KiTEC

Commissioning through Evaluation:

Stereotactic ablative body radiotherapy (SABR) for patients with hepatocellular carcinoma report

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Contents

Project details

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Produced by	KiTEC - King's Technology Evaluation Centre King's College London 5th Floor, Becket House 1 Lambeth Palace Road London, SE1 7EU, UK Phone: +44 (0) 207 8489527
Project lead	Anastasia Chalkidou
Health economics lead	Mark Pennington
Statistics lead	Janet Peacock
Authors (alphabetical)	Bourmpaki, Elli Bunce, Catey Chalkidou, Anastasia Coker, Bola Eddy, Saskia Elstad, Maria Goddard, Kate Grzeda, Mariusz Jin Huajie Keevil, Stephen Macmillan, Thomas Peacock, Janet Pennington, Mark Radhakrishnan, Muralikrishnan Reid, Fiona Summers, Jennifer
Correspondence to	Joanne Boudour, joanne.boudour@kcl.ac.uk
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Authorship and acknowledgements

About KiTEC

KiTEC (King's Technology evaluation Centre) is a health technology assessment (HTA) organisation which is part of King's College London with experience in carrying out medical technology evaluations. Since 2011, KiTEC has worked as an External Assessment Centre (EAC) that carries out work for the National Institute for Health and Care Excellence (NICE) Medical Technologies Evaluation Programme (MTEP) and Diagnostic Assessment Programme (DAP). MTEP selects and evaluates innovative medical technologies (including devices and diagnostics) and helps the NHS adopt efficient and cost-effective medical devices and diagnostics more rapidly and consistently. KiTEC uses specialist expertise to produce systematic reviews, meta-analyses, economic models, outcomes research, as well as services for horizon scanning, real world data analysis, data linkage and registry analysis. KiTEC works with a variety of stakeholders including the NHS, academic research groups, and private manufacturers of medical technologies.

Authorship

Dr Anastasia Chalkidou was project lead for the SABR CtE scheme. She was responsible for obtaining ethics and HRA approvals for the data analyses, worked on developing the study protocol, data dictionary, and active surveillance plan. She co-authored the executive summary and sections 1, 2, 3, 6, 7, 8 and 10 and contributed to sections to sections 4 and 9. AC collated and reviewed all sections of this report.

Thomas Macmillan carried out the literature searches for the clinical evidence and co-authored section 6 and appendices A and B and reviewed section 5.

Dr Kate Goddard interviewed the 17 centres for the providers' feedback and wrote section 9. She also co-authored section 6 and reviewed section 4.

Professor Janet Peacock, Fiona Reid, Dr Jennifer Summers, Saskia Eddy, Bola Coker, Dr Catey Bunce, Elli Bourmpaki, and Maria Elstad performed the CtE data statistical analysis and co-authored section 4 and 8. JP, BC, and FR also co-authored the active surveillance plan for the SABR CtE scheme. JP, BC, and FR contributed to the development of the study protocol and data dictionary. JP, SE, BC, and JS reviewed the executive summary and the conclusions. JP was the statistical analysis lead, and quality checked section 5.

Mr Mariusz Grzeda contributed to the analysis of the CtE data and co-authored section 4.
Dr Mark Pennington, Dr Jin Huajie, and Dr Muralikrishnan Radhakrishnan produced the cost-effectiveness model and wrote section 5. MP was the health economics lead, co-authored the executive summary, conclusions of the report and quality checked section 6.
Professor Steve Keevil reviewed all sections, provided comments, and approved the final version prior to submission to NICE.

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Abbreviations

ACR	American College of Radiology
ADL	Activities of daily living
AE	Adverse events
A&E	Accident and emergency
ALT	Alanine aminotransferase
ASTRO	American Society for Radiation Oncology
BCLC	Barcelona clinic liver cancer
BED	Biologically equivalent dose
CEA	Carcinoembryonic antigen
CP	Child Pugh
CI	Confidence interval
CRC	Colorectal
CtE	Commissioning through Evaluation
DEB	Drug eluting beads
DOB	Date of birth
DOD	Date of death
EQD2	Equivalent dose in gray-2
GTV	Gross tumour volume
Gy	Gray
HCC	Hepatocellular carcinoma
HES	Hospital Episode Statistics
HPB	Hepato-Pancreato-Biliary
HRA	Health Research Authority
IQR	Inter quartile range
ICER	Incremental cost-effectiveness ratio
KCL	King's College London
KiTEC	King's Technology Evaluation Centre
LC	Local control
MDT	Multidisciplinary team
NICE	National Institute for Health and Care Excellence
NHS Digital	National Health Service Digital

NMB	Net monetary benefit
NSCLC	Non-small cell lung cancer
ONS	Office for National Statistics
OS	Overall survival
PFS	Progression free survival
QALY	Quality-adjusted life years
Pts	Patients
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RD	Research and Development
REC	Research Ethics Committee
RCT	Randomised controlled trial
RR	Relative risk
SAP	Statistical analysis plan
SD	Standard deviation
SE	Side effects
SA	Sensitivity analysis
SABR	Stereotactic ablative body radiotherapy
SD	Standard deviation
TACE	Transarterial chemoembolization
TNM	TNM classification of malignant tumours
TPN	Total parenteral nutrition
TVI	Tumour vascular invasion
UHB	University Hospital Birmingham
UK	United Kingdom

Executive summary

Stereotactic Ablative Body Radiotherapy (SABR) is an emerging treatment that uses external beam radiation therapy to precisely deliver a high dose of radiation to a cancer lesion, using either a single dose or a small number of fractions. As a result, SABR is considered a more precise treatment than standard radiotherapy allowing the delivery of a high, biologically effective dose (BED) to the tumour while minimising the dose received by normal tissues, and thus could potentially minimise radiotherapy treatment toxicity and adverse events (AEs). Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. Treatment of HCC depends on a number of factors associated with the patient's performance status, the size and location of the lesion in the liver, and prior liver function (Bruix and Sherman 2011). Treatment options for patients with HCC include surgical resection, liver transplant, transarterial chemoembolization (TACE), local ablative treatments, and targeted chemotherapy, including targeted treatments such as sorafenib (Bruix and Sherman 2011). In cases when other treatment options are not feasible or may result in high toxicity rates, SABR can be considered as an alternative treatment option.

In 2015 NHS England launched the Commissioning through Evaluation (CtE) scheme for SABR. The scheme, which is part of NHS England's Evaluative Commissioning Programme provided funding to treat patients with HCC (estimated 300 for the duration of the scheme) with SABR within the NHS (National Health Service England 2014). This report summarises the findings of the scheme and all available published literature until May 2019 on the efficacy, safety, and cost-effectiveness of SABR in patients with HCC.

Between 2015 and 2018, the CtE scheme collected outcomes from 91 patients recruited from 7 centres nationally. The mean age of patients was 72 years, and most (72.5%) were men. The cohort was mainly comprised of patients with a single lesion. The majority of the patients (95%) were treated with a standard linear accelerator[1]. Most patients were treated with 5 fractions of radiotherapy receiving a median dose of 45 Gy of radiation in total. Cone beam[2] CT (CBCT) image guidance was the most commonly used technique to assist treatment delivery in this patient cohort.

[1] A medical linear accelerator is a device used for external beam radiotherapy treatment.
[2] Cone beam CT is an imaging technique using CT images to guide the delivery of radiotherapy.

