Consolidated stakeholder feedback

HTA report

Tumour treating fields (TTFields) therapy for patients with glioblastoma

Stakeholders (SH; in alphabetical order) that have provided comments:

1	curafutura
2	Novocure GmbH
3	Onkologiepflege Schweiz
4	santésuisse
5	Schweizerische Neurologische Gesellschaft SNG
6	Schweizerische Gesellschaft für Medizinische Onkologie SGMO
7	Schweizerische Gesellschaft für Neurochirurgie SGNC

SH	SH comment	Reply authors / BAG & implemented changes
1	Evidenz und Nutzen TTF bei ndGBM-Patienten Die Evidenz ist auf Grund nur weniger Studien niedrig. Der klinische Nutzen in Bezug auf overall survival für TTF bei ndGBM-Patienten erscheint auf Grundlage einer multi-country RCT als gegeben. TTF bei Patienten mit GBM at first recurrence Die Evidenz ist niedrig, der klinische Nutzen ist nur in einer posthoc Analyse über ein längeres overall survival beschrieben worden. Für Patienten at all recurrences, ist ein längeres overall survival nur beschrieben, wenn man diese auf die Gruppe mit zumindest einem course of TTF beschränkt, was deutliche Bias/Unsicherheiten birgt. Es ist aus unserer Sicht nicht möglich, eine Empfehlung für die TTF bei rGBM zu geben. Cost-effectiveness Die Behandlung ist gemäss gesundheitsökonomischen Standards (QALY-Grenzwerte) nicht kosteneffizient. Translation: Evidence and utility of TTF in ndGBM patients The evidence is low due to only a few studies. The clinical benefit in terms of overall survival for TTF in	No change needed.

	ndGBM patients appears to be given based on a multi-country RCT. TTF in patients with GBM at first recurrence The evidence is low, the clinical benefit has only been described in a post hoc analysis of longer overall survival. For patients with all recurrences, a longer overall survival is only described if this is limited to the group with at least one course of TTF, which harbors significant bias/uncertainties. In our opinion, it is not possible to give a recommendation for the TTF in rGBM. Cost effectiveness The treatment is not cost-effective according to health economic standards (QALY limits).	
1	Weitere Bemerkungen: - Indikation: Die Fragestellung „TTFields alone or in combination with second-line systemic therapy“ ist in der Schweiz nicht relevant, da keine Zulassung besteht. Translation: Further remarks: - Indication: The question “TTFields alone or in combination with second-line systemic therapy” is not relevant in Switzerland as there is no approval.	In addition to the ndGBM population, the evidence base also allows TTFields to be investigated in patients with rGBM. In order to assess the complete evidence base, the rGBM population was also included.
1	- Results: Bei ndGBM war PFS der primäre Endpunkt (nicht OS) im einzigen RCT (Ref11876). Translation: - Results: In ndGBM, PFS was the primary endpoint (not OS) in the only RCT (Ref11876).	Data on the primary endpoint progression-free survival as well as the secondary endpoint overall survival was extracted. No change needed.
1	- Compliance: Wir erachten die Compliance als nicht wirklich beurteilbar, denn es fehlen Angaben darüber, wie lange die TTF pro Tag tatsächlich getragen wurden. Translation: - Compliance: We do not consider compliance to be really assessable because it is missing information about how long the TTF was actually worn per day.	Reported data on compliance was extracted and described in the results section of Chapter 7, but these outcomes were not included in the GRADE summary of findings tables. Furthermore, factors that can impact compliance were discussed in the ELSO domains. No change needed.
1	- Reproduzierbarkeit: Die im initialen RCT (Ref11876) erzielten Resultate konnten in anschliessenden Trials nicht reproduziert werden. Translation: - Reproducibility: The results achieved in the initial RCT (Ref11876) could be achieved in cannot be reproduced in subsequent trials.	A broad systematic literature search was conducted and no new RCTs were found. In addition, two comparative non-randomised studies on TTFields treatment in patients with ndGBM were included. No change needed.
2	A. The HTA report does not correspond to the predefined research questions. The described patient population is broader than in the 2nd research question defined. Specification: The 2nd research question is inadequately addressed in the report: The two predefined populations in the research questions (ndGBM and rGBM at 1st recurrence) are differently represented afterwards in three populations as: A. ndGBM, B. rGBM at first and C. rGBM at all recurrences (EF-11). Notably, the EF-11 in rGBM patients included 88% of patients at 2nd and later recurrences. Consequently, this study should not be considered for the response of the 2nd research question.	The population in PICO and the eligibility criteria was defined broad (i.e. adult patients with glioblastoma [newly diagnosed and recurrent] after tumour resection/biopsy and radiochemotherapy), to provide a complete overview of the scarce evidence base and to include the pivotal trial on TTFields in rGBM which resulted in the first FDA approval of TTFields. As outlined in the HTA protocol, the options for clinically relevant data merging/stratification were explored based on the heterogeneity of the study characteristics and data reported in the included studies, and it was decided to report the results of the clinical evaluation systematic review stratified for 3 GBM populations. The economic modelling focused on the populations ndGBM and GBM at first recurrence. The details of the recurrence distribution of the EF-11 rGBM population were specified in the study characteristics section

