Fact check comments form

for manufacturers

EUnetHTA JA3 WP4: OTCA18- Regional hyperthermia for high-risk soft tissue sarcoma treatment

Please return comments to sonja.myhre@fhi.no no later than Thursday, March 7, 2019 Please complete the checklist (next page) and use this form to provide comments regarding errors or inaccuracies on the draft project plan. Please provide a detailed description of your comment and provide a suggestion for an amendment using a new row for each comment. We welcome comments on the entire project plan including the PICO table. All comments (either on your own product or on the product of a competitor) must be validated by published sources (full reference). Comments outside the scope of the fact check are not included and will not be answered by the authors. It is not necessary to comment on typos or wording as long as they do not lead to inaccuracy.

All comments will be formally responded to in a combined document that will be published on the EUnetHTA website with company names disclosed.

In the fourth column, please indicate a 1, 2 or 3 where 1 refers to "major" comment that is a highly relevant aspect and a thorough answer is expected from the author(s); 2 is a "minor" comment that does not require a detailed reply and 3 is a "linguistic" comment concerning grammar, wording, or comprehensibility, if it leads to inaccuracy.

Page number	Line or section number	Description of factual inaccuracy and proposed amendment (in the PICO table) *(Please insert each new comment in a new row.)*	Character of comment 1= 'major' 2= 'minor' 3= 'linguistic'	Authors' reply
7	Line 131	Please note, that resource demands (the price of the device, installation conditions, operating personnel) are very different in case of various devices. It could cause differences in resource demands.	1	When completing the checklist for potential ethical, organisational, patient and social and legal aspects these a aspects will be considered. Cost aspects will not be addressed within this assessment.
14	Tab.2-5. Intervention	The following points must be taken into consideration depending on the device or treatment modality (these may be different in every case because of the method of the device or the intended use): 1. Mild hyperthermia (staring from 39°C) is also curative, not wellness intended. Excluding it is incorrect. (See new literature, mainly the immune-oncology combinations.) 2. Where and how the temperature is measured? (Which homogeneity is expected?) 3. Which area must be over the threshold? 4. A definite phantom is necessary to define the temperature and unify the achievements of the methods. 5. The ESHO guideline is constructed based on the Pyrexar (BSD) heating technology. It does not cover all the participants. For example, Oncotherm applies heterogenic heating and targets the malignant cells and the immune processes with high temperature. 6. We did not see the certificates of all the manufacturers, some of them could not be found on the internet by us. However, we think, that only devices with the MDD CE (medical device certificate) and ISO13485 (medical device production certificate) certificates should be included in the assessment, both are necessary.	1	We collected feedback from the external clinical experts that are appointed for this assessment. Below we summarize their response. We will also consider the Kadota Fund International Forum 2004 which defined hyperthermia as a temperature elevation between 39-45 °C versus 40-44°C as defined by ESHO. The temperature cannot be expected to be homogenous in the tumour, nor is this intended as it has to be tailored onto individual patient's tolerance. Noninvasive point measurements can be carried out on skin or intraluminal. Invasive point measurements are not always feasible nor practicable. Moreover a few invasive points will never give the spatial distribution of temperature in a tumor volume. PRS using MRI is feasible for a volumetric assessment of temperature but this too has its own limitations. Moreover this can only be done with hybrid units. In the text we have nuanced that we did not receive confirmation about CE approval for every device that we