The data analysis 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 95% confidence interval of the CtE data contains the survival[3] target set at the beginning of the SABR CtE scheme (2-year target = 50%). The findings of the CtE scheme on the effect of SABR in OS of patients with HCC is supported by low quality evidence from the literature. The main evidence comes from a systematic review and meta-analysis (Rim et al. 2019) that included 32 observational single-arm studies involving 1950 patients with HCC who underwent SABR. Pooled 1-, 2-, and 3-year OS rates were 72.6% (95% CI 65.7-78.6), 57.8% (95% CI 50.9-64.4), and 48.3% (95% CI 40.3-56.5), respectively. Although the meta-analysis included studies with heterogeneous patient populations and study designs, the pooled result resulted in a patient cohort with similar characteristics to the CtE scheme.

The main evidence from the literature for the effect of SABR in comparison with radiofrequency ablation (RFA) comes from two retrospective propensity matched cohort studies (Wahl et al. 2016, Parikh et al. 2018). They reported equivalent OS results between SABR and RFA with 1-year OS of approximately 70-80% and a 2-year OS of 50%. The combined findings from the published literature and the CtE scheme provide low[4] quality evidence that SABR treatment in patients with HCC results in similar OS in comparison with RFA. There is additional low quality evidence from one retrospective, propensity matched cohort study that the OS following treatment with SABR is better than sorafenib. SABR resulted in superior OS in comparison to sorafenib with a median OS of 17.0 (95% CI 10.8-23.2) months compared to 9.6 (95% CI 8.6-10.7), respectively (Bettinger et al. 2018).

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 95% confidence interval of the CtE data contains the LC target set at the beginning of the SABR CtE scheme (1-year target = 80%). The findings of the CtE scheme on the effect of SABR on LC is partially supported by the findings of the meta-analysis by Rim et al. (2019). Pooled 1-, 2-, and 3-year LC rates from the meta-analysis were 85.7% (95% CI 80.1-

[3] The proportion of patients still alive at a predefined time point. For the SABR CtE scheme the overall survival at 1-year and 2-year post treatment were selected. All target rates set for the CtE were agreed by the working group by consensus, based on findings from a systematic review conducted in 2015. These targets were used to aid the interpretation of the survival and local control estimates observed in the CtE patients reported in the evaluation.

[4] The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework for developing and presenting summaries of evidence was used for rating the quality of evidence for each outcome included in the report.

90.0), 83.6% (95% CI 77.4-88.3), and 83.9% (95% CI 77.6-88.6), respectively. Only the 1-year and not the 2-year LC rate of the CtE is within the 95% confidence interval reported by Rim et al. (2019). Contrary to the rest of the studies, the CtE has not used RECIST[5] to calculate LC. Therefore, the results are not easily comparable[6]. The combined findings from the published literature and the CtE provide low quality evidence that SABR achieves high LC rates.

The CtE data analysis reported a grade 3[7] adverse event rate of 12.1% (95% CI 6.8-20.7) and a grade 4[8] adverse event rate of 3.3% (95% CI 1.1-9.9%), above and within the proposed targets of 15% and 10%, respectively. No grade 5 adverse events were reported. Longitudinal analysis of the adverse events rates showed that a high proportion of patients (57%) reported symptoms consistent with CTCAE[9] grade 1 and above adverse events at baseline before SABR treatment started. The most frequently reported adverse event was fatigue. Other frequently recorded adverse events were associated with increased blood levels of alanine aminotransferase (ALT) and bilirubin. Longitudinal analysis of these results suggests that the abnormal liver function test results were not treatment related.

The main evidence from the literature on the safety of SABR is provided by the meta-analysis by Rim et al. (2019). The most commonly reported grade 3+ adverse events observed following SABR treatment were gastrointestinal (GI) or hepatic. For GI adverse events, the grade 3+ event rate was less than 5% in 16 of 17 included studies. It was 15% in one study and was not reported in 6 of the studies. The combined event rate from all studies for grade 3+ GI adverse events using random effects analysis was 3.9% (95% CI 2.6-5.6%). For hepatic adverse events, the rates of grade 3+ events were <10% in 23 of 24 cohorts. The pooled rate was 4.7% (95% CI 3.4-6.5%). Meta-regression analysis showed that Child-Pugh (CP) class was significantly correlated with hepatic complications of grade 3+ ($p = 0.013$). With the exception of ALT and bilirubin, the analysis of the CtE adverse events

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[5] RECIST (Response Evaluation Criteria In Solid Tumors) is a set of published rules that define when cancer patients improve (respond), stay the same (stable) or worsen (progression) during treatments.

[6] Although RECIST is a universal tool commonly used to measure local control, the clinicians participating in the SABR scheme did not feel that they had sufficient resources to use it outside a clinical trial setting and therefore a pragmatic solution was adopted instead.

[7] Defined as severe or medically significant but not immediately life-threatening adverse events resulting in hospitalisation or prolongation of hospitalisation; may also limit self-care or be disabling.

[8] Defined as toxicity resulting in life-threatening consequences that need urgent intervention.

[9] The Common Terminology Criteria for Adverse Events (CTCAE), are a set of criteria for the standardised classification of adverse effects of anticancer treatments. Depending on the severity of the adverse event different grades are assigned with grade 1 considered mild, grade 2 moderate, grade 3 severe, grade 4 life threatening and grade 5 resulting in death.

did not take into account the timing of the event. It is therefore not possible to separate acute and late adverse events. The combined findings from the CtE and the published literature, provide low quality evidence that SABR does not result in high rates of adverse events in this patient cohort.

Data on quality of life (QoL) were available for 88 patients (97%) at baseline. 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. It should be noted, however, that the small number of patients with follow-up beyond 12 months increases the uncertainty of these results. The CtE QoL results are supported by 1 observational study that reported no significant impact in most QoL outcomes following SABR treatment in patients with liver cancer. The combined findings from the CtE scheme and the published literature provide low quality evidence that SABR does not significantly affect QoL in this patient cohort.

Data on pain scores were available for 90 patients (99%) at baseline. According to the summary analysis, the majority of patients (87%) did not report any pain at baseline or during follow-up. There was an increase in the number of patients who report severe pain, from 1% at baseline to 9% and 19% at 12 and 18 months, respectively. This finding is in agreement with the analysis of the QoL pain/discomfort dimension that reported a small increase in the number of people reporting worsening symptoms between baseline and follow-up (from 0% to 6% at 18 months). For both QoL and pain scores, the analysis assumed that missing data have a random distribution and do not introduce bias. Based on the providers' feedback, however, missing data are often associated with a decline in the patient's performance status and clinical condition. There is, therefore, a lot of uncertainty about the QoL and pain conclusions and the results should be interpreted with caution.

According to the patient experience questionnaire, 87% of CtE HCC cohort were extremely likely or likely to recommend the SABR service to their friends and family.

The main limitation of the current evidence (including the analysis of the CtE data) is that the majority comes from non-comparative (often retrospective) observational studies. These studies include heterogeneous patient populations, and study designs that limit the generalisability of the results. The evidence from retrospective comparative studies that used propensity score matching to account for baseline differences between SABR and RFA, and SABR and sorafenib, also suffer from the same limitations as the inherent biases of retrospective design, such as patient selection bias, lack of information on important baseline clinical characteristics and adverse events outcomes,

which cannot be fully addressed by statistical methods. Finally, the small size of the CtE scheme cohort and the small number of patients with more than 12 months follow-up, increases the uncertainty around any conclusions drawn for this cohort.

