HTA Protocol

Stakeholder feedback

Tumour treating fields (TTFields) for patients with glioblastoma multiforme

Version 1.1, 15.03.2023

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1 Preface

According to the predefined HTA process which can be consulted on www.bag.admin.ch/hta, the FOPH conducts a stakeholder consultation on the HTA protocol. A stakeholder consultation was held from 23.01.2023 to 17.02.2023 for the HTA-Protocol on “Tumour treating fields (TTFields) for patients with glioblastoma multiforme”. The protocol is submitted to stakeholders, such as health insurance associations, patient organisations, healthcare professional associations, professional societies, industry associations or other interested parties. Stakeholders are notified of the protocol 20 working days in advance and are given 20 working days to comment on the protocol.

This document details the authors’ responses to stakeholder feedback on the HTA Protocol for a Health Technology Assessment (HTA) on “Tumour treating fields (TTFields) for patients with glioblastoma multiforme”. The stakeholder feedback and corresponding author responses are detailed in tables. The tables are listed by comment boxes and stakeholder, in alphabetical order. Where multiple stakeholders provided similar feedback, the authors have only provided a response to the first comment; subsequent comments instruct the reader to cite the original response.

2 List of invited stakeholder for consultation

The following stakeholder have been invited on 23.01.2023 to submit a stakeholder feedback regarding the HTA protocol:

ACSI – Associazione consumatrici e consumatori della Svizzera Italiana
BSV – Bundesamt für Sozialversicherung, Invalidenversicherung
curafutura – Die innovativen Krankenversicherer
DVSP – Dachverband Schweizerischer Patientenstellen
FMCH - Dachverband der chirurgisch und invasiv tätigen Fachgesellschaften
FMH – Verbindung der Schweizer Ärztinnen und Ärzte
FRAGILE Suisse
FRC – Fédération romande des consommateurs
GDK – Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und –direktoren
GSASA – Schweizerischer Verein der Amts- und Spitalapotheker
H+ – Die Spitäler der Schweiz
Intergenerika – Swiss Generics and Biosimilars
Interpharma – Verband der forschenden pharmazeutischen Firmen der Schweiz
Konsumentenforum
Krebsliga Schweiz
MTK – Medizinaltarif-Kommission
Novocure GmbH
Onkologiepflege Schweiz
pharmaSuisse – Schweizerischer Apothekerverband
palliative.ch
PUE – Preisüberwachung
SAKK – Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung
SAMW – Schweizerische Akademie der Medizinischen Wissenschaften
santésuisse – Die Schweizer Krankenversicherer
SAPhW – Schweizerische Akademie der Pharmazeutischen Wissenschaften
SBK – ASI – Schweizer Berufsverband der Pflegefachfrauen und Pflegefachmänner

Schweizer Hirntumorstiftung
SGAIM – Schweiz. Gesellschaft allgemeine Innere Medizin
SGNC – Schweizerische Gesellschaft für Neurochirurgie
SGNR – Schweizerische Gesellschaft für Neuroradiologie
SGV – Schweizerische Gesellschaft der Vertrauens- und Versicherungsärzte
SKS – Stiftung für Konsumentenschutz
SNG – Schweizerische Neurologische Gesellschaft
SPO – Patientenschutz
SRO SSRO – Schweizerische Gesellschaft für Radioonkologie
SSMO - Swiss Society of Medical Oncology
SVBG/FSAS – Schweizerischer Verband der Berufsorganisationen im Gesundheitswesen
Swiss Medtech
SwissNOS – Swiss Neuro-Oncology Society
VIPS – Vereinigung Pharmafirmen in der Schweiz

3 List of stakeholders who submitted feedback

The following stakeholders have submitted a stakeholder feedback form within the stakeholder consultation round:

Novocure GmbH (in alignment with Swiss MedTech)
santésuisse – Die Schweizer Krankenversicherer
SSMO - Swiss Society of Medical Oncology
SGNC – Schweizerische Gesellschaft für Neurochirurgie
SNG – Schweizerische Neurologische Gesellschaft
Onkologiepflege Schweiz

4 Stakeholder feedback

4.1 Comments regarding the research question

The following comments have been submitted by stakeholders regarding the research question of the HTA-protocol “Tumour treating fields (TTFields) for patients with glioblastoma multiforme”.