		of the HTA report and based on this stakeholder comment this information is added also to the executive summary, summary statements and conclusions.
2	B. An HTA report is expected to apply a thorough, consistent, systematic and well-balanced scientific approach and reflect information impartially. Specification: The HTA analysis on comparative, non-randomized studies includes two studies only. Based on these two single-centre retrospective cohort studies in patients with ndGBM, it was stated that effectiveness results are inconclusive. In contrast, a recently published, peer-reviewed systematic pooled meta-analysis (Ballo et al, 2023) including six comparative non-randomized studies, including the two articles mentioned above, suggests survival may be improved with the addition of TTFields to SOC in ndGBM patients.	The systematic review methodology described in this HTA report is developed in line with the Cochrane Handbook for Systematic Reviews of Interventions and the report is drafted in adherence to the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. The literature search for comparative non-randomised studies followed a systematic approach. The 6 comparative non-randomised studies included by Ballo et al 2023 were all captured with our systematic literature search: 2 studies were included; 2 studies were excluded during the title/abstract selection (i.e. determinants for compliance and subgroup comparisons of molecular drivers were out of scope); and 2 studies were excluded during full-text selection (see reason for exclusion in Table 1S. 6). No change needed.
2	C. The cost effectiveness analysis in the HTA report differs considerably to the evaluation of a Swiss health economist: •The BAG HTA report CEA yields an Incremental Cost-Effectiveness Ratio (ICER) of 569,895 CHF when assessing the quality-adjusted life years (QALYs). •In contrast, the Novocure Swiss CEA localized in partnership with a Swiss health economist has a lower ICER of 179,203 CHF per QALY. Key Differences: •Both models employ similar input parameters; however, two significant distinctions exist: -OS and PFS extrapolation […] Underestimation of LYs and QALYs: •The differences in the extrapolation methods result in an underestimation of life years (LYs) and QALYs gained in the BAG HTA report CEA, leading to lower value. *Specification* C. The cost effectiveness analysis in the HTA report differs considerably from the model adapted by the York Health Economic Consortium (YHEC) with support from the University of Lucerne. […] ICER and QALYs: • The BAG HTA report CEA yields an Incremental Cost-Effectiveness Ratio (ICER) of 569,895 CHF when assessing the quality-adjusted life years (QALYs). • In contrast, the Novocure Swiss CEA localized in partnership with a Swiss health economist from the University of Lucerne has a lower ICER of 179,203 CHF per QALY. Key Differences: • Both models employ similar input parameters; however, two significant distinctions exist: o OS and PFS extrapolation.	In the final report, the ICER was estimated to be CHF 555,465 per QALY gained. Three cost-effectiveness studies were identified in the systematic review: Bernard-Arnoux et al 2016, Guzauskas 2019 and Connock et al 2019. The differences between the three published studies are described in chapter 8.2.2.1. The stakeholder refers and uses a cost-effectiveness analysis published by Guzauskas et al (2019). The Guzauskas et al 2019 analyses applies a Bayesian three-stage method to estimate survival: using survival from the EF-14 trial for the first 5 years; US epidemiological data for years 5-10 and years 10-15; and age adjusted general population estimates from year 16 onwards. This approach is rebutted by Connock et al 2019. They argue that the Bayesian approach overestimates the survival for patients receiving TTFields: after 20 years, the Bayesian model predicts approximately 8% of patients receiving TTFields to still be alive, which is considered an overestimate. Connock et al argue that there is an apparent inconsistency of the modelled trajectory for the first 5 years and later years. In addition, there are likely important differences between the population of 5-year survivors from the EF-14 trial and the population in the epidemiological study, which makes the Bayesian approach questionable. In addition, Connock et al argue that costs for the TTFields arm are underestimated. A version of the Bayesian model was submitted to Haute Autorité de santé (HAS), France. There, reviewers also raised concerns about this approach, restating the issues identified by Connock et al 2019. HAS' reviewers viewed the choice for the Bayesian approach to be unjustified with a lack of sufficient clinical validation. In contrast, two other studies (Bernard-Arnoux et al 2016 and Connock et al 2019) used information from the EF-14 trial as the single source for effects. These studies have substantially higher ICER estimates. When mimicking the Bayesian approach used by Guzauskas et al, Connock et al find markedly lower ICER estimates. This underlines the impact of the model structure on the ICER. In addition to the observation that the Bayesian approach is methodologically inferior, the methodology would require additional information on the long-term effects. The epidemiological data used in the stems from the US and might not be representative for the Swiss population. Swiss-specific data is not available. In line with the studies by Bernard-Arnoux et al and Connock et al, the cost-effectiveness analyses in the current HTA are based on the EF-14 trial. The results of the cost-effectiveness analysis in the current HTA are consistent