The objective of the economic evaluation in the CtE scheme was to determine whether SABR is a cost-effective intervention compared with radiofrequency ablation (RFA) and surgery for patients with resectable HCC. Despite entry criteria for the CtE scheme excluding patients whose HCC was suitable for treatment by surgery or RFA, these interventions were considered potential alternatives to SABR if the use of SABR is to be expanded in the future. Therefore, they were selected by the data working group as comparators to SABR. The cost-effectiveness[10] analysis found that for adult patients with 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. The results are limited by the lack of a control group in the CtE data; it is likely that comparisons with data from the literature on survival and progression rates are confounded by differences in patient characteristics. A randomised trial might provide the robust data required to conclusively assess the cost-effectiveness of treatments for HCC.

[10] Cost-effectiveness analysis is a form of economic analysis that compares the relative costs and clinical outcomes of two or more treatments. It is used to aid decisions about which medical care should be offered.

1 Background

1.1 Stereotactic ablative radiotherapy

Stereotactic Ablative Body Radiotherapy (SABR) is an emerging radiation technology. The American College of Radiology (ACR) and the American Society for Radiation Oncology (ASTRO) define SABR as "an external beam radiation therapy method used to very precisely deliver a high dose of radiation to an extra-cranial target within the body, using either a single dose or a small number of fractions." SABR is a more precise treatment than standard radiotherapy. This results in the delivery of a high, biologically effective dose (BED) to the tumour while minimising the dose received by normal tissues, and thus could potentially minimise radiotherapy treatment toxicity and adverse events (AEs). In addition, as the technique uses a smaller number of fractions (and, consequently, requires a smaller number of hospital visits) than standard radiotherapy, it may provide the opportunity for financial savings and improved patient experience. The technique requires specialist positioning equipment and imaging to confirm correct targeting.

1.2 Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. The incidence of HCC is increasing worldwide due to the increase in hepatitis C infection rates and a rise in non-alcohol fatty liver disease (Parikh et al. 2018). Treatment of HCC depends on a number of factors associated with the patient's performance status, the size, and location of the lesion in the liver and prior liver function (Bruix and Sherman 2011). Surgical resection, liver transplant, and local ablative treatments are available choices to treat early stage disease (Bruix et al. 2011). In some cases however, severe comorbidities or advanced disease exclude treatment with surgery and liver transplant is not always available. More advanced disease can be treated with Transarterial chemoembolization (TACE) but responses are often incomplete, and the treatment is associated with cumulative toxicity imposing a limit in the amount of times a patient can undergo TACE. Systemic targeted chemotherapy such as the use of the oral tyrosine kinase inhibitor sorafenib can be used with palliative intent offering small improvements in LC. For patients with HCC that are not candidates for any of the previously mentioned treatments SABR can be used to offer local ablation. It is estimated that SABR treatment will be suitable for 100-150 patients per year in England (Policy Working Group consensus).

1.3 Commissioning through Evaluation programme

Despite the potential of SABR, there is limited evidence of its effectiveness except in early stage non-small cell lung cancer (NSCLC) and, therefore, extracranial SABR is currently only commissioned by National Health Service (NHS) England for this indication. To address the evidence gap, in 2015 NHS England launched the Commissioning through Evaluation (CtE) scheme for SABR. The scheme, which is part of NHS England's Evaluative Commissioning Programme provides funding for a limited number of patients to access medical treatments and technologies that are not routinely commissioned within the NHS (National Health Service England 2014). CtE enables patients to access promising new treatments, whilst new data is collected within a formal evaluation programme. Outcomes data are considered by NHS England in order to inform future review of clinical commissioning policy. The SABR CtE scheme included the following cohorts:

- Patients with oligometastatic disease;
- Patients with primary liver tumours (hepatocellular carcinoma);
- Patients undergoing re-irradiation of cancers in the pelvis and spine.

NHS England commissioned NICE and its External Assessment Centre (KiTEC) to lead data collection and evaluation of the SABR CtE (work package RX116). This report covers the HCC disease cohort; results for the re-irradiation and oligometastatic cohorts are reported in separate documents.

1.4 Aim of the project

To evaluate the clinical effectiveness, safety and cost-effectiveness of SABR in patients with HCC.

1.5 Stages

The project was carried out in two stages – a feasibility stage and a data collection and analysis stage, each with specific tasks and outputs. The purpose of the feasibility stage was to plan the data collection and analysis stage. The feasibility stage of the SABR CtE project started on in June 2015 and KiTEC completed the following tasks as part of that stage:

- Develop the variables/dataset required to capture essential information to answer NHS England's questions;
- Develop the interim data collection tool;

- Establish the roles and responsibilities for the project between KiTEC, NICE, NHS England and the clinical leads;
- Contact the centres that have commenced recruitment and establish the type of data they are collecting;
- Establish the governance requirements for the project and obtained REC, HRA and RD approvals.

KiTEC's overall goal for the second stage of the project was to oversee, co-ordinate and manage the data collection and to conduct the analysis. The results of this stage are reported in this document.

1.6 Database provider

The SABR CtE project required a centralised database to collect data from all of the participating clinical centres for the purpose of analysis. Following various discussions on this subject, it was decided that King's College London would hold the contract with the database provider. Following a successful competitive procurement process, University Hospitals Birmingham (UHB) was selected as the database provider.

1.7 Project scope

The scope for the SABR CtE scheme is outlined in Table 1 below.

Table 1: Project scope

Population	Patients with hepatocellular carcinoma*
Intervention	SABR (5 fractions)
Comparator	There was no comparator
Outcomes	• Overall survival • Local control† • Pain control • Quality of life • Adverse events • Cost effectiveness
* Inclusion and exclusion criteria are listed in sections 1.7.1 and 1.7.2.	

† Local control is the proportion of patients for which the treated area does not increase in size at a defined follow-up point after beginning treatment. Local control is different to progression-free survival (PFS) that 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. Worsening of the disease usually means the development of metastases elsewhere in the body and/or an increase in the size of the treated lesion. There is significant variability on how different studies report this outcome. The CtE scheme assessed only local control and not PFS.

1.7.1 Inclusion criteria

- Patients with metastatic disease who have been discussed by the Hepato-Pancreato-Biliary (HPB) MDT.
- Patients with an HCC diagnosis (initial, recurrent, progressive, and/or refractory to other therapies).
- Unsuitable for resection, transplant, or RFA.
- Unsuitable for or refractory to transarterial hepatic TACE or drug eluting beads (DEB); no response to TACE or DEB.
- History/physical examination including examination for encephalopathy, ascites, and Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status 0-1.
- Adequate haematological and organ function.
- Barcelona clinic liver cancer (BCLC) stage: Intermediate (B) or advanced (C).
- Liver volume minus intrahepatic gross tumour volume (GTV) > 700 cm^3 and intrahepatic tumour GTV/liver volume ratio <80%.
- Maximum tumour dimension 5 cm.
- Childs-Pugh Class A only (Childs Pugh scoring system classification).
- Life expectancy > 6 months.
- Patients must have recovered from the effects of previous surgery, radiotherapy, or chemotherapy with a minimum of 4 weeks break prior to SABR.
- Suitability for treatment established in Hepatobiliary MDT and Stereotactic MDT.
- All patients willing to attend follow up and have details collected on prospective database for a minimum of two years.