Comment no.	Stakeholder	Stakeholder comment	Authors’ response
1.1	Novocure GmbH (in alignment with Swiss MedTech)	1st question (Q): Proposal:“…compared to maintenance chemotherapy (CT) alone and after maintenance CT has stopped?” Rationale: to be clarified that TTFields is to be continued after maintenance CT has ended following the evidence of the EF-14 design	Thank you for the feedback. The MiGeL criteria for TTFields specifies treatment only in combination with concomitant TMZ maintenance therapy. We therefore excluded TTFields in 1L alone (stopping when maintenance CT stops) prior to stakeholder feedback. However, we agree with your suggestion as the suggested approach follows the clinical trial evidence. We have adjusted the research question to include TTFields alone (or in addition of CT) and allow for TTFields to be given post maintenance CT until 1st progression.
1.2	Novocure GmbH (in alignment with Swiss MedTech)	2nd Q: Proposal: “…TTFields alone or in addition to 2L systemic therapy (physician’s choice CT) in the treatment of ndGBM patients (as per 1st research questions) after 1st progression until 2nd progression in CH compared to 2L systemic therapy (physician’s choice CT) alone?” Rationale: A. Pts treated in 1L with TTFields alone or in addition to CT (as assessed in the 1st Q), and after the 1st progression occurred until 2nd progression. Patients that did not receive TTFields in 1L are not eligible to initiate TTFields at	Thank you for the feedback. A. As in comment 1.1, TTFields is to be continued after maintenance CT has ended following the evidence of the EF trial. We therefore included the TTFields alone or in addition to maintenance CT in the research questions. We agree with excluding TTFields naïve rGBM patients as the EF trial rGBM patients primarily constitute previously exposed patients.

		progression. B. The 1st and 2nd Q address the same patient as per EF-14 study protocol incl. the continuation of TTFields after 1st progression, and resulted for the investigated population in a sign. OS benefit of 4.9m	B. Thank you for the observation. In the primary RQ, we address the situation where patients do not receive TTFields after 1st progression, following the Mittel- und Gegenständeliste (MiGeL), while in the secondary RQ we address the situation if TTFields were extended to rGBM patients (from 1st to 2nd progression).
1.3	santésuisse	The primary and secondary research questions are clearly formulated. While the primary research question focuses on the "TTFields" accompanying the apparently largely standardized treatment ("maintenance chemotherapy") of ndGBM, the secondary research question examines the "TTFields" supplementing the apparently less standardised treatment (second-line systemic therapy / physician's choice chemotherapy) of rGBM. Of additional interest would also be the investigation of any subgroups in which the treatment of ndGBM or rGBM "TTFields" might have different effects.	Thank you for the feedback. We agree with your suggestion and plan to identify subgroups in which TTFields treatment might have different effects in the systematic literature searches.
1.4	SSMO	Tumor Treating Fields (TTFields) are approved and reimbursed for therapy in first line glioblastoma therapy. Questions as stated in the primary research are rationale and justified. However, given the design of the 2 phase 3 trials, the difference between newly diagnosed and recurrent disease must be clarified. Newly diagnosed GBM should be understood as patients that have completed surgical resection/biopsy, radiation therapy with concomitant Temozolomide (TMZ) and are eligible to receive maintenance TMZ. Moreover, as in EF-14, these patients should be treated with TTFields during the 6 cycles of maintenance TMZ and beyond (if progression free at that timepoint). Moreover, as in EF-14, these patients should be eligible to pursue TTFields	Thank you for the feedback. We agree with the description of ndGBM following the trials. With regard to treatment post maintenance CT (TMZ) and prior to progression, the trials indeed allow for patients to continue without concomitant TMZ maintenance therapy. Please see our response to comment 1. 2 B. regarding the approach decided for the HTA project. With regard to eligibility to pursue TTFields treatment for rGBM up to second

		treatment up to their second progression (given possible pseudoprogression). The recurrent setting should be understood as patients that show progressive/recurrent disease and have not received TTField therapy in the context of first line therapy.	progression: in our base case analysis we follow the MiGeL restrictions, i.e. TTFields is not reimbursed in case of tumour progression, as well as no reimbursement for recurrent glioblastomas. In a scenario analysis, the cost-effectiveness of TTFields in rGBM patients will be evaluated.
1.5	Schweizerische Neurologische Gesellschaft (SNG)	TTFields sind als zus. Behandlungsoption erg. zur Standardtherapie von GBM verfügbar & werden seit 2021 von den KV übernommen, wenn def. Kriterien erfüllt sind. So ist die "primäre Forschungsfrage" korrekt & nachvollziehbar. Zur Bestimmung der Indikation, ist es wichtig, dass Ein/Auschlusskriterien & Design der Phase 3-Studie konsequent berücksichtigt werden. Somit sollte sich die Forschungsfrage auf erwachsene Patienten(>18 Jahre) mit GBM nach WHO 2016 Kriterien (IDH Wildtyp GBM und IDH mutated WHO grade IV GBM) beschränken, die Optune als Therapie der 1. Linie mit Temozolomid-Erhaltungstherapie bekommen haben. Hierbei ist wichtig, dass es zu einer Pseudoprogression kommen kann, sodass in der EF-14 Studie, Patienten bis zum 2en Progress behandelt werden konnten, was Einfluss auf das Gesamtüberleben (sekundärer Endpunkt) jedoch nicht auf das progressionsfreie Intervall (primärer Endpunkt) hat. Da Optune beim Rezidiv nicht zugelassen ist, ist fraglich, ob es Sinn macht diese Situation zu untersuchen.	Thank you for the comments. We understand the importance of defining the populations according to the trial definitions. During the HTA phase, we will extract information on for example 2016 and 2021 population definitions along with other study characteristics and outcomes. Therefore, we refrain from specifying the population to WHO 2016 criteria and retain the broader definition. In the interest of clarity however, we have added a description to the medical background section regarding the definition of the population.