		with the outcomes of the Bernard-Arnoux et al and Connock et al estimates. The argumentation described in Connock et al 2019 that the Bayesian approach is inferior was followed in the current HTA. The following text was added to chapter 8.2.2.1 to explain differences between the Guzauskas et al 2019 and Connock et al 2019 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). 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.“ In addition, the following text was added to the discussion chapter: “Connock et al 2019 identify the drawbacks of the Guzauskas et al 2019 model, which lead to an overoptimistic ICER value. This critique has been reiterated in the HTA submission to HAS in France. The cost-effectiveness model in the current HTA was therefore in line with the methodology employed in the Connock et al 2019 study." The interested reader is referred to the cited reference for a more detailed description.
2	-Time Horizon: The BAG HTA report CEA has a 10-year time horizon, while the Novocure Swiss CEA extends to 40 years. A longer horizon in the latter model contributes to higher QALYs and reduces the ICER. Incomplete Benefits Consideration: •The 10-year horizon in the BAG HTA report CEA does not fully capture the long-term advantages of TTFields+TMZ compared to TMZ mono treatment. This results in the ICER not fully reflecting the extended benefits. Other HTA Assessments: •Other HTA assessments in countries such as Sweden (TLV) and France (HAS) have adopted a 20-year time horizon. *Specification* The time horizon considered in the BAG HTA report is a lifetime horizon, which in their model is 10 years. Novocure Swiss CEA, on the other side, considers a life-time horizon of 40 Years; this is based on the article published by Guzauskas et al., where epidemiological observations suggest a positive trend in GBM survival prognosis over time. Building upon this insight, the average lifetime survival for ndGBM patients undergoing treatment with TTFields and maintenance Temozolomide (TMZ) was calculated. Hence, the Novocure Swiss CEA for ndGBM contemplates a lifetime horizon of 40 years (considering the patients average age in the EF14 is 56 years). Furthermore, the Novocure model also considers the Guzauskas et al. extrapolation approach, discussed in the Overall Survival and progression-free survival curves section. Considering a horizon of 10 years, as the BAG HTA has suggested, the benefits of TTFields+TMZ vs. TMZ mono are not considered in the analysis. The ICER results do not fully capture the long-term advantages due to shorter treatment durations.	When using the Bayesian approach published by Guzauskas et al 2019 and described above, there is a substantial proportion of patients still alive after 10 years. To fully capture costs and effects of TTFields, this would indeed necessitate a longer time horizon. TLV in Sweden and HAS in France have adopted the Bayesian approach, and thus a longer time horizon is necessary. It should be noted that TLV’s clinical experts criticized the time horizon of 40 years used in the company submission. The TLV therefore estimated that there is no reason for using a time horizon longer than 20 years in the cost-effectiveness analyses. In contrast to the Bayesian estimates and because of an alternative modeling approach, in the current HTA over 99.5% of patients in the TTFields arm have died in the model used after 10 years. Chapter 8.1.5.6 of the HTA report describes that most patients have died after 10 years as the rationale for using this time horizon. Extending the time horizon to for instance 20 or 40 years would therefore not affect the results in the current HTA. No change needed.

	Another point to consider in the lifetime horizon is HTA assessments, such as Sweden (TLV) and France (HAS); the time horizon has been 20 years.	
2	Data Sources and Extrapolation: •The BAG HTA report CEA employs a lognormal distribution to extrapolate both survival curves for both arms. •The Novocure Swiss CEA uses a published and accepted by other HTA bodies approach for the TTFields+TMZ arm, involving a 3-phase approach for OS and a Weibull distribution for PFS.	The choice for log-logistic distribution for the extrapolation of survival curve was based on AIC and BIC. This is explained in chapter 8.1.5.13. Alternative distributions have been used in scenario analyses. Using a Weibull distribution results in an ICER of CHF 618,292 per QALY gained. No change needed.
2	3. Summary of guidelines do not reflect contemporary recommendations. The HTA report highlights discrepancies between guidelines based on a poster from 2019 (McLean et al.), and without providing accurate context to the interpretation. The poster reveals discrepancies between guidelines due to their outdated status and calls for updating them according to current practices. Moreover, it underlines that many accredited neurologic therapy centers in Switzerland and Germany include TTFields in their SOPs, showing that internal guidelines are more current and more recently updated. Current guideline status in countries with TTFields availability: A. latest NCCN guidelines (USA) recommend TTFields/TMZ as preferred treatment option in ndGBM patients; B. DGHO, SSMO, ÖGHO (Onkopedia) and Swedish (TVL) clinical guidelines as well recommend TTFields/TMZ. The in-depth described NICE guidelines are applicable in the UK, where TTFields is available on a single case base only.	Chapter 9.2.4 reports on the findings from the search on the ELSO domains. Information that has not been identified in the ELSO search has therefore not been added to this section. The description of the McLean et al 2019 study has been specified with the following phrase: “at the moment the McLean et al 2019 study was conducted". The information on guidelines and recommendations on reimbursement of TTFields in chapter 10.1 from has been expanded.
2	4. Further inaccuracies were identified in the report. Examples: • The EF-14 study protocol foresaw treatment with TTFields until 2nd disease progression. Approximately 50% of the patients followed this therapy schema. The significant progression-free survival and overall survival benefit is derived from the analysis of the whole patient population. This information is not adequately described but crucial for evidence-based decision making. There is no scientific basis to estimate safety and efficacy for the subpopulation of patients, who stopped treatment at 1st progression. • Citations from articles are taken out of context. For example, the report states “In the TTFields plus chemotherapy arm the number of patients with more than 1 grade 3-4 severe adverse event was higher than in the chemotherapy arm, however, no p-value was reported for this difference.” In the EF-14 trial, the difference in number of adverse events between treatment arms is commented as follows: “The numerically slightly higher incidence of hematological toxicity, fatigue, and some other adverse effects are due to the longer treatment duration and observation time in the experimental group. The differences disappear when data are normalized to treatment duration.” • The statements in the conclusions of the executive summary are not accurate. Regardless of the fact that the EF-11 (all recurrences, monotherapy) does not provide an adequate response to the 2nd (at first progression only, in addition to chemo), the EF-11 is described as: “...TTFields treatment alone compared	• The population of the EF-14 trial and the post-hoc analysis of Kesari et al 2017 is highlighted shortly in the discussion section. Agreed, this should be emphasized in the HTA report. This was added these details to the study characteristics description and to the limitations of the clinical evaluation systematic review. • In the HTA report the following is reported on the safety data of the EF-14 trial: “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.” This is in line with the article of Stupp et al 2017: “The addition of TTFields to temozolomide therapy was not associated with any significant increase in rates of systemic adverse events compared with temozolomide therapy alone (48% vs 44%,respectively; P=.58).” Since this is a non-significant result, the additional explanatory sentence in the article (“The numerically slightly higher incidence of hematological toxicity, fatigue, and some other adverse effects are due to the longer treatment duration and observation time in the experimental group. The differences disappear when data are normalized to treatment duration.”) was not added to the HTA report. For the post-hoc analysis in patients with GBM at first recurrence no p-value was reported for the difference in the number of patients with more than 1 grade 3-4 severe adverse event, and Kesari et al 2017 did not report that “The differences disappear when data are normalized to treatment duration.“ No change needed.