1.7.2 Exclusion criteria

- Active hepatitis or clinically significant liver failure (encephalopathy, oesophageal varices, portal hypertension).
- Prior abdominal radiotherapy precluding SABR, defined as any previous radiation therapy in which a mean dose to the liver of 15 Gy in conventional fractionation was delivered or previous doses to critical normal structures that would make re-irradiation unsafe. Prior pelvic radiation is permitted, as long as there is no overlap between pelvic and liver radiation fields.
- Clinically apparent ascites.
- Any one hepatocellular carcinoma tumour > 6 cm.
- More than 5 discrete intrahepatic parenchymal foci of HCC.
- Direct tumour extension into the stomach, duodenum, small bowel, or large bowel.
- Extrahepatic metastases or malignant nodes (that enhance with typical features of HCC) > 3.0 cm in sum of maximal diameters (e.g. 2 lung lesions > 2 cm).
- Active hepatitis, prior liver transplant.

1.7.3 Recruiting centres

Out of 17 centres participating in the SABR CtE scheme (which also included the evaluation of SABR for the treatment of patients with oligometastatic disease and patients undergoing re-irradiation), 7 centres were selected by NHS England to provide SABR treatments for patients with HCC. The participating centres are listed below:

- University Hospitals Birmingham NHS Foundation Trust
- Oxford University Hospital NHS Trust
- Bart's Health NHS Trust
- Guys and St Thomas' NHS Foundation Trust
- Mount Vernon Cancer Centre (North and East Hertfordshire NHS Foundation Trust)
- Leeds Teaching Hospitals NHS Trust
- The Royal Marsden NHS Foundation Trust

2 Commissioning through Evaluation questions

NHS England required the following research questions to be addressed:

1. What is the 1-year and 2-year survival following treatment with SABR for the indications covered by the CtE scheme (presented as estimates with confidence intervals)? How do these survival estimates compare with the target outcomes (see section 4), in terms of superiority or non-inferiority?
2. Does treatment with SABR for the clinical indications covered within the CtE scheme increase local control?
3. What Adverse Events occur as a result of SABR in the CtE cohort of patients?
4. What is the patient experience of treatment with SABR for the clinical indications covered within the CtE programme?
5. What is the cost-effectiveness of providing SABR in three subgroups of patients covered within the CtE scheme (oligometastases (liver), re-irradiation (pelvis) & hepatocellular carcinoma)?
6. What are the outcomes by indication in the CtE cohort of patients? The cohort can potentially be stratified based on the location or histology of metastasis treated.
7. Are there any factors from the experience of provision within centres participating in the scheme that should be taken into account in terms of future service provision?
8. Are there any research findings that have become available during the course of the CtE scheme that should be considered alongside the evaluative findings of the CtE scheme?

3 Information governance

3.1 Ethics approval

To answer the NHS England's evaluation questions for this project the centres needed to collect routine clinical data, data on quality of life (QoL), pain symptoms, and patient experience using questionnaires and to store this locally, with standard NHS patient consent. This phase of the project was classified as an audit and all patient data were stored and viewed only by the patients' clinical team. KiTEC submitted a REC application for proportionate review at the North East - York Research Ethics Committee to gain permission to analyse these patient data in a non-identifiable format. The patients undergoing SABR as part of the scheme signed a standard NHS consent form to the treatment. The patients were consented separately to their treatment consent for their data to be analysed by KiTEC. Ethics approval for the project was obtained in August 2016 (REC reference: 16_NE_0285) and HRA approval was obtained in October 2016. Following that R&D approvals for all participating centres needed to be obtained separately.

The data flow between NHS Trusts and KiTEC was as follows:

1. Patient identifiable data were entered electronically at each NHS Trust site and were stored locally by the local clinical teams involved in patient care using an interim access tool (IAT) database developed by KiTEC.
2. Identifiable data from the IAT were subsequently uploaded from each centre to PROPEL the SABR national database developed by the database provider (UHB). The database can only be accessed from within the NHS by the clinicians involved in the project and each Trust will only be able to access its own data.
3. Patient pseudo-anonymised data were subsequently sent from PROPEL to KiTEC for analysis.

3.2 Data linkage approvals

Hospital Episodes Statistics (HES) is a data warehouse containing details of all admissions, outpatient appointments, and A&E attendances at NHS hospitals in England. Centres involved with SABR were submitting returns to HES monthly. The database provider submitted an application to NHS Digital to request data from HES and ONS. These patients' records from HES/ONS were subsequently linked with patient level data captured in the PROPEL database. The purpose of this linkage was to enable accurate mortality data to be captured, as well as data on other diagnoses or procedures that

patients may have had at other departments (internal or external to the treating hospital), thus increasing the accuracy of the recording of both adverse event and mortality in the database. This process required UHB to collect non-anonymised patient data (NHS number as a minimum), as well to obtain access to equivalently non-anonymised HES/ONS patient records. On April 2018 the database provider submitted a formal application to NHS Digital (NIC-150435-R7X1Q) outlining the legal basis for linking the CtE collected data to non-anonymised HES/ONS patient records. After the application was reviewed by the IGARD[11] committee (the application was reviewed in 3 separate dates between September and November 2018) it was finally approved in November 2018. The database provider submitted the patient identifiers to NHS digital on December 2018. Final data linkage between PROPEL and HES/ONS took place at the end of December 2018.

4 Analysis of CtE registry data

4.1 Statistical analysis plan

The data was analysed as per the SABR Data Analysis Protocol 17/02/2016 – Version 2.2 (please see appendix C).

4.2 Sample size

As this was a CtE project and not a clinical trial, a sample size calculation was not performed. The number of patients receiving SABR in England as part of the CtE scheme was fixed and dependent on the funding available from NHS England. For the total duration of the scheme (3 years), 2,250 people were expected to undergo SABR treatment for the three indications. Of this number, approximately 100 patients per year (total 300) were estimated to receive treatment for HCC.

4.3 Database

Data for the CtE were collected on three different instruments:

[11] The Independent Group Advising on the Release of Data (IGARD) considers all requests for dissemination of confidential information by NHS digital, as defined in Section 263 of the Health & Social Care Act, through the Data Access Request Service (DARS).

4.3.1 Paper CtE monitoring form: July 2015 to May 2016

NHS England provided paper forms to the recruiting centres (see appendix C). These were used for data collection at baseline and follow up clinical assessments as well as EQ-5D (EuroQol Group 1990, Dolan P 1997, Feng Y et al. 2017), CTCAE (Common Terminology Criteria for Adverse Events, U.S. Department of Health and Human Services 2010), and the Visual Analogue Pain score (Brief Pain Inventory).

4.3.2 KiTEC-developed interim access tool: June 2016 to May 2018

In line with information governance requirements, KiTEC developed an interim tool for hospital trusts to store data before sending it to the national database. The interim tool was developed using the specification from an agreed SABR data dictionary using MS Access. It allowed data collection at baseline, 4-6 week, 3-month, 6-month, 12-month, 18-month and 24-month clinical assessments as well as EQ-5D, CTCAE, Visual Analogue Pain score, patient experience and radiotherapy parameters (Table 2 lists the data collected during each follow-up). Each provider site had their own interim tool and managed it in compliance with NHS information governance procedures. The information governance department at each NHS Trust approved the use of the interim access tool.

Table 2: Data collected at each follow-up appointment as part of the scheme.

TIME POINTS							
Forms	Baseline	4-6 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
Demographics	√						
Clinical Assessment - Baseline	√						
Clinical Assessment - Follow Up	√	√	√	√	√	√	√
EQ-5D	√	√	√	√	√	√	√
CTCAE	√	√	√	√	√	√	√
Pain Score	√	√	√	√	√	√	√
Patient experience		√					
Radiotherapy planning details (Trt 1)	√						
Radiotherapy planning details (Trt 2)	√						
Radiotherapy planning details (Trt 3)	√						
Death		√	√	√	√	√	√
Trt = treatment							

4.3.3 UHB-developed PROPEL database: June 2018 to December 2018

The national PROPEL database was created by UHB and mirrored the functionality of the KiTEC-developed interim tool with a few modifications. It was a web application based at UHB and was accessible only through the NHS N3 network. UHB performed the collation and migration of the KiTEC interim tools from the 7 centres. The PROPEL database had ethical approval and was managed by the UHB NHS IT department in compliance with NHS security procedures.

