 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.

7.2.2.3 Data synthesis

Data synthesis will be done using descriptive comparisons of the study question, methods, and results. Summary tables will be included which will present key information described in the data extraction chapter 7.2.2.1. The incremental cost-effectiveness ratios will be presented and the reliability (internal validity) and relevance (generalisability) of the estimates will be 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.

7.2.2.4 Quality control

The following quality control measures during the search strategy will be applied in a similar manner to the quality control approach for clinical evaluation:

- The titles and abstracts retrieved by the systematic literature searches will be screened in duplicate by two independent researchers. If the two researchers disagree on the relevance of an article, this will be discussed. If the differences remain after discussion, the article will be assessed in full text.
- The screening of full-text articles will be done in duplicate by two independent researchers. Any differences will be resolved by discussion, if needed a third researcher will be consulted.
- The data extraction spreadsheet will be fully checked with the original articles by a second researcher.

7.2.3 Economic model protocol

7.2.3.1 Target population

The population will be adult patients with GBM grade 4 (ndGBM and rGBM) after tumour resection and radiochemotherapy.

7.2.3.2 Setting and location

The analysis will be performed for the Swiss healthcare setting. This means that where possible and relevant input parameters will be based on data from Switzerland, e.g. Swiss lifetables for background mortality and Swiss sources for healthcare costs.

7.2.3.3 Study perspective

The analysis will be performed from a healthcare payer perspective. This means that only direct healthcare costs will be included. Societal costs, such as informal care and productivity costs, will not be included.

7.2.3.4 Intervention(s)

The intervention of interest is TTFields in addition to maintenance chemotherapy (TMZ) which in the base case will be provided the ndGBM patients until progression. A scenario analysis will be performed in which TTFields is extended in addition to second-line systemic therapy (physician's choice chemotherapy) to the rGBM patient population.

7.2.3.5 Comparator(s)

The comparison for the intervention is maintenance chemotherapy (TMZ) until progression and second-line systemic therapy (physician's choice chemotherapy) after progression.

7.2.3.6 Time horizon

The preferred time horizon of the base-case analysis is lifetime. A lifetime horizon will depend on the feasibility and availability of data. Shorter time horizons will be considered in scenario analyses, if relevant.

7.2.3.7 Discount rate

In the base-case analysis, costs and effects will be discounted at 3.0%. In scenario analyses, the impact of not discounting or using a discount rate of 5.0% will be explored.

7.2.3.8 Health outcomes

Health outcomes will be reported in life years (LYs) and quality-adjusted life years (QALYs).

7.2.3.9 Currency, price data, and conversion

Costs from the Swiss Federal Statistical Office will be reported in CHF adjusted for inflation to 2022 price levels using inflation rates, which will be accessed from the Organization for Economic Co-operation and Development (OECD) website (https://data.oecd.org).

7.2.3.10 Model structure

The structure of the GBM model will be based on previously published models comparing TTFields in combination with TMZ versus TMZ alone. Published studies identified through pragmatic literature searches on the cost-effectiveness of TTFields in ndGBM patients were based on the French, US, and Swedish setting. [32–35]

The general approach of the published cost-effectiveness models was a three-health-state Markov structure, including health states corresponding to 'Stable', 'Progression', and 'Dead'. Patients progress through the health states as illustrated in the conceptual model in ***Figure 2***. The stable state (or progression-free state) includes the time until first progression or until death from the stable state. The progression state represents the time until death. The dead state is an absorbing state.