	with chemotherapy … probably reduces severe adverse events … have no effect on HRQoL …" 1. As it is not added to chemo it does not reduce sAEs, it shows less compared to BPC. 2. the data don't show if TTFields therapy has effects on QoL or not. It shows that the QoL differs from those patients that received BPC. Furthermore, those patients receiving TTFields monotherapy had a better QoL compared to BCP (presumably due to lower rate of AEs). Those are examples that demonstrate that the evaluation is not fully accurate and may be misleading. Overall the quality of the data interpretation is not consistent and accurate.	Agreed. The two conclusion statements for SAEs and HRQoL in the populations GBM at all recurrences are rephrased in 'shows'. … "probably reduces severe adverse events (1 RCT; moderate certainty evidence), and may have little or no effect on HRQoL but the evidence is very uncertain (1 RCT; very low certainty evidence)" is rephrased in … "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)"
2	Underestimation of LYs and QALYs: • The differences in the extrapolation methods result in an underestimation of life years (LYs) and QALYs gained in the BAG HTA report CEA, leading to lower values. BAG HTA Report: Health economic section The cost-effectiveness analysis (CEA) for newly diagnosed Glioblastoma (ndGBM) from the BAG HTA report is a partitioned survival model; the ICER/ QALYs from this analysis is 569,895CHF. On the other side, the Novocure Swiss CEA for ndGBM is also a partition survival model; the ICER/ QALYs from this analysis is 179,203 CHF. Overall, both models consider the same inputs, but the time horizon and Optune price are two significant differences. Table 1 is a comparative table of both models, and Table 2 is a comparative table adjusting price and horizon to be equal to the BAG HTA CEA. In Table 1, the time horizon is one of the main drivers leading to a lower ICER. Another variable influencing the results, which explains the lower ICER in Table 2, is the extrapolation of the Overall Survival (OS) and progression-free survival (PFS) curves. […] Overall Survival and progression-free survival curves In healthcare decision-making, including PFS and overall survival OS curves within CEAs is crucial in providing a comprehensive assessment of medical interventions' clinical and economic implications. In the case of the BAG HTA report and the Novocure Swiss CEA, EF14 trial data was used for the OS and PFS Kaplan-Meier (KM) curves. Since the information of the EF14 is up to 5 years, these curves are extrapolated using different types of distributions, and through statistical tests, the best extrapolation is incorporated into a model. Based on their statistical test, the BAG HTA report CEA considers a lognormal parametric distribution to extrapolate both survival curves in both arms. On the other side, the Novocure Swiss CEA for ndGBM considers a different approach for the TTFields+TMZ arm extrapolation. The OS uses a 3-phase approach, the EF14 data up to year 5, long-term conditional survival probabilities from the epidemiological literature up to year 15, and Switzerland background mortality for patients who survived beyond year 15. For the PFS survival, data from the EF14 is directly incorporated up to year 5 and Weibull distribution thereafter. The choice of methodology for using a 3-phase approach for the OS is outlined in Guzauskas et al. Their study involved employing a regression-based analysis to conclude that a 3-phase extrapolation method proved a better approach for estimating lifetime survival. For the regression-based analysis, the development of parametric distribution models included the exponential, Weibull, log-logistic, and log-normal	In the final report, the ICER was estimated to be CHF 555,465 per QALY gained. Three cost-effectiveness studies were identified in the systematic review: Bernard-Arnoux et al 2016, Guzauskas 2019 and Connock et al 2019. The differences between the three published studies are described in chapter 8.2.2.1. The stakeholder refers and uses a cost-effectiveness analysis published by Guzauskas et al (2019. The Guzauskas et al 2019 analyses applies a Bayesian three-stage method to estimate survival: using survival from the EF-14 trial for the first 5 years; US epidemiological data for years 5-10 and years 10-15; and age adjusted general population estimates from year 16 onwards. This approach is rebutted by Connock et al 2019. They argue that the Bayesian approach overestimates the survival for patients receiving TTFields: after 20 years, the Bayesian model predicts approximately 8% of patients receiving TTFields to still be alive, which is considered an overestimate. Connock et al argue that there is an apparent inconsistency of the modelled trajectory for the first 5 years and later years. In addition, there are likely important differences between the population of 5-year survivors from the EF-14 trial and the population in the epidemiological study, which makes the Bayesian approach questionable. In addition, Connock et al argue that costs for the TTFields arm are underestimated. A version of the Bayesian model was submitted to Haute Autorité de santé (HAS), France. There, reviewers also raised concerns about this approach, restating the issues identified by Connock et al 2019. HAS' reviewers viewed the choice for the Bayesian approach to be unjustified with a lack of sufficient clinical validation. In contrast, two other studies (Bernard-Arnoux et al 2016 and Connock et al 2019) used information from the EF-14 trial as the single source for effects. These studies have substantially higher ICER estimates. When mimicking the Bayesian approach used by Guzauskas et al, Connock et al find markedly lower ICER estimates. This underlines the impact of the model structure on the ICER. In addition to the observation that the Bayesian approach is methodologically inferior, the methodology would require additional information on the long-term effects. The epidemiological data used in the stems from the US and might not be representative for the Swiss population. Swiss-specific data is not available. In line with the studies by Bernard-Arnoux et al and Connock et al, the cost-effectiveness analyses in the current HTA are based on the EF-14 trial. The results of the cost-effectiveness analysis in the current HTA are consistent with the outcomes of the Bernard-Arnoux et al and Connock et al estimates. The argumentation described in Connock et al 2019 that the Bayesian approach is inferior was followed in the current HTA. The following text was added to chapter 8.2.2.1 to explain differences between the Guzauskas et al 2019 and