PROPEL also collected DICOM data as a separate project funded by NHS England – analyses are not provided as part of this CtE report.

4.4 Data extraction

Data were extracted from the UHB PROPEL database and were provided to KiTEC in pseudo-anonymised form along with a data dictionary (see Appendix D: Data dictionary for PROPEL). KiTEC did not have access to the paper CtE monitoring form or the data from the KiTEC-developed Interim tool used at each clinical site. Data extracts were provided by UHB in July 2018, September 2018, November 2018, January 2019 and the final data extract in February 2019. KiTEC fedback data quality issues to UHB after each extract except the final one.

Minor structural inconsistencies between the data dictionary provided by PROPEL and the data provided were resolved when possible through personal communication with UHB for the relevant variables for this current analysis. None of the inconsistencies resulted in data loss or affected the clinical outcomes included in this report.

4.5 Data management and HES-ONS linkage

On 21/12/2018, after obtaining the HES/ONS records from NHS Digital, UHB provided linked HES-ONS (NHS Digital 2018a, NHS Digital 2018b, NHS Digital 2018c) data for 80 CtE patients who had consented for their identifiable data to be used. UHB provided KiTEC with the HES-ONS data, and KiTEC merged the HES-ONS data with the PROPEL data extract from UHB provided in February 2019 using the pseudo-anonymised patient identifiers in both extracts. The linked HES/ONS data covered the period from June 2015 to October 2018. To understand inconsistencies between data sources, UHB contacted all centres that had date of death (DOD) discrepancies between ONS (last updated 31/10/2018) and PROPEL (last updated 22/01/2019).

The PROPEL dataset was provided in long format and required re-formatting by KiTEC to check for and address issues of duplication within patients' own data over the various assessment time points. Only after these extensive checks were completed could KiTEC merge the PROPEL data with the HES/ONS data.

4.6 Data completeness

UHB and KiTEC using both the KiTEC- developed interim tool and the UHB PROPEL database conducted data completion explorations. The interim tool had an inbuilt aggregate report facility designed by KiTEC that provided percentage completion figures for patients who had records in the database. Data completion from the PROPEL tool used a similar aggregate report. The PROPEL tool also provided another report that allowed for patients who were missing from follow-ups. UHB reported to KiTEC that they had followed up data completeness and quality issues with centres. Between September 2016 and January 2018 KiTEC monitored the completeness of the database mandatory fields using aggregate figures from the interim access tool. Centres were sent newsletters every two months showing their mandatory fields' completion rate.
From February 2018, UHB were responsible for monitoring both the completeness of the mandatory fields as well as the patients lost to follow up. UHB started sending participating centres the mandatory field completeness newsletters in May 2018 and continued sending them every two months thereafter. UHB also monitored the data completeness at baseline and during follow-up for each patient. UHB reported regularly to KiTEC through reports and teleconferences that they had followed up data completeness and quality issues with centres. Table 3 shows the final data completeness rates for each recruiting NHS Trust.

Table 3: Final data completeness rates achieved by each participating NHS Trust. Please note that due to the way data completeness was calculated it is provided for all three indications treated under the SABR CtE scheme.

Centre	Data completeness rate (%)
UNIVERSITY COLLEGE LONDON HOSPITALS NHS FOUNDATION TRUST	40
SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST	98
UNIVERSITY HOSPITALS OF LEICESTER NHS TRUST	95

SOUTH TEES HOSPITALS NHS FOUNDATION TRUST	90
THE CHRISTIE NHS FOUNDATION TRUST	89
UNIVERSITY HOSPITALS BRISTOL NHS FOUNDATION TRUST	97
THE CLATTERBRIDGE CANCER CENTRE NHS FOUNDATION TRUST	71
THE NEWCASTLE UPON TYNE HOSPITALS NHS FT	96
BARTS HEALTH NHS TRUST	91
GUY'S AND ST THOMAS' NHS FOUNDATION TRUST	83
ROYAL SURREY COUNTY HOSPITAL NHS FOUNDATION TRUST	97
OXFORD UNIVERSITY HOSPITALS NHS TRUST	65
NOTTINGHAM UNIVERSITY HOSPITALS NHS TRUST	96
LEEDS TEACHING HOSPITALS NHS TRUST	73
THE ROYAL MARSDEN NHS FOUNDATION TRUST	87
EAST AND NORTH HERTFORDSHIRE NHS TRUST	97
UNIVERSITY HOSPITALS BIRMINGHAM NHS FOUNDATION TRUST	96
Total	Overall completeness: 87.7 %

4.7 Statistical methods

KiTEC calculated summary statistics by CtE indication for demographics, baseline clinical characteristics, primary tumour histology, SABR procedural characteristics, QoL, pain scores, and the patient experience questionnaire. Median follow-up time with inter quartile ranges (IQR) are reported where appropriate. Survival function estimates with 95% confidence intervals were estimated for one and two years from the start of SABR treatment using the Kaplan-Meier method, that takes into account differential follow-up times among the patient group. Where patients were still alive at the final documented clinical visit, they were censored at that date in the analysis. Median overall survival (OS) and median local control (LC) are reported if within the two-year follow-up period.

The first occurrence of failure of local control was considered as the event.

These analyses were performed for each of the three CtE indications and reported only for patients with HCC in this report. Kaplan-Meier survival curves were drawn with a 95% confidence interval for

the curve. Where there were fewer than 6 deaths in a group or subgroup of patients, Kaplan-Meier estimates were not calculated as they are considered unreliable (Peacock JL and Peacock PJ 2011). In these cases, indicative Kaplan-Meier plots have been given but without estimated survival.

To determine date of death, where available the HES/ONS date of death was considered the gold standard. This was therefore used when there was lack of consistency between the date of death reported in HES/ONS and the PROPEL database or when it was missing. HES/ONS data were only linked for patients who had consented. In order to maximise the number of patients who could be included, patients who had not provided consent for linkage with HES/ONS were included but their data were censored at the last point at which they were known to be alive.

Frequency of adverse events by type were calculated. Adverse events with a start date occurring prior to commencement of SABR treatment were excluded. Duplicated adverse events were also excluded. Data recorded outside of the CTCAE grading system were excluded. Adverse event toxicity variables based on anatomical treatment location, were not accurately provided in the PROPEL database nor did the data dictionary received from UHB reflect the PROPEL dataset. Therefore, it was not possible to assess the quality and accuracy of this variable in relation to the adverse event types. The following summary statistics were calculated for adverse events: percentage of patients with i) one or more adverse events overall, ii) with grade 3 adverse events and iii) with grade 4 or 5 adverse events. Please see appendix F for details about the adverse events data quality checks. These were each calculated with a 95% CI using the exact binomial method to accommodate the very small frequencies.

The 'friends and family test' (https://www.england.nhs.uk/ourwork/pe/fft/), a short generic instrument, designed to provide some patient experience feedback was used to collect information for all SABR patients. This test has been widely used in the NHS. The frequencies have been given in this report with the percentages and 95% CIs for each category.

STATA version 15, plus STATA graph addition (Jann B 2018) and SPSS version 25 were used for analysis in this report.