Table 1: Stakeholder comments to research question

4.2 Comments regarding the PICO

The following comments have been submitted by stakeholders regarding the PICO of the HTA-protocol “Tumour treating fields (TTFields) for patients with glioblastoma multiforme”.

Comment no.	Stakeholder	Stakeholder comment	Authors' response
2.1	Novocure GmbH (in alignment with Swiss MedTech)	HTA should refer to current CE-mark of Optune (Ref. 1) including the WHO grade 4 glioma definition (WHO CNS5 2021) that corresponds to the diagnosis of histologically confirmed GBM (IDH wt & mt) as per WHO CNS4 2016 and EF-14 study. P: Adult patients (≥18y) with WHO grade 4 glioma after tumor resection/biopsy and radio- and/or CT concomitant to maintenance CT AND after CT has stopped including 1L and consecutive 2L; excl. TTFields-naïve patients that start after progression) I: TTFields in addition to maintenance CT and after CT has stopped in 1L, and 2L TTFields alone or in addition to other therapies (e.g. CCNU, TMZ and BEV) C: Maintenance CT and 2L therapy O: Adherence, compliance and usage (previously compliance) should be referred to as in the literature As per MiGeL change request (att.) resolve restrictions: #2: usage ≥75% - EF-14 study data show threshold at 50% (Ref.3), #6: KPS <70, and #4: continue TTFields alone after maintenance TMZ has stopped	Thank you for the suggestions. We agree with including both WHO 2016 and 2021 criteria in the systematic literature review (SLR) in the interest of including all literature of interest. We agree with changing the PICO to reflect the treatment as per the clinical trials, i.e. TTFields treatment alone post maintenance CT until 1st progression. Please also see our response to comment 1.1 and 1.2 B We recognize the need to clarify the definition of the population with regard to the WHO 2016 and 2021 diagnosis criteria and have included a description to the medical background section.
2.2	santésuisse	With regard to population and intervention, the question of uniformity and comparability of prerequisites, limitations and therapeutic procedures (e.g. standards, guidelines, therapy algorithms, duration of TTF treatment) in different countries and centres or studies arises. While the treatment of ndGBM seems to be relatively standardised, there seem to be different approaches with more options for rGBM treatment. According to MiGeL, there are numerous limitations for the applications of the "Tumortherapiefelder" with regard to indication and reimbursement prerequisites. The possibly existing differences between the studies with regard to relevant criteria concerning population and therapies (SoC) are to be	Thank you for the observations. We agree with the potential concern regarding heterogeneity in populations and studies, and therefore this will be taken into consideration during the evidence synthesis of the HTA phase and when evaluating the best fit for the Swiss setting. To avoid missing potentially relevant studies, we do not restrict the search terms regarding country. Additionally, if needed, heterogeneity can be addressed in sensitivity