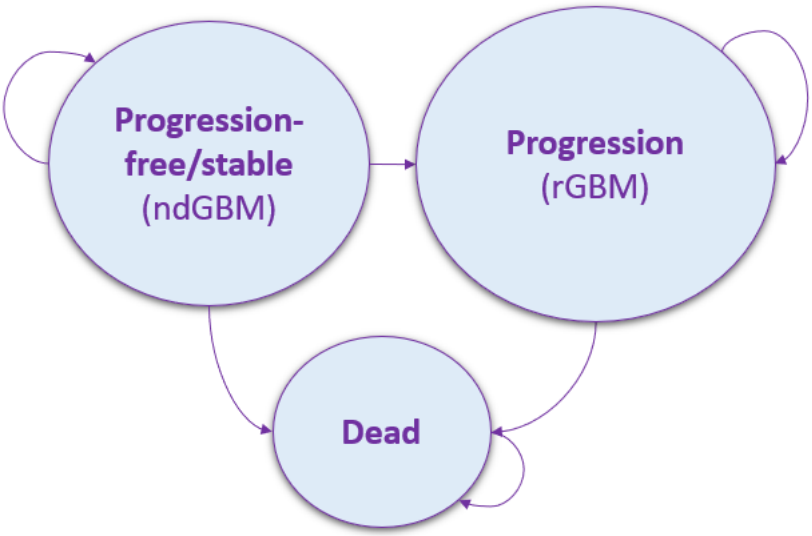

Figure 2. Model structure TTFields in glioblastoma

In addition to the published TTFields cost-effectiveness models, previous cost-effectiveness studies on GBM treatment follow a similar structure. This includes a cost-effectiveness study of TMZ in the treatment of rGBM in Finland, in which the initial health state is labelled 'Progression free' instead of the health state 'Stable'. [36–38]

The model will be programmed in statistical programming language R [39] based on the framework developed by the Decision Analysis in R for Technologies in Health (DARTH) workgroup. [40–42]

7.2.3.11 Input parameters

7.2.3.11.1 Health state transitions

The model input parameters on clinical outcomes will be informed mainly from the results of the data extraction of the systematic literature search of efficacy, effectiveness, and safety. Clinical expert opinion will be used whenever data is unavailable from the literature.

7.2.3.11.2 Adverse events

Adverse events will be modelled if sufficient data on relevant adverse events is available. The inclusion of adverse events in the previous cost-effectiveness models varied. Guzauskas et al 2019 modelled adverse events based on the EF-14 reported grade III-IV events, when occurring in more than 5% of trial patients (pulmonary embolism; seizure; infections; leukopenia or lymphopenia; general disorders; thrombocytopenia). [34] The cost-effectiveness report by Tandvårds-Läkemedelförmånsverket (TLV) 2017 describes adverse events in the EF-14 trial but does not mention inclusion in the adapted model. [35]

Bernard-Arnoux et al 2016 and the subsequent update to the French model by Connock et al 2019 did not include adverse events. [32,33]

While negative aspects of the TTFields treatment mentioned in literature includes dermatological events and uncomfortableness from social stigma of wearing the TTFields pads, such discomfort may be difficult to quantify and may only be addressed in the ethical, legal, social, and organisational (ELSO) domains. [18]

7.2.3.11.3 Background mortality

The background mortality, i.e. mortality not related to GBM, will be based on Swiss lifetables. [43] Because of the high mortality of GBM, background mortality is likely to play a minor role in the cost-effectiveness analysis.

7.2.3.11.4 Utilities

The model input parameters on utility will be based on findings in cost-effectiveness systematic literature review or from pragmatic searches in literature. Preferably, the applied utilities would be validated and disease-specific, however a preliminary pragmatic search suggests ndGBM and rGBM utility estimates are relatively scarce. While some of the previous models on European GBM models have applied utility parameters, the utility data used previously seems to be of limited quality. An updated version of the French model by Bernard-Arnoux applied estimates of health-state utilities associated with GBM by Garside et al 2007 as a scenario analysis. These values are based on 36 healthy volunteers from the general UK population and are therefore limited in their representativeness to the GBM patient population. [44] The Finnish cost-effectiveness analysis of TMZ in rGBM utilised quality of life (QoL) scores obtained from questionnaires (visual analogue scale method) filled in by six neuro-oncologists. [37] A pragmatic literature search for HRQoL in GBM patients yielded a 2020 Swedish study on HRQoL and emotional well-being of the Short Form 36 (SF-36) in GBM patients and their relatives based on a sample of 89 GBM patients. [45]

7.2.3.11.5 Resource use and costs

The following costs will be included in our model:

- costs of TTFields
- costs of TMZ
- healthcare costs of follow-up in every health state (follow up costs can include cost items such as clinical consultations, blood tests, and MRI)
- if modelled, cost of adverse events.