4.8 Proposed target outcomes

Proposed target OS, LC, and adverse events rates were agreed by the working group by consensus, based on findings from a systematic review conducted in 2015. These targets were used to aid the interpretation of the overall survival and local control estimates observed in the CtE patients reported in the evaluation. The targets proposed for each outcome are listed in Table 4.

Table 4: NHS England/NICE CtE Evaluation Questions

Agreed NICE and EAC evaluation questions	SABR subgroup specific question
What is the 1-year and 2-year survival following treatment with SABR for the indications covered by the CtE scheme (presented as estimates with confidence intervals)? How do these survival estimates compare with the target outcomes, in terms of superiority or non-inferiority?	Proposed target: The literature reports a 2-year OS rate of approximately 50%. This is the best defined of the 3 SABR cohorts. In addition, there are numerous SRs and meta-analyses for treating patients with HCC with other treatments, such as RFA. Any target outcomes set for this cohort will need to be non-inferior to clinical outcomes provided with these treatments.
Does treatment with SABR for the clinical indications covered within the CtE scheme increase local control?	Proposed target: LC rate of 80% at 1 year for SABR. This estimate takes into account both findings reported in the literature, and clinical experts' consensus.
What Adverse Events occur as a result of SABR in the CtE cohort of patients?	Proposed target: Based on the published evidence and the accreditation scheme for all the NHS Trusts included in the CtE scheme a target outcome rate for grade 3 adverse events of 15% and for grade 4-5 adverse events of 10% was proposed.
What is the patient experience of treatment with SABR for the clinical indications covered within the CtE programme? The 'friends and family test' (https://www.england.nhs.uk/ourwork/pe/fft/), a short generic instrument, designed to provide some patient experience feedback will be used to collect information for all SABR patients. This test has been widely used in the NHS.	NA

What is the cost-effectiveness of providing SABR in three subgroups of patients covered within the CtE scheme (Oligometastases (liver), Re-irradiation (Pelvis) & Hepatocellular carcinoma)? Cost-effectiveness will be assessed using a Markov model to synthesise evidence on SABR and from literature on relevant comparators over the time horizons specified. The Markov model will model the following four health states for SABR and comparators: Progression free survival Local progression Systemic progression Death Data for survival will be obtained from the SABR dataset and literature for comparators. In the absence of literature estimates distinguishing local and systemic progression, the health states will be combined. Utilities will be estimated from the EQ5D of the SABR dataset and from literature for the comparators.	NA
What are the outcomes by indication in the CtE cohort of patients?	NA
Are there any factors from the experience of provision within centres participating in the scheme that should be taken into account in terms of future service provision?	NA
Are there any research findings that have become available during the course of the CtE scheme that should be considered alongside the evaluative findings of the CtE scheme?	NA

4.9 Results

4.9.1 Data quality

KiTEC only assessed data quality of variables that feed into the outcomes assessed in this report as per the agreed Statistical Analysis Plan. Examples of some of the data errors identified by KiTEC in the variables utilised for the purposes of this report were:

- Incompatible SABR treatment/assessment dates.
- Follow-up assessment dates occurring before the start of first SABR treatment.
- Follow-up assessments occurring on the same date as the first SABR treatment.
- Extensive duplication of data across time points.
- Patients who were missing dates of baseline or follow-up assessment.
- Multiple patients who only had baseline data and no follow-up.
- Dates of assessment occurring in non-chronological order.
- Adverse events which were non-compatible with CTCAE grades (see appendix F for a discussion about the adverse events data quality checks).
- Patients whose start date for SABR treatment was the same day as their end date.
- Follow-up assessment dates occurring after death (HES/ONS or PROPEL listed death).
- Patients with empty rows of data.

Only patients who contributed to the overall survival with at least one follow-up appointment following SABR treatment were included in the analysis in this report. Based on the reasons outlined above, a total of n=17 patients were excluded from the analysis in this report.

4.9.2 Patient recruitment

Data were collected from the 7 centres. Figure 1 shows the flow diagram for patient recruitment in the scheme. From an estimated 300 patients at the beginning of the scheme 105 were finally recruited. Centres screened patients through their MDT meetings but this information was not recorded as part of the CtE scheme. It is therefore unknown how many patients were originally screened for eligibility.

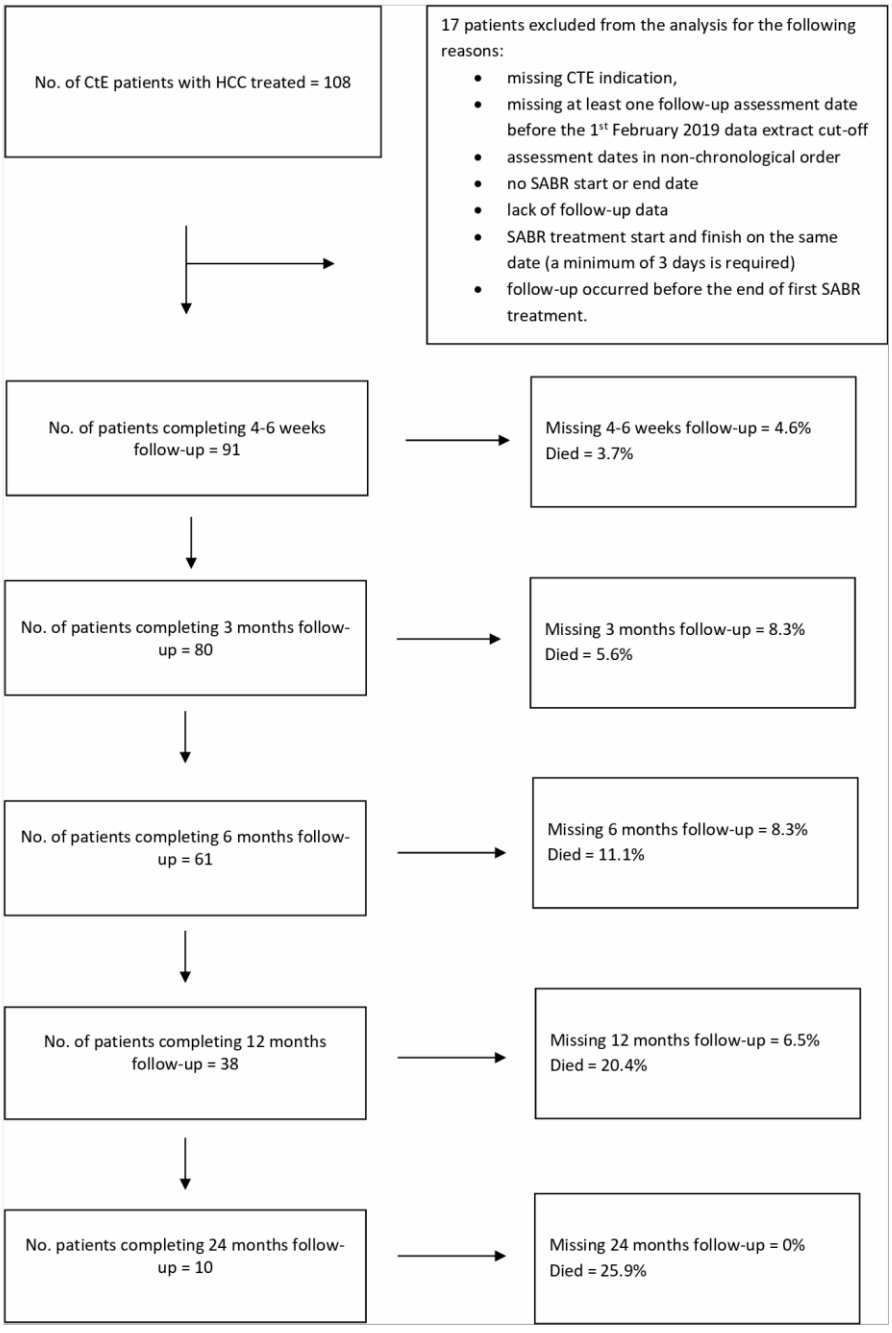


Figure 1: Patient recruitment flowchart.