	functions, utilizing the Kaplan-Meier survival data from the EF14 trial to assess their accuracy vs real-world evidence. Their analysis concluded that log-normal distribution was the best fit for patients under treatment with TTFields+TMZ and the log-logistic distribution for TMZ monotherapy. This analysis showed that the parametric model underestimated the actual survival outcomes for the TMZ Monotherapy group and the conditional survival within the 5-10-year range for patients on TTFields+TMZ compared to those solely on maintenance TMZ. These findings underscore the complexities associated with relying on parametric models to accurately represent patient outcomes compared to real-world data. The 3-phase approach has been used in other HTA such as the Tandvårds- och läkemedelsförmånsverket (TLV) in Sweeden and the Haute Autorité de santé (HAS) in France Due to the information presented above, a parametric extrapolation underestimates the LYs and QALYs gained in the BAG HTA report CEA, leading to lower values and a higher ICER. […] The table below considers all the relevant outputs of the analysis, considering a horizon of 10 years and an Optune price list of 14,320 CHF. The last table considers the costs of the BAG HTA report CEA and the utilities from the Novocure model, meaning that it includes an extrapolation without underestimating the long-term benefits of TTFields+TMZ (which the BAG HTA report CEA curves do).	Connock et al 2019 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). 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." In addition, the following text was added to the discussion chapter: "Connock et al 2019 identify the drawbacks of the Guzauskas et al 2019 model, which lead to an overoptimistic ICER value. This critique has been reiterated in the HTA submission to HAS in France. The cost-effectiveness model in the current HTA was therefore in line with the methodology employed in the Connock et al 2019 study." The interested reader is referred to the cited reference for a more detailed description. 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. These were therefore used in the economic model. The choice for log-logistic distribution for the extrapolation of survival curve was based on AIC and BIC. This is explained in chapter 8.1.5.13. Alternative distributions have been used in scenario analyses. Using a Weibull distribution results in an ICER of CHF 604,693 per QALY.
2	It is stated that patients or caretakers have to recharge the batteries every 2-3 hours for 3-4 hours. In daily clinical practice, several spare batteries are provided together with a charging station. This allows patients to switch the batteries on the spot. Empty batteries can be recharged during the night when the device is powered via the power grid.	Additional information on spare batteries, charging station, and the device's direct connection to power supply has been added in the technology description section.
3	Thank you for including the role of carers in detail and it is sufficiently described in the following sections from our point of view: - Importance of social support and caregiver's role - Nurse's role in education and compliance It is not uncommon for radiotherapy to be required during the course of treatment, and we therefore suggest that the detailed recommendations be amended to state that skin observation becomes more important after radiotherapy and is mentioned in the section. 9.2.6 Importance of social support and caregiver's role	Additional information on skin toxicity during concurrent treatment with TTFields and radiotherapy was added to the section.
4	Der Bericht ist gut strukturiert. Die Aussagekraft des HTA-Berichtes ist insofern limitiert, als die zugrundeliegenden RCT's zu ndGBM und first rGBM auf dem einzigen anbieter-gesponserten EF-14 Trial (open-label) mit unterschiedlichen Analysen beruhen (Stupp 2017 / 2015, Kesari 2017, Taphoom 2018). Die RCT's zu all rGBM basieren auf dem vorangehenden, ebenfalls anbieter-gesponserten EF-11 Trial (Stupp 2012, Kanner 2014). Bei den RCT's handelt es sich teilweise um nicht-geplante post-hoc Analysen. Nur bei einer von zwei nicht-randomisierten, retrospektiven, single-center Kohortenstudien (Liu, 2020, Chen, 2021) konnte hinsichtlich ndGBM bei tiefen Fallzahlen und niedriger Evidenz ein positiver Effekt (PFS) gezeigt werden. Weitere Einschränkungen zum Bericht	The aim of this HTA was not to study the prognostic/predictive relevant factors. RCTs apply randomisation for an equal distribution of these factors and the risk of bias for the unplanned post-hoc analyses in subgroups was considered high. The comparative non-randomised studies applied analysis methods to control for confounding. No change needed.