		examined and taken into account with regard to the informative value and transferability of the HTA. In addition, the feasibility of corresponding subgroup analyses must be examined (e.g. age, KPS, MGMT status, localisation of GBM; radio- and chemotherapy, etc.).	analyses in the CE analyses and listed as limitation of the study.
2.3	SSMO	It is important to reflect, as much as possible the design and inclusion/exclusion criteria of the clinical trials that have established the conditions for approval. Therefore 2 PICOs are required: P: Adult patients (>18 years old) with newly diagnosed glioblastoma as defined by WHO 2016 criteria that have completed tumor resection/biopsy and radiochemotherapy and present a KPS □70. I: TTFields started in addition to maintenance chemotherapy (and maintained during 1st & 2nd line therapy) C: Maintenance chemotherapy without TTfields O: Efficacy and effectiveness, safety, compliance, economics P: Adult patients (>18 years old) with progressive glioblastoma as defined by WHO 2016 criteria following recurring or progressive disease that have not been exposed previously to TTFields. I: TTFields started during progressive disease (any line of treatment) C: Chemotherapy for progressive disease, without TTFields O: Efficacy and effectiveness, safety, compliance, economics	Thank you for the detailed comment, please see our response to the comments on definition of the population, TTFields post maintenance CT and TTFields naïve rGBM patients in comment 1.1, 1.2, and 1.4. Furthermore, we appreciate the feedback to divide the PICO into two separate PICOs. We treat the GBM population in this HTA as one, with the base case evaluating TTFields treatment provided to ndGBM patients as the primary RQ. The evaluation of a potential expansion of TTFields to rGBM is treated as a scenario analysis.
2.4	Schweizerische Neurologische Gesellschaft (SNG)	Nach den Kommentaren der Forschungsfrage wird empfohlen, die PICO folgendermassen zu modifizieren: P: Adult patients (>18 years old) with newly diagnosed glioblastoma as defined by WHO 2016 criteria that have completed tumor resection/biopsy and	Thank you for the detailed comments, please see our response on definition of the population, TTFields post maintenance CT and TTFields naïve rGBM patients in comment 1.1, 1.2, and 1.4. Please see our response in the choice of one

		radiochemotherapy without progression I: TTFields started in addition to maintenance chemotherapy C: Maintenance chemotherapy without TTfields O: Efficacy and effectiveness, safety, compliance, economics Sollte Optune Therapie im Rezidiv trotzdem untersucht werden, sollte eine zweite PICO bestimmt werden: P: Adult patients (>18 years old) with progressive glioblastoma as defined by WHO 2016 criteria following recurring or progressive disease that have not been exposed previously to TTFields I: TTFields started during progressive disease C: Therapy for progressive disease (i.e. chemotherapy, radiotherapy, targeted therapy,…) without TTFields O: Efficacy and effectiveness, safety, compliance, economics	PICO in comment 2.3.

Table 2: Stakeholder comments to PICO

4.3 Comments regarding databases and search strategy

The following comments have been submitted by stakeholders regarding the databases and search strategy of the HTA-protocol “Tumour treating fields (TTFields) for patients with glioblastoma multiforme”.

Comment no.	Stakeholder	Stakeholder comment	Authors’ response
3.1	Novocure GmbH (in alignment with Swiss MedTech)	1. Search terms and strategy using MEDLINE filter in Pubmed as in this draft would not find recent peer-reviewed publications. A. We suggest to remove the MEDLINE filter. B. in our perspective RWE informs decision making to a large degree: very recent RWE data don’t have a PMID and are not searchable on Pubmed. Please see addition publications that fulfill the	Thank you for the comments. A. Please note that MEDLINE is not a filter, but a specification of which website is used for the systematic literature searches. B. The focus of HTAs conducted by the FOPH is to search for the highest available scientific evidence provided by RCTs. Based on the amount of evidence found on a specific topic, it is optional to conduct an additional literature search for observational studies. Therefore,

		criteria as in table 2 that cannot be found in Pubmed and under the current criteria.	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. Additionally, to PubMed (MEDLINE), searches will be conducted in Embase.com and Cochrane library. Embase.com also provides preprint documents. The reference shared with us as key article without PMID is found in PubMed (MEDLINE) with our search strategy.
3.2	Novocure GmbH (in alignment with Swiss MedTech)	2. In 9.2 “Table 8. Search strategy for the cost-effectiveness systematic literature search for systematic reviews:” We propose to go beyond the “systematic review” filter in your search strategy as relevant publications could not be found - to also include “original” publications.	Thank you for the comment, we agree with removing “systematic review” from the heading of this table.
3.3	Novocure GmbH (in alignment with Swiss MedTech)	3. We attached a list of relevant literature on clinical data publications in ndGBM (as per EF-14) (appendix B)	Thank you for sharing these key articles. All key articles are covered with our search strategy.
3.4	santésuisse	The literature search for assessing the cost-effectiveness of the therapy can be understood and is supported.	Thank you for the supportive comment.
3.5	SSMO	The Database selection and search strategies are broad and likely to collect all relevant publications. Please ensure that you correct “Tumourtreating” to “Tumour treating”. Please also add the older term for Optune: NovoTTF-100A.	Thank you for the suggestions. We want to ensure we will identify all relevant studies. This necessitates the use of “tumourtreating” in addition to other search terms. Also, the suggested additional term Tumour treating would be capured using the “tumour-treating field*” term. Likewise, the term “NovoTTF-100A” is already enclosed in the search strategy (novoTTF*[tiab] OR novo-TTF*[tiab]). For these reasons, we will not