4.9.3 Demographics

Baseline demographics and clinical information of patients with HCC are in Table 5 and Table 6.

Table 5: Cohort demographics

	HCC (n=91)	
Age		
Age - N (%)	91	100%
Age – Median (IQR) years	72	(67 to 80)
Sex		
Male - N (%)	66	72.5%
Female - N (%)	25	27.5%
Ethnicity - N (%)		
White - British	61	69.3%
White - Irish	0	0.0%
White - Any other white background	1	1.1%
Mixed - White and Black Caribbean	0	0.0%
Mixed - White and Black African	0	0.0%
Mixed - White and Asian	0	0.0%
Mixed-Any other mixed background	1	1.1%
Asian or Asian British - Indian	1	1.1%
Asian or Asian British - Pakistani	7	8.0%
Asian or Asian British - Bangladeshi	0	0.0%
Asian or Asian British - Any other Asian Background	2	2.3%
Black or Black British - Caribbean	1	1.1%
Black or Black British - African	1	1.1%
Black or Black British - Any other Black background	0	0.0%
Other Ethnic Groups - Chinese	1	1.1%
Other Ethnic Groups - Any other ethnic group	0	0.0%
Not stated	12	13.6%
Total Ethnicity	88	

	HCC (n=91)	
Missing* Ethnicity	3	3.3 %

Table 6: Baseline clinical characteristics

WHO performance status		
0 - Fully active, able to carry on all pre-disease performance without restriction	28	30.8%
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	50	54.9%
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	13	14.3%
Total WHO performance status	91	
Size of largest lesion (cm)		
1	4	7%
2	17	29.8%
3	11	19.3%
4	13	22.8%
5	9	15.8%
6	3	5.3%
Total Size of largest lesion (cm)	57	
Missing Size of largest lesion (cm)	34	37.4%
Prior systemic therapy		
Yes	29	31.9%
No	62	68.1%
Total Prior systemic therapy	91	

4.9.4 Procedural information

The CtE scheme also collected information relevant to the SABR treatment. Table 7 lists the procedural information for patients with HCC. The majority of the patients (95%) were treated with a standard linear accelerator. Most patients were treated with 5 fractions of radiotherapy receiving

45 Gy of radiation (median). Cone beam CT (CBCT) image guidance was the most commonly used technique to assist treatment delivery.

Table 7: SABR procedural information

	n=91	
SABR treatment platform – N (%)		
Elekta	76	83.5%
Varian	10	10.9%
Cyberknife	5	5.4%
IGRT* technique – N (%)		
CBCT (soft tissue)	81	89.0%
CBCT (fiducial)	5	5.4%
kV planar (fiducial)	5	5.4%
Number of fractions - N (%)		
3	3	3.3%
5	87	95.6%
Missing	1	1.1%
Radiotherapy dose - Gy		
Median	45	NA
*IGRT = image-guided radiotherapy NA = not applicable		

4.9.5 Overall survival analysis

Median follow-up time for patients with HCC was 0.58 years (IQR 0.35 to 1.06). The median overall survival time was 1.83 years. Overall survival estimates at one and two years were calculated (Table 8) along with a corresponding Kaplan-Meier plot for patients with HCC (Figure 2).

Table 8: Overall survival estimates

Survival interval	Probability of survival	95% confidence interval
One year	76.5%	62.4 to 85.9%
Two year	41.7%	22.4 to 60.0%

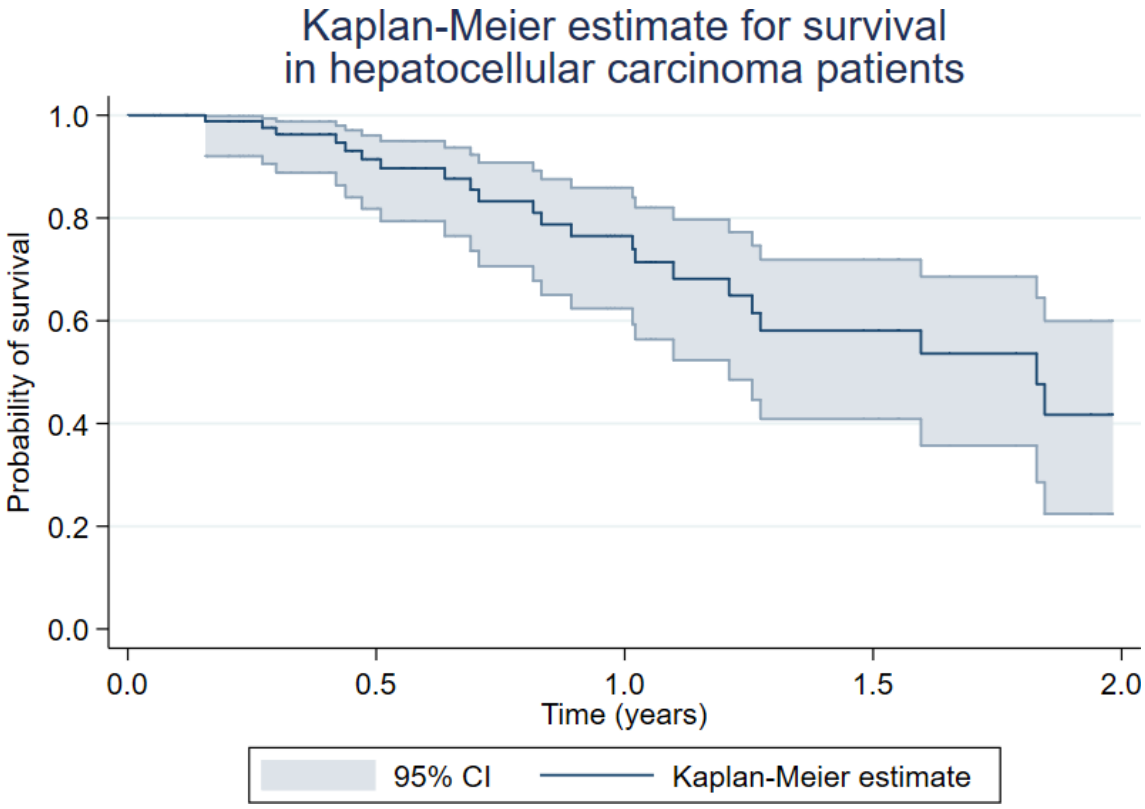


Figure 2: Kaplan-Meier estimate for overall survival

4.9.6 Local control analysis

Overall local control estimates at one and two years were calculated (Table 9) along with a corresponding Kaplan-Meier plot for patients with HCC (Figure 3). It was not possible to calculate the median local control because it was past the two-year follow-up cut-off (see methods).

