CPAG Summary Report for Clinical Panel – Efficacy, toxicity and cost-effectiveness of stereotactic ablative radiotherapy (SABR) in patients with HCC [URN: 1913]

No	*Outcome measures*	*Summary from evidence review*
1	Survival	**Benefits of the Proposition in comparison with sorafenib** Median overall survival (OS) is the length of time from either the date of diagnosis or the start of treatment, that half of the patients in a group of patients diagnosed with the disease are still alive. The best evidence on median OS is provided by the retrospective observational study by Bettinger et al. (2018) that included 190 patients in the matched cohort and compared SABR to sorafenib. Median OS in the SABR group was 18.1 (95% CI 10.3-25.9) months compared to 8.8 (95% CI 8.2-9.5) in the sorafenib group. Given the alternative treatment options for patients with HCC overall survival is a clinically meaningful outcome. The study performed a retrospective comparison between the two groups. Despite the use of a statistical method (propensity score matching) to account for baseline differences among the participants, patient selection bias cannot be excluded between the two cohorts. In both groups the inclusion of patients with Child Pugh score B will make the population less comparable to the scope of the review. Overall, there is considerable uncertainty about this outcome and additional randomised controlled studies will need to verify this finding.
		Benefits of the Proposition in comparison with RFA Actuarial overall survival is reported as the proportion of patients surviving at a defined follow-up point, such as 1- or 2-years after beginning treatment. The best evidence on OS is provided by the retrospective observational study by Wahl et al (2016) that included 224 patients and compared SABR with radiofrequency ablation (RFA) and reported OS at 1 and 2 years of 69.6% and 52.9% after RFA and 74.1% and 46.3% after SABR.

		Given the alternative treatment options with the possibility of curative intent for patients with non-metastatic HCC overall survival is a clinically meaningful outcome for patients. The study performed a retrospective comparison between the two groups. Despite the use of a statistical method (propensity score matching) to account for baseline differences among the participants, patient selection and outcome detection bias cannot be excluded between the two cohorts. The 1- and 2-years LC rates reported by Wahl et al. (2016) are comparable to the SABR results reported by the Rim et al. (2019) meta-analysis of non-comparative studies. Overall, there is some uncertainty about this outcome.
		The Benefits of the Proposition in non-comparative studies Actuarial overall survival is reported as the proportion of patients surviving at a defined follow-up point, such as 1- or 2-years after beginning treatment. The best non-comparative evidence on actuarial survival is provided by the Rim et al. (2019) systematic review and meta-analysis that included 32 observational single-arm studies (n=1950 patients) and reported 1-year OS of 72.6% (95% CI 65.7–78.6) and 2-year at 57.8% (95% CI 50.9–64.4). Given the alternative treatment options with the potential of curative intent for patients without metastatic HCC, overall survival is a clinically meaningful outcome. Actuarial overall survival was a primary outcome in a number of the studies included in the systematic review, however, almost none of them reported sample size calculations. There is some consistency between the results reported by Rim et al. (2019) and the OS evidence for SABR provided by Wahl et al. (2016) and Parikh et al. (2018) as the 1-year 95%CI show overlap with the same outcome reported in these studies.Differences in the included population and treatment could account for the different rates observed among studies. The results were less consistent for the 2-year OS rates.
		CtE The Commissioning through Evaluation (CtE) scheme collected data on a number of outcomes, including survival. Data was collected on 91 patients recruited from 7 centres nationally. The data analysis of the CtE reported overall survival (OS) of 76.5% (95% CI: 62.4 to 85.9%) at 1 year and 41.7% at 2 years (95% CI: 22.4 to 60.0%). The reported OS (including 95%CIs) is in agreement with the findings of the literature.
2.	Local control	**Benefits of the Proposition in comparison with sorafenib** Not reported