	ergeben sich teilweise aus cross-over (Kontrolle zu Intervention), substantiellen Risiken von Biases sowie aus fehlenden Erläuterungen zu möglichen Effekten von prognostisch / prädiktiv relevanten Faktoren (bspw. IDH-Mutation, MGMT-Status), welche sich teilweise in Interventions- und Kontrollgruppen unterscheiden. Ergänzende Angaben sowohl zur zugrundeliegenden Literatur als auch zur Begründung der befristeten Regelung in der MiGeL (2021) wären zweckmässig, wobei die Relevanz der mit dem HTA zusätzlich gewonnen Erkenntnis unklar bleibt. Bei einem verhältnismässig geringen klinischen Vorteil der TTFields-Behandlung von nur wenigen Monaten (OS: 4.9m, PFS: 2.7m) sowie einem fehlenden Effekt auf HRQoL stellt sich insbesondere bei sehr hohen Kosten und der fehlenden Kosten-Effizienz die Frage der klinischen Relevanz. Das Kosten-Nutzen-Modell für die Beurteilung der Intervention ist gut beschrieben. Die verwendeten Modellparameter sind plausibel. Die TTFields-Behandlung plus TMZ kosten im Vergleich mit der Standardbehandlung rund 570'000 Franken pro QALY mehr. santésuisse kommt aus den genannten Gründen zum Schluss, dass die Voraussetzungen zur Kostenübernahme der Leistung durch die OKP nicht erfüllt sind. Translation: The report is well structured. The significance of the HTA report is limited in that the underlying RCTs on ndGBM and first rGBM are based on the only provider-sponsored EF-14 trial (open-label) with different analyzes (Stupp 2017 / 2015, Kesari 2017, Taphoom 2018). The RCTs for all rGBM are based on the previous, also provider-sponsored EF-11 trial (Stupp 2012, Kanner 2014). Some of the RCTs are unplanned post-hoc analyses. Only one of two non-randomized, retrospective, single-center cohort studies (Liu, 2020, Chen, 2021) was able to show a positive effect (PFS) with regard to ndGBM with low case numbers and low evidence. Further limitations to the report arise partly from cross-over (control to intervention), substantial risks of bias and a lack of explanations about possible effects of prognostically/predictively relevant factors (e.g. IDH mutation, MGMT status), which partly differ between intervention and control groups. Additional information on both the underlying literature and the justification for the temporary regulation in the MiGeL (2021) would be useful, although the relevance of the additional knowledge gained with the HTA remains unclear. With a relatively small clinical benefit of the TTFields treatment of only a few months (OS: 4.9m, PFS: 2.7m) and a lack of effect on HRQoL, the question of clinical relevance arises, especially given the very high costs and the lack of cost-effectiveness. The cost-effectiveness model for evaluating the intervention is well described. The model parameters used are plausible. The TTFields treatment plus TMZ costs around 570,000 francs per QALY more compared to the standard treatment. For the reasons mentioned, santésuisse comes to the conclusion that the conditions for the OKP to cover the costs of the service are not met.	
5	This is a comprehensive report analyzing the efficacy, effectiveness, safety, and cost-effectiveness of tumor-treating fields (TTFields) in glioblastoma patients. Clinical evidence stems mostly from a randomized clinical trial (EF-14), which demonstrated prolonged survival of glioblastoma patients receiving additional	No change needed.

	treatment with TTFields compared to patients receiving standard treatment alone. The major conclusion of the assessment, that is, that TTFields prolongs survival is supported by the results of the EF-14 study. Furthermore, the HTA report concludes that treatment with TTFields increases costs, which is in line with many other new development in the field of oncology. As stated in the report, only a fraction of glioblastoma patients in Switzerland decides for additional treatment with electric fields. However, for these patients, the technology represents a valuable treatment modality.	
6	Well written report, with detailed summaries and analyses, extensive literature review (yet some retained reports may be of rather low methodological quality. Effectiveness is based on 2 large randomized trials, EF-11 (recurrent GBM) and EF-14 (newly diagn. GBM).	No change needed.
6	Overall well written report, with adequate summaries and analyses. Authors provide a comprehensive overview of all relevant data and reports to the topic. While acknowledging the paucity of data, the summary statement does not distinguish the quality of the reports analyzed (some of which in my opinion do not meet methodological quality standards to even be taken into account, eg. French reports (same institution, similar publication 2016 + 2019) on cost-effectiveness performed by non-expert authors and published in non-economical journals, ref. 54 + 58).	The two cost-effectiveness studies the stakeholder refers to are from Bernard-Arnoux et al 2016 and Connock et al 2019. These studies met the inclusion criteria and were therefore included in the report.
6	The report has put a lot of emphasis on review of (large) 2 randomized clinical trials in recurrent GBM (n=237) and newly diagnosed GBM (n=695) and associated reports, as well as external retrospective comparative cohort analyses, overall supporting the significant and clinically meaningful prolongation of both progression-free and overall survival in newly diagnosed GBM. Similarly, in a non-prespecified analysis of EF-11 trial in recurrent GBM, a significant improvement in survival could also be demonstrated when restricting analysis to patient who have completed 1 months of TTFields therapy or have received their 1st cycle of chemotherapy. Although not prespecified, this seems appropriate as due to the novelty of the intervention and the skepticism of the physicians, some 25% of patients in the TTFields arm discontinued treatment after a few days, while patient in the control arm would have receive their full dose of chemotherapy already (even if they ultimately also would want to discontinue).	No change needed.
6	The HTA report falls short in the section 8 financial analysis); it limits itself on resource utilization after end of TMZ/RT (largely multiplication of monthly device costs x number of months of therapy. Not considered were costs of the multiple interventions that the patient has undergone prior to TTFields start (ie. surgery, neuropathology and molecular pathology, adjuvant radiotherapy (30 fractions) and concomitant TMZ chemotherapy, rehabilitation and physical therapy, seizure management. A profound analysis of patient pathways is lacking. The benefit of TTFields (hazard ratio of 0.63) is identical to the hazard ratio observed with the introduction of TMZ in 2005, however, for TMZ the benefit is largely restricted to tumors harboring MGMT	Information on health state costs was limited. In the base case analysis, costs were based on Panje et al 2019. Although a number of assumptions had to made to conduct the cost-effectiveness analyses, these cost estimates were considered the most appropriate since these were estimated for the Swiss setting specifically. To address the structural uncertainty underlying the estimates, several scenario analyses were performed to study the impact of the health state costs on the ICER, including scenarios in which the relative differences between progression health state were changed and scenarios in which input values for both health states were changed. The impact of alternative assumptions showed to be very small. No scenario analyses were run for the rGBM population.