			change the search terms.
3.6	Schweizerische Neurologische Gesellschaft (SNG)	Die Datenbankabfragen und Suchstrategien sind umfassend und beinhalten zahlreiche Suchbegriffe. Da das Gerät bzw. die Therapiemodalität unterschiedlich bezeichnet wird und zahlreiche unterschiedliche Abkürzungen benutzt wurden und werden, sind die vorgeschlagenen Suchbegriffe korrekterweise breit gewählt. Die Suchstrategie könnte noch um die ursprüngliche Bezeichnung "NovoTTF-100A" ergänzt werden. Bitte sicherstellen, dass «Tumour (BE)» und «Tumor (AE)» gesucht werden (i.e. tumour treating fields und tumour treating fields).	Thank you for the suggestions. The term NovoTTF-100A is already enclosed in the search strategy (novoTTF*[tiab] OR novo-TTF*[tiab]). Additionally, British English and American English terms are incorporated in our search strategy. For these reasons, we will not change the search terms.
3.7	Onkologiepflege Schweiz	Ethical, legal, social, and organisational aspects should also aim to reflect patient and caregiver burden and experiences during therapy. We think that QoL questionnaires will only partially reflect these issues. Since the therapy is based on a very demanding patient adherence to the treatment, we believe that this issue should be investigated.	Thank you for the comment. We agree with the importance of recognizing the patient and caregiver burden. These are indeed issues which are of interest in the QoL measurement, and if appropriate, will be investigated and discussed in the ELSO domains.

Table 3: Stakeholder comments to databases and search strategy

4.4 Comments regarding data extraction, analysis, and synthesis

The following comments have been submitted by stakeholders regarding the data extraction of the HTA-protocol “Tumour treating fields (TTFields) for patients with glioblastoma multiforme”.

Comment no.	Stakeholder	Stakeholder comment	Authors’ response
4.1	Novocure GmbH (in alignment with Swiss MedTech)	- For clinical and economic analyses please refer to the PICO. - ESMO MCBS / ASCO NHB	Thank you for the suggestions. With regard to the ESMO MCBS / ASCO NHB framework, these will

		framework could be used in addition for clinical evaluation - Treatment guidelines could also include the DGHO / Onkopedia guidelines that were created by Dr. Hofer, Switzerland, as a representative of the SGMO. - Refer to other HTAs (att, IQWIG, TLV, French) - Relevant HTA conclusion from European countries (see appendix D): “Tumor Treating Fields for newly diagnosed GBM has undergone clinical and economic assessment by national European HTA bodies in Germany (IQWIG), Sweden (TLV), and France (HAS). IQWIG found clinical benefit from TTFields in OS, cognitive functioning, and daily activities. The TLV concluded that the clinical evidence for TTFields was convincing and the survival benefits were relevant. HAS decided that TTFields constituted a significant advance in the management of glioblastoma and granted TTFields a favorable, ASA III designation. ”	be reviewed for potential additional insights of interest in the ELSO domains. With regard to the treatment guidelines by Dr. Hofer, these will be reviewed for relevant information on the ELSO domains. With regard to other HTAs, the protocol contains the results of a preliminary pragmatic search to inform the conceptual model. The systematic search during the HTA phase should identify all relevant HTAs. The relevant HTA outcomes and conclusions will be extracted in the HTA phase.
4.2	santésuisse	The economic model for assessing the cost-effectiveness of the intervention is well described. The procedure is supported.	Thank you for the feedback.
4.3	SSMO	No comment. As stated above. Most data and patients available for analysis will be derived from the 2 phase 3 trials (EF-14 for newly diagnosed GBM patients) and EF-11 for patients with recurrent GBM.	Thank you for the feedback, we will take your observations into account in the HTA phase.
4.4	Schweizerische Neurologische Gesellschaft	Es ist geplant, die über die o.g. Suchstrategie identifizierten Studien umfassend zu	Thank you for the feedback, we will take your observations into account in the HTA phase.

	(SNG)	analysieren und alle Daten in eine Matrix zu übertragen. Die zur Auswertung vorgeschlagenen Parameter sind nachvollziehbar und umfangreich. Basierend auf dieser Datengrundlage sollte es möglich sein, die geplanten Analysen durchzuführen. Es ist zu erwarten, dass abgesehen von den 2 gut bekannten, randomisierten Studien, nur wenige nennenswerte Studien oder Fallsammlungen mit guter Datenqualität identifiziert werden.	

Table 4: Stakeholder comments to data extraction, analysis, and synthesis