		Benefits of the Proposition in comparison with RFA Local control (LC) is the proportion of patients for which the treated lesion does not increase in size at a defined follow-up point after beginning treatment. The best evidence on LC is provided by the retrospective observational study by Wahl et al (2016) that included 224 patients and compared SABR with radiofrequency ablation (RFA). The study reported LC at 1 and 2 years of 97.4% and 83.6% with SABR and 83.6% and 80.2% with RFA. After adjusting for tumour size LC was no statistically different between the two groups. The clinical benefit to the patient group is that a less invasive treatment such as SABR can provide equivalent results. The study performed a retrospective comparison between the two groups. Despite the use of a statistical method (propensity score matching) to account for baseline differences among the participants, patient selection and outcome detection bias cannot be excluded between the two cohorts. The 1- and 2-years LC rates reported by Wahl et al. (2016) are comparable to the SABR results reported by the Rim et al. (2019) meta-analysis of non-comparative studies. Overall there is some uncertainty about this outcome.
		The Benefits of the Proposition in non-comparative studies Local control (LC) is the proportion of patients for which the treated lesion does not increase in size at a defined follow-up point after beginning treatment. The best non-comparative evidence on actuarial survival is provided by the Rim et al. (2019) systematic review and meta-analysis that included 32 observational single-arm studies (n=1950 patients) and reported 1-year LC of 85.7% (95% CI 80.1-90.0) and 2-years LC of 83.6% (95% CI 77.4-88.3). The clinical benefit to the patient group is that a less invasive treatment such as SABR can provide good LC results. LC was a secondary outcome in most of the studies included in the meta-analysis. There is some consistency between the results reported by Rim et al. (2019) and the LC evidence for SABR provided by Wahl et al. (2016) and Parikh et al. (2018) as the 1-year 95%CI show overlap with the same outcome reported in these studies.
		CtE The CtE data analysis also reported a local control (LC) rate of 72.3% (95% CI: 57.9-82.5%) at 1 year and 52.4% (95% CI: 25.2-73.9%) at 2 years. The 2-year LC rate is lower than the rate reported in the literature. However, the CtE used a different definition of local control to the published studies so the results are not easily comparable.

3.	Progression free survival	**Benefits of the Proposition in comparison with sorafenib** Progression free survival (PFS) is the length of time during which the disease does not worsen, or the proportion of patients without worsening disease at a defined follow-up point after beginning treatment. PFS was defined from the day of starting sorafenib or SABR treatment until death or radiological progression. The best evidence on PFS is provided by the retrospective observational study by Bettinger et al. (2018) that included 190 patients in the matched cohort and compared SABR to sorafenib. Median PFS in the SABR group was 9.0-months (95% CI 5.8-12.2) months compared to 6.0-months (95% CI 4.8-7.2) in the sorafenib group (p=0.004). In patients with metastatic disease treatment is not given with curative intent and secondary outcomes such as PFS are clinically meaningful. The study performed a retrospective comparison between the two groups. Despite the use of a statistical method (propensity score matching) to account for baseline differences among the participants, patient selection bias cannot be excluded between the two cohorts. In both groups the inclusion of patients with Child Pugh score B will make the population less comparable to the scope of the review. Overall, there is considerable uncertainty about this outcome and additional randomised controlled studies will need to verify this finding.
		Benefits of the Proposition in comparison with RFA Not reported
		The Benefits of the Proposition in non-comparative studies Not reported
		CtE The CtE report did not include progression free survival as one of its outcomes.
4. 5. 6. 7.	Mobility Self-care Usual activities Pain	**Benefits of the Proposition in comparison with sorafenib** Not reported
		Benefits of the Proposition in comparison with RFA Not reported
		The Benefits of the Proposition in non-comparative studies

8.	Anxiety / Depression	Quality of life (QoL) is a composite patient-reported outcome that captures the impact of an intervention on a patient's psychology and everyday life activities. The best evidence on QoL is provided by the prospective, non-comparative observational study by Klein et al (2015) that included 99 patients with hepatocellular carcinoma and captured QoL outcomes up to 12 months post SABR treatment. The study did not report a difference in QoL between baseline (137.4) and after SABR treatment (3 months = 133.4, 12 months = 135.1) using the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) checklist. No difference was also reported using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) checklist with baseline=65.8, 3-months=62.9 and 12-months=64.5.One of the factors weighting in treatment decisions for HCC is the possible impact that treatment may have on their quality of life. Given that SABR is less invasive than other forms of treatment for HCC this is a clinically important outcome. The SABR group was heterogeneous including patients with HCC, cholangiocarcinoma, and liver metastases. Maximum follow-up was only 12 months and it is unknown what proportion of patients completed follow-up. Overall there is considerable uncertainty about this outcome.
		CtE Data on QoL were available for 88 (97%) patients of the CtE. According to the summary analysis, the proportion of patients reporting no problems, some problems and severe problems remained stable for the mobility and anxiety/depression outcomes. There was a small increase in the proportion of patients reporting problems with their self-care, usual activities, and pain/discomfort between baseline and 12 months follow-up. The result seems to be in agreement with the literature that reported no significant impact in most QoL outcomes of SABR treatment in patients with liver cancer.
9.	Replacement of more toxic treatment	**Benefits of the Proposition in comparison with sorafenib** *Not specified in the protocol*
		Benefits of the Proposition in comparison with RFA *Not specified in the protocol*
		The Benefits of the Proposition in non-comparative studies *Not specified in the protocol*