	methylation, while TTFileds has shown antitumor benefit in all subgroups. At 2 years, the benefit with the addition of TMZ was an increase from 10%-->27%, TTFields improved 2-year survival from 31% 43%, at 4-years from 8% 20% (Ref. Stupp, JAMA 2017) The costs of treatments at progression, ie. repeat surgery, re-irradiation and/or bevacizumab have not been accounted for. None of these commonly proposed interventions has demonstrated to prolong survival, bevacizumab may offer some short-lived improvement in quality of life, with potential for cost-savings. *Specification:* The report falls short in the section 8 when a detailed financial analysis expected. It limits itself on resource utilization, and ultimately concludes the cost of a certain number of cycles of TTFields multiplied by its price. The international expert authors lack knowledge of particularities of the disease, clinical management and the Swiss Healthcare system. A profound analysis of patient pathways is lacking. The report ignores disease costs overall and investment made in current standard of care. TTFields has demonstrated to prolong progression-free survival (an accepted proxy for maintenance of quality of life) and overall survival, and thus makes the prior major therapeutic investments meaningful, ie. care including debulking surgery, extensive neuropathological and molecular workup, 6-weeks of daily adjuvant radiotherapy with concomitant TMZ chemotherapy, seizure management as well as rehabilitation and physical therapy. The relative benefit of TTFields with a hazard ratio of 0.63 is identical to the benefit observed with the introduction of TMZ in 2005, however, for TMZ the benefit is largely restricted to tumors harboring MGMT methylation, while TTFields has shown antitumor benefit in all subgroups. At 2 years, the benefit with the addition of TMZ was an increase from 10%-->27%, TTFields improved 2-year survival from 31% □ 43%, at 4-years from 8% □ 20% (Ref. Stupp, JAMA 2017, table 2) The costs of alternative treatments, in particular of repeat surgery, re-irradiation and/or bevacizumab have not been evaluated. None of these commonly proposed interventions has demonstrated to prolong survival, bevacizumab may offer some short-lived improvement in quality of life. Bevacizumab (Avastin®) has been approved for recurrent GBM based on an uncontrolled phase 2 study approx. 10 years ago. At the time the drug costs were approx. 20.000 CHF per month. In the meantime with generic competition the price as dropped to approx. 5.000 CHF/month of treatment. Not counted in this costs are expenses for a 1-hour infusion every other week, regular (with every or every other infusion) of blood counts, kidney function and urine analysis, commonly paired with a short medical visit.	Costs for patients prior to TTFields initiation were not considered in the analyses, since these costs would already have been incurred before model start, and would apply to both treatment arms equally. As such, the ICER would not have been affected had these costs been added. Costs of bevacizumab are indeed higher than TMZ costs. The costs of bevacizumab are included in the costs for Panje et al 2019, and are therefore included in the analyses. Information on the usage of bevacizumab was not available in the Panje et al 2019 study. To address the structural uncertainty underlying the estimates from Panje et al 2019, several scenario analyses were performed to study the impact of the health state costs of the ICER, including scenarios in which the relative differences between progression health state were changed and scenarios in which input values for both health states were changed. The impact of alternative assumptions showed to be very small. No change needed.
6	An in-depth cost effectiveness analysis [Guzauskas, J Med Economics 2019] based on an US health care system concluded on an incremental cost of 188,637 USD (95% credible range: $145,324–$225,330) with an incremental cost-effectiveness ratio (ICER) of $150,452 per life year gained. Knowing both health care systems, I would assume that ICER for Switzerland is substantially lower. *Specification:* The cost effectiveness analysis was provided by an in-depth analysis by Guzauskas et al [J Med Economics 2019] based on an US health care system. They	Three cost-effectiveness studies were identified in the systematic review: Bernard-Arnoux et al 2016, Guzauskas 2019 and Connock et al 2019. The differences between the three published studies are described in chapter 8.2.2.1. The stakeholder refers and uses a cost-effectiveness analysis published by Guzauskas et al (2019. The Guzauskas et al 2019 analyses applies a Bayesian three-stage method to estimate survival: using survival from the EF-14 trial for the first 5 years; US epidemiological data for years 5-10 and years 10-15; and age adjusted general population estimates from year 16 onwards. This approach is rebutted by Connock et al 2019. They argue that the Bayesian approach overesti-