Where possible, Swiss resource use will be used. If not available, international data on resource use will be used instead, multiplied with Swiss unit costs as supplied by the FOPH. If resource use data is not available, international cost estimates will be used.

If no Swiss-specific data on costs, resource use, and utilities are identified in the systematic literature searches for efficacy, effectiveness, and safety and cost-effectiveness described in this report, additional pragmatic searches will be performed.

7.2.3.12 Analytical methods

7.2.3.12.1 Base-case analysis

The base-case analysis will be conducted using the settings for the input parameters and assumptions as described in the previous sections.

7.2.3.12.2 Subgroup and scenario analyses

Subgroup analyses will be based on the results of systematic review and may include analysis of MGMT methylation and of elderly patients, as these are both clinically very relevant groups. Structural uncertainty will be explored in several scenario analyses, using alternative assumptions and sources compared to the base case. Scenario analyses will include, but will not be limited to, a scenario analysis with the total GBM population (ndGBM and rGBM) treated with TTFields, and a scenario analysis based on the EF-14 trial data.

7.2.3.12.3 One-way sensitivity analyses (OWSA)

Parameter uncertainty is first tested using one-way sensitivity analyses (OWSA); model parameters are systematically and independently varied over a plausible range (e.g. using the 95% confidence interval (CI) or a 20% increase/decrease of the parameter value used in the base-case). The ICER is recorded at the upper and lower limits to produce tornado diagrams.

7.2.3.12.4 Probabilistic sensitivity analyses (PSA)

Joint parameter uncertainty is explored through probabilistic sensitivity analysis (PSA) where all parameters, to which probability distributions are assigned, are varied jointly. Monte Carlo simulations will be performed, and the results will be recorded. Results will be plotted on the cost-effectiveness plane (CE-plane). From these results, a cost-effectiveness acceptability curve (CEAC) will be estimated.

7.2.4 Budget Impact Analysis

In addition to the cost-effectiveness model, a budget impact (BI) model will be developed to calculate the projected population-level overall costs of TTFields in adults with ndGBM from the healthcare payer

perspective. The BI model will be built as an extension to the cost-effectiveness model, described above. Hence, the core model characteristics for the BI model will be dependent on the cost-effectiveness model. The time horizon of the BI model will be restricted to 5 years, for the period 2024-2028. For the BI model, data is required about the current use of TTFields in adults with ndGBM in Switzerland. Data on current use will be provided by FOPH if such data is available. If this data is not available, assumptions will be made based on data from other comparable countries and/or expert opinion. Like the cost-effectiveness analysis, the secondary research question will be addressed in a scenario analysis in the BIA. Any subgroups of interest identified in the systematic reviews can be analysed, and uncertainty can be addressed with scenario analyses.

7.2.5 Ethical, legal, social, and organisational aspects protocol

The full texts of studies identified for ethical, legal, social, and organisational aspects encountered during the efficacy, effectiveness, and safety and cost-effectiveness systematic literature searches will be reviewed. In addition, grey literature on these HTA domains will be searched for on relevant websites, such as the Swiss Neuro-Oncology Society and European Association of Neuro-Oncology.

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9 Appendices

9.1 Search strategy for clinical evaluation systematic literature search

Table 4. Search strategy for clinical evaluation systematic literature search: 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 5. Search strategy for clinical evaluation systematic literature search: 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

Table 6. Search strategy for clinical evaluation systematic literature search: 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 7. Search strategy for ongoing RCTs on 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

9.2 Search strategy for economic evaluation systematic literature search

Table 8. Search strategy for the cost-effectiveness systematic literature: 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]

Table 9. Search strategy for the cost-effectiveness systematic literature search: 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
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 (lifeyear* OR lifeyear*)) OR qaly*):ab,ti

9.3 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