				identified. EUnetHTA only requires CE approval and relies on the assessments made by the notified bodies that are accredited by EU-member states to assess whether the device conforms to the relevant EU directives which define the standards for medical devices.
16	Tab.2-5. Outcomes	1. The overall survival as the main endpoint is one of the main goals but only with a good quality of life (we cannot accept that we increase lifetime, but the patient has to go to intensive care for the rest of his/her life) 2. Burning as a minor or major event should be considered (due to the hyperthermia method)	2	1.Both overall survival and health related quality of life are included as outcomes 2. We will report all types of adverse events, including burns.
10	References	We think, that the mentioned references are one-sided. Private doctors and patients often do not have the opportunity to access pubmed listed articles, therefore, most of the manufacturers publish their studies in open-access journals. Also, those manufacturers, who developed their devices with the help of the EU or national funds have an obligation to make their publications accessible by anyone. It would only be correct if the references published in open-access Journals were also included, because these are readable by both the private doctors and patients. It would be wise to ask manufacturers to send their open-access publications, and these could also be evaluated by the authors and experts of this assessment.	1	This assessment will include all relevant papers (as defined in the scope of the assessment), including studies that are published in open-access journals. Pubmed and other bibliographic databases include a large amount of open-access articles. Within EUnetHTA assessments it is a standard procedure to ask manufacturers to send any published clinical studies/clinical data and any unpublished but non-confidential data about their device(s).
15		Device name: Celsius TCS device	1	Corrected.
14	152	The Population intended to treat includes “the various types of soft tissue sarcoma in different locations, i.e. extremity, trunk, head and neck.” Please consider that Sarcomas of the extremity and Head& Neck can be treated also with ALBA ON4000 and BSD 500 system. ALBA ON 4000 in particular is working at 434 MHz, allowing for heating up to 4 cm of depth. Applicators of different sizes allow for the treatment of different target size areas. Please find enclosed the ALBA ON4000 brochure and see a paper [1] where sarcomas up to 4 cm of depth have been treated with the device. 1: Gabriele P, Ferrara T, Baiotto B, Garibaldi E, Marini PG, Penduzzu G, Giovannini V, Bardati F, Guiot C. Radio hyperthermia for re-treatment of superficial tumours. Int J Hyperthermia. 2009 May;25(3):189-98. doi: 10.1080/02656730802669593. PubMed PMID: 19212860.	1	We collected feedback from the external clinical experts that are appointed for this assessment, who responded that these could be used as long as they can heat to the needed tumour depth. We will follow up on this during the assessment.
14	152	The authors describe the intervention almost correctly. Only the parts related to the ESHO guidelines and classification of technologies (next row) should be improved. With regards to ESHO guidelines, the authors correctly state that “Hyperthermia treatment aims to increase the temperature in target tissue to levels above normal systemic temperature. Quality assurance guidelines for regional hyperthermia recognized by the European Society for Hyperthermic Oncology (ESHO) define 40 °C as the temperature where the treatment starts, while the temperature in the target tissue should not exceed 44 °C.” But it should be taken into account that ESHO guidelines also state the following: - “ The proven effectiveness of hyperthermia in clinical studies relies exclusively on its thermal effect on tumours. For this reason hyperthermia treatments must be conducted using hyperthermia devices that are technically capable of controlled heating of a specific target volume defined	1	Within the analysis we will account for temperature parameters in target tissues that do not adhere with the criteria formulated in the ESHO guidelines. For this purpose we have stated to conduct a subgroup analysis based on: Outcomes of studies that report the temperature within the target tissue that is in the acceptable range versus the effect of studies that either did not report temperature or reported temperature outside of acceptable range. We have further specified this statement by referring to the ESHO guidelines as to what is considered acceptable.