	concluded on an incremental cost of 188,637 USD (95% credible range: $145,324–$225,330) with an incremental cost-effectiveness ratio (ICER) of $150,452 per life year gained. Knowing both health care systems, I would assume that ICER for Switzerland is substantially lower.	mates the survival for patients receiving TTFields: after 20 years, the Bayesian model predicts approximately 8% of patients receiving TTFields to still be alive, which is considered an overestimate. Connock et al argue that there is an apparent inconsistency of the modelled trajectory for the first 5 years and later years. In addition, there are likely important differences between the population of 5-year survivors from the EF-14 trial and the population in the epidemiological study, which makes the Bayesian approach questionable. In addition, Connock et al argue that costs for the TTFields arm are underestimated. A version of the Bayesian model was submitted to Haute Autorité de santé (HAS), France. There, reviewers also raised concerns about this approach, restating the issues identified by Connock et al 2019. HAS' reviewers viewed the choice for the Bayesian approach to be unjustified with a lack of sufficient clinical validation. In contrast, two other studies (Bernard-Arnoux et al 2016 and Connock et al 2019) used information from the EF-14 trial as the single source for effects. These studies have substantially higher ICER estimates. When mimicking the Bayesian approach used by Guzauskas et al, Connock et al find markedly lower ICER estimates. This underlines the impact of the model structure on the ICER. In addition to the observation that the Bayesian approach is methodologically inferior, the methodology would require additional information on the long-term effects. The epidemiological data used in the stems from the US and might not be representative for the Swiss population. Swiss-specific data is not available. In line with the studies by Bernard-Arnoux et al and Connock et al, the cost-effectiveness analyses in the current HTA are based on the EF-14 trial. The results of the cost-effectiveness analysis in the current HTA are consistent with the outcomes of the Bernard-Arnoux et al and Connock et al estimates. The argumentation described in Connock et al 2019 that the Bayesian approach is inferior was followed in the current HTA. The following text was added to chapter 8.2.2.1 to explain differences between the Guzauskas et al 2019 and Connock et al 2019 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). 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." In addition, the following text was added to the discussion chapter: "Connock et al 2019 identify the drawbacks of the Guzauskas et al 2019 model, which lead to an overoptimistic ICER value. This critique has been reiterated in the HTA submission to HAS in France. The cost-effectiveness model in the current HTA was therefore in line with the methodology employed in the Connock et al 2019 study." The interested reader is referred to the cited reference for a more detailed description.
6	TTFiedls are "hypothesized". There is a growing body of solid research describing the mechanisms of action for TTFields.	The sentence was rephrased to remove the implied uncertainty.
6	Batteries will last for 3-4 hours (rather than 2-3 hours), patient has sufficient supplies (usually 4 rechargeable batteries), and when patient is stationary, the device is directly connected to a standard power outlet.	Information about the battery duration was derived from the manufacturer's website where it is stated as 2-3 hours, however additional information on the provided batteries and the device's ability to be connected directly to the power grid was added in the section.

6	Here the HTA report references 2 independent retrospective comparative cohort studies, which are cited that one was not in support of TTFields (Liu, Univ of Rochester, NY) while the other study (Hashuan Hospital, Shanghai, China) did reproduce the results of EF-14 trial. Both reports are limited by their retrospective nature, absence of random allocation of treatment and numerous obvious and occult imbalances. I would read both reports as highly supportive of TTFields. In the report for Rochester, NY only 16% of the TTFields-treated patients had MGMT gene promoter methylation, the strongest predictor to improved outcome after treatment with alkylating agent chemotherapy compared to 36% in the control group. Despite this unfavorable distribution, progression-free survival and overall survival up to > 12 months was improved, while as expected for this unfavorable molecular subgroup, no difference in survival could be shown at 2 years.	By Liu et al 2020 was concluded “our real-world clinical experience showed that adding TTF to the Stupp protocol appeared to provide a small survival benefit and short-term 6-month intervals to a subset of patients with GBM, however, these favorable benefits may be due partly to selection bias.” No change needed.
6	Deviations from the allocated treatments were rare, adequately documented and on exploratory analyses have not influenced the main conclusions for the randomized controlled rials EF-11 and EF-14. Thus in my opinion, the “judgement of risk for bias should state low rather than some concern.	It is reported in the articles how many patients did or did not receive the treatments to which they were allocated, however it is not reported if there were deviations from the intended intervention that arose because of the trial context. Furthermore, even when changing this judgement of risk of bias this would not affect the overall certainty of the evidence. No change needed.
6	The dose of TMZ is 200 mg/m2, 150 mg/m2 is only recommended in cycle 1 after prior chemotherapy exposure. In Europe, an average BSA is 1.7 -1.8 m2, not 2.0 m2.	The EF-14 trial did not report on the dose of TMZ. Guzauskas et al 2019 therefore have used 150 mg/m2 per day “as the average dose during the clinical trial was not reported”. The other two cost-effectiveness did not provide evidence on the dose. This was specified in chapter 8.1.5.17.2. BSA was based on a study by Verbraeken et al 2006. Although the geographic location of the study was not specified, the researchers were affiliated to Belgian and Dutch hospitals. The patient population might therefore be originating from these two European countries. No change needed.
7	The submitted HTA report adequately describes the current literature concerning TTFields for ndGBM and rGBM. The overall survival benefit of TTFields for ndGBM may seem moderate at significant costs, and evidence is largely derived from a single RCT. Patients with ndGBM have few treatment options: At diagnosis, only concomitant RT/TMZ, lomoustine wafers and TTFields demonstrated increased OS in an RCT. At recurrence, there`s yet no treatment that showed a survival benefit in a RCT. Hence, especially for patients with ndGBM TTFields represents a valuable addition to standard RT/TMZ. Given the better documented survival benefit for ndGBM compared to rGBM we support offering TTFields as part of the first-line treatment, and not at a later time point.	No change needed.
7	However, TTFields is not for everyone. In their conclusion, the authors mention that the RCTs did not observe increased severe side effects or decreased HRQoL in those undergoing TTFields therapy. In daily practice, many patients (including the majority of women) refuse TTFields despite the presumed survival benefits. They do so because they do not want to keep their head shaved, covered by plates connected by cables to a battery backpack with all the stigmatization	The number of patients in the budget impact analysis was based on actual utilization in Switzerland in the period Dec-21 to Mar-23. As such, these numbers already account for uptake in the population. In addition, a scenario analysis was run in which the number of patients was reduced. No change needed.

	that this entails. The overall budget impact may therefore be overestimated.	
7	In conclusion, the Swiss Society for Neurosurgery strongly supports including adjuvant TTFields as part of the standard of care for patients with ndGBM, while acknowledging that many patients will refuse it.	No change needed.