		CtE The CtE report did not include replacement of more toxic treatment as one of its outcomes.
10.	Dependency on care giver / supporting independence	**Benefits of the Proposition in comparison with sorafenib** *Not specified in the protocol*
		Benefits of the Proposition in comparison with RFA *Not specified in the protocol*
		The Benefits of the Proposition in non-comparative studies *Not specified in the protocol*
		CtE The CtE report did not include dependency on care giver / supporting independence as one of its outcomes.
11.	Safety	**Benefits of the Proposition in comparison with sorafenib** Toxicity is defined based on the number and severity of adverse events a patient can experience after undergoing treatment. Treatment-related toxicity in patients with cancer is usually recorded and graded according to the Common Toxicity Criteria Adverse Events (CTCAE). The best evidence on toxicity is provided by the retrospective observational study by Bettinger et al. (2018) that included 190 patients in the matched cohort and compared SABR to sorafenib. 73.6% of sorafenib-treated patients experienced at least one adverse event at any grade. For the group treated with SABR, 6.5% developed grade 2 toxicity. Grade 3 toxicity was reported in 10.6% of the SABR-treated patients. However, it should be noted that as the two modalities have different toxicity profiles a direct comparison is difficult. Given that alternative treatment options with different toxicity profiles exist for patients with HCC, toxicity is clinically meaningful outcome. The study performed a retrospective comparison between the two groups. Despite the use of a statistical method (propensity score matching) to account for baseline differences among the participants, patient selection and outcome detection bias cannot be excluded between the two cohorts. In both groups the inclusion of patients with Child Pugh score B will make the population less comparable to the scope of the review. Overall, there is considerable uncertainty about

		this outcome and additional randomised controlled studies will need to verify this finding.
		Benefits of the Proposition in comparison with RFA Toxicity is defined based on the number and severity of adverse events a patient can experience after undergoing treatment. Treatment-related toxicity in patients with cancer is usually recorded and graded according to the Common Toxicity Criteria Adverse Events (CTCAE). The best evidence on toxicity is provided by the retrospective observational study by Wahl et al (2016) that included 224 patients and compared SABR with RFA. The rates of late grade 3+ GI toxicity in the study were similar in the RFA and SABR groups at 1 (3.4% v 5.4%; p =0.49) and 2 years (6.4% v 8.3%; p =0.66). There were no late grade 5 adverse events in either group. Given the alternative treatment options with different toxicity profiles for patients with HCC, toxicity is clinically meaningful outcome. This outcome is even more important for patients with advanced disease that treatment-related toxicity may result in significant impairment of their quality of life. The study performed a retrospective comparison between the two groups. Despite the use of a statistical method (propensity score matching) to account for baseline differences among the participants, patient selection and outcome detection bias cannot be excluded between the two cohorts. Overall, there is considerable uncertainty about this outcome and additional randomised control studies will need to verify this finding.
		The Benefits of the Proposition in non-comparative studies Toxicity is defined based on the number and severity of adverse events a patient can experience after undergoing treatment. Treatment-related toxicity in patients with cancer is usually recorded and graded according to the Common Toxicity Criteria Adverse Events (CTCAE). The best non-comparative evidence on actuarial survival is provided by the Rim et al. (2019) systematic review and meta-analysis that included 32 observational single-arm studies (n=1950 patients) and reported grade ≥3 GI and hepatic complications of 3.9% and 4.7%, respectively. Given the alternative treatment options with different toxicity profiles for patients with HCC, toxicity is clinically meaningful outcome. This outcome is even more important for patients with advanced disease

		that treatment-related toxicity may result in significant impairment of their quality of life. There is consistency between the results reported by Rim et al. (2019) and the evidence from comparative studies with grade ≥3 rates <10%.
		CtE The analysis of CTCAE adverse events showed 12.1% (95% CI 6.8-20.7) of patients suffered grade 3 events, while 3.3% (95% CI 1.1-9.9%) suffered grade 4 events. No patient suffered grade 5 toxicity. Longitudinal analysis of the adverse events rates showed that a high proportion of patients (57%) reported symptoms consistent with CTCAE grade 1 and above adverse events at baseline before SABR treatment started.
12.	Delivery of intervention	**Benefits of the Proposition in comparison with sorafenib** *Not specified in the protocol*
		Benefits of the Proposition in comparison with RFA *Not specified in the protocol*
		The Benefits of the Proposition in non-comparative studies *Not specified in the protocol*
		CtE The CtE report did not include delivery of intervention as one of its outcomes.
13.	Cost-effectiveness	**Benefits of the Proposition in comparison with sorafenib** *No applicable studies were found during the evidence review.*
		Benefits of the Proposition in comparison with RFA *No applicable studies were found during the evidence review.*
		The Benefits of the Proposition in non-comparative studies *No applicable studies were found during the evidence review.*

		CtE Using data from the CtE report, a cost-effectiveness analysis was performed, which compared SABR to surgery. Initial analysis showed that for adult patients with borderline resectable HCC who may be candidates for surgery, SABR is the most cost-effective intervention. There was considerable uncertainty surrounding this finding and the results were sensitive to assumptions on the cost of SABR and RFA and the impact of treatment modality on mortality.