		by imaging (CT, MRT) while sparing normal tissue at the same time. Technically this can only be achieved by radiating and focusing electromagnetic waves on the target volume. Recording the temperature directly in the target volume or surrounding tissue is pivotal to treatment quality." - "Hyperthermia systems that are not able to achieve a temperature rise in the target volume up to between 40 and 43 °C, or devices that do not intend to measure temperatures, cannot be regarded as hyperthermia devices in terms of this recommendation." -" This guideline for deep regional hyperthermia is limited to "phased array" hyperthermia systems as the authors feel that patients in the western world are more adequately treated with "phased array" systems because the surface fat layer thickness in the relevant body region is often more than 2 cm (see also appendix 7.1)." Important aspect to be considered when evaluating hyperthermia device is that they have to be able to achieve the target temperature of 41-43 °C measured by multiple sensors (one or 2 sensors are not enough) for the entire duration of the treatment (60 minutes above 41°). Indeed it has been seen that thermal dose is related to the clinical outcomes [2]. This is explained by the fact that hyperthermia main effects are related to achieved temperature for 60 minutes treatment [3]: - DNA repair inhibition is effective at temperature > 40°C - Blood vessels open up and thus re-oxygenation happens at temperature >40 °C and < 44°C. 2. Franckena M, Fatehi D, de Bruijne M, Canters RA, van Norden Y, Mens JW, van Rhoon GC, van der Zee J. Hyperthermia dose-effect relationship in 420 patients with cervical cancer treated with combined radiotherapy and hyperthermia. Eur J Cancer. 2009 Jul;45(11):1969-78. doi: 10.1016/j.ejca.2009.03.009. Epub 2009 Apr 8. PubMed PMID: 19361982. 3: Crezee H, van Leeuwen CM, Oei AL, Stalpers LJ, Bel A, Franken NA, Kok HP. Thermoradiotherapy planning: Integration in routine clinical practice. Int J Hyperthermia. 2016;32(1):41-9. doi: 10.3109/02656736.2015.1110757. Epub 2015 Dec 15. Review. PubMed PMID: 26670625.		
14	152	With regards to classification of hyperthermia devices the authors didn't consider that hyperthermia RF devices can be radiative, as Pyrexar and Alba devices, or capacitive (all the others devices mentioned by the authors). Technical differences between radiative and capacitive systems have to be taken into account by the authors. The ESHO Guidelines for Deep Hyperthermia state that "patients in the western world are more adequately treated with "phased array" systems because the surface fat layer thickness in the relevant body region is often more than 2 cm (see also appendix 7.1)." Please find here enclosed a paper [4]showing differences between the radiative and capacitive hyperthermia technologies and their impact on the clinical performances, both on phantom and patients. As it is possible to see from this paper radiative phased array systems, as BSD-2000 and the 4 waveguides phased array working at 70 MHz, as ALBA 4D, evaluated on the	1	We collected feedback from the external clinical experts that are appointed for this assessment, who responded that this is a debatable issue and has not been resolved. However, as long as the temperature measurements indicate that a temp of 39-45C is attainable, the experts do not see any problem with any system. However, the user has to be aware of the limitations of these two systems and has to take needed precautions. Within the assessment we will describe the technology and we will report that devices can be capacitive or radiative.

		paper, can properly heat tumors at any depth in the abdominal and pelvic area. On the other hand, in the same paper, capacitive systems evaluated reach lower temperature at depth, having some limitations in properly heating deep seated targets because of the presence of fat layer. In particular authors [4] conclude that: “Radiative hyperthermia generally yields much more favourable heating patterns for deepseated pelvic tumours, compared with capacitive heating. With radiative heating higher tumour temperatures are predicted before treatment limiting hot spots occur, which will benefit clinical outcome.” In particular the authors explain that: - “the possibility to focus the electromagnetic field is very minimal with capacitive heating, since only different electrode sizes can be chosen. Radiative heating is typically performed with phased-array systems providing phase-amplitude steering to focus heating to the target and minimize hot spots.” - “treatment limiting hot spots at fat-muscle tissue interfaces are more dominant for capacitive heating than for radiative heating and adaptations in bolus cooling etc. to improve capacitive heating only have a limited effect.” - “ adequate temperatures can only be obtained with capacitive heating when accepting very high temperatures in the superficial fat and muscle layers”….”“Precooling is often applied clinically in order to reduce the incidence of treatment limiting hot spots with capacitive heating, even though clinical experience shows that this is not always effective in avoiding preferential heating at fat–muscle interfaces.”….”Precooling in combination with switching the active electrodes from top and bottom to the sides can improve patient comfort since hot spot complaints are resolved temporarily. However, the target temperature is not expected to improve sufficiently to realize a substantial improvement in treatment outcome.” - “The fundamental problem that causes the treatment limiting hot spots is the E-field direction that is perpendicular to the fat–muscle interface in combination with the lack of steering possibilities. Switching electrode positions does not overcome these fundamental problems, but continuously changes the location of the treatment limiting hot spot which does improve the target temperature, but again not sufficiently to meet the clinical requirements. “ Authors should take these aspects in serious consideration when evaluating the technologies to heat deep seated Sarcoma, seen the importance of delivery adequate thermal dose to achieve the clinical outcome. 4. Kok HP, Navarro F, Strigari L, Cavagnaro M, Crezee J. Locoregional hyperthermia of deep-seated tumours applied with capacitive and radiative systems: a simulation study. Int J Hyperthermia. 2018 Sep;34(6):714-730. doi: 10.1080/02656736.2018.1448119. Epub 2018 Apr 18. PubMed PMID: 29509043.		
14	152	ALBA 4D and ALBA ON4000 manufacturer is Med-logix srl, via A.Olivetti 24 00131- Rome (Italy)	1	Corrected.