Table 9: Overall local control estimates

Year of local control	Probability of local control	95% confidence interval
One year	72.3%	57.9 to 82.5%
Two year	52.4%	25.2 to 73.9%

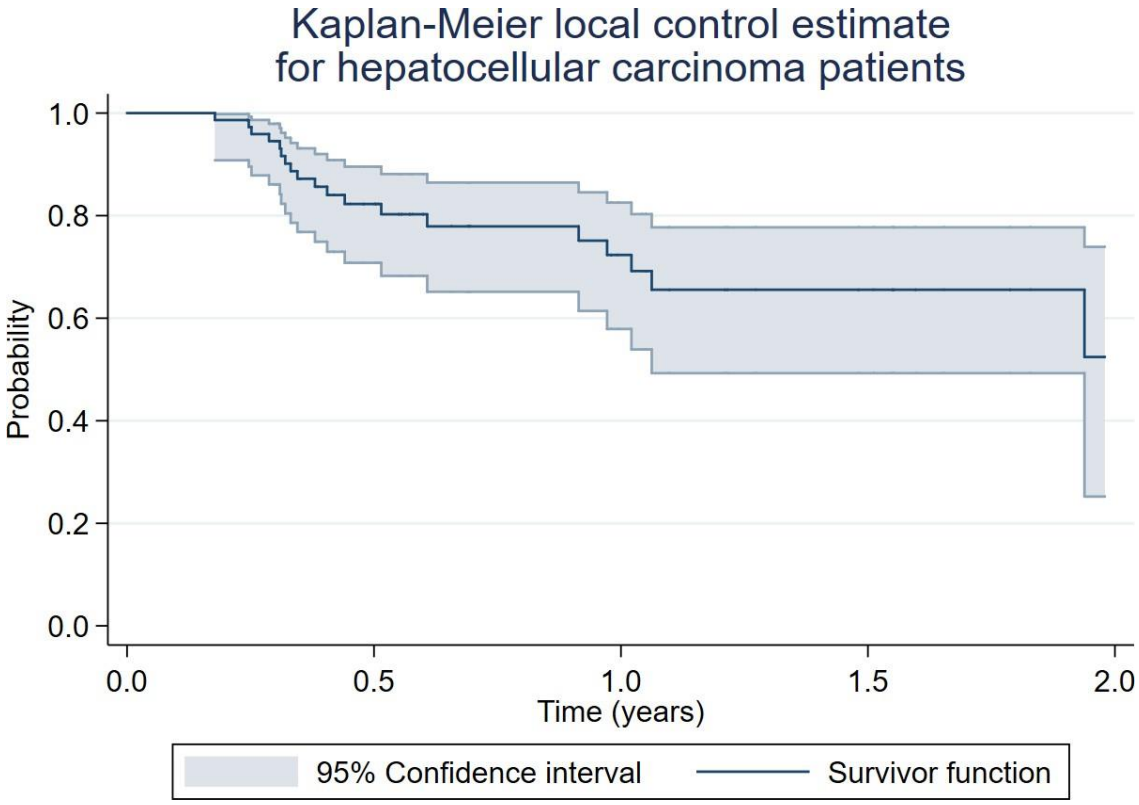


Figure 3: Kaplan-Meier estimate for local control

4.9.7 Adverse events

Patients with HCC undergoing SABR were monitored over time for adverse events. Due to relatively small number of available patients at the baseline (n=91) and very small number of patients at t2-years follow-up point (n=10), only basic descriptive statistics and description of their pattern (where it was reasonable) are provided below. Total number of adverse events recorded across all patients is displayed in Table 10 and a summary of the percentages of patients with 1 or more adverse event reported is in Table 11.

Table 10: Frequency of adverse events

CTCAE grade	HCC
Grade 1	252
Grade 2	133
Grade 3	15
Grade 4	6
Grade 5*	0
All grades	406

*Please see more information about the triangulation of adverse events in appendix E.

Table 11: Summary table for adverse events: percentage of patients with 1 or more adverse event reported

CTCAE grade	Number of patients	Percentage of patients with AE	95% confidence intervals
All grades (any AE)	80/91	88.0%	79.0 to 94.0%
Grade 3	11/91	12.1%	6.8 to 20.7%
Grade 4	3/91	3.3%	1.1 to 9.9%

Table 12 provides a break-down of all adverse events by CTCAE grade. Please note that empty grade fields (*) reflect the CTCAE grading criterion, where there are not grading categories up to grade 5.

Table 12: Total number of adverse events by CTCAE grade. The information provided is given as the total number of events experienced by all patients

Adverse event type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Dysphagia	Grade 1 - Symptomatic, able to eat regular diet	Grade 2 - Symptomatic with altered eating/swallowing	Grade 3 - Severely altered eating/swallowing; tube feeding or TPN or hospitilization indicated	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	
	14	3	0	0	0	17
Gastritis	Grade 1 - Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Grade 2 - Symptomatic; altered GI function; medical intervention indicated	Grade 3 - Severely altered eating or gastric function; TPN or hospitalization indicated	Grade 4 - Life-threatening consequences; urgent operative intervention indicated	Grade 5 - Death	
	8	1	0	0	0	9
Nausea	Grade 1 - Loss of appetite without	Grade 2 - Oral intake decreased	Grade 3 - Inadequate oral	*	*	

Adverse event type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	alteration in eating habits	without significant weight loss, dehydration or malnutrition	caloric or fluid intake; tube feeding, TPN, or hospitalization indicated			
	32	22	1			55
Fatigue	Grade 1 - Relieved by rest	Grade 2 - Fatigue not relieved by rest; limiting instrumental ADL	Grade 3 - Fatigue not relieved by rest, limiting self-care ADL	*	*	
	118	81	11			210
Spinal fracture	Grade 1 - Mild back pain; nonprescription analgesics indicated	Grade 2 - Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Grade 3 - Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty);	Grade 4 - Life-threatening consequences; symptoms associated with neurovascular compromise	Grade 5 - Death	

Adverse event type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
			limiting self-care ADL; disability			
	1	1	0	0	0	2
Duodenal/Gastric ulcer	Grade 1 - Asymptomatic ulcer, intervention not indicated	Grade 2 - Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Grade 3 - Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self-care ADL; disability	Grade 4 - Life-threatening consequences; urgent operative intervention indicated	Grade 5 - Death	
	0	0	1	0	0	1
Fever	Grade 1 - 38.0-39.0 degrees	Grade 2 - 39.1-40.0	Grade 3 - >40.0 degrees for <24 hours	Grade 4 - >40.0 degrees for >24 hours	Grade 5 - Death	
	3	0	0	0	0	3

Adverse event type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Liver enzymes : ALT	Grade 1 - ULN-3*ULN	Grade 2 - 3*ULN – 5*ULN	Grade 3 - >5.0 - 20.0 x ULN; >5 x ULN for >2 weeks	Grade 4 ->20 *ULN	Grade 5 -Death	
	48	3	0	0	0	51
Bilirubin	Grade 1 - ULN- 1.5* ULN	Grade 2 - >1.5 - 3.0 x ULN	Grade 3 - >3.0 - 10.0 x ULN	Grade 4 - >10.0 x ULN	*	
	26	22	2	6	0	56
Diarrhoea	Grade 1 - Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Grade 2 - Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Grade 3 - Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	
	1	0	0	0	0	1

Adverse event type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Bone pain	Grade 1 - Mild pain	Grade 2 - Moderate pain; limiting instrumental ADL	Grade 3 - Severe pain; limiting self-care ADL	*	*	
	1	0	0			1
Total adverse events	252	133	15	6	0	406

Note: Empty grade fields with * reflect the CTCAE grading criterion, where there are no grading categories up to Grade 5.

†The data dictionary was setup to map adverse events to the treated area. For example, a patient treated in the thorax would be mapped to upper GI toxicity reported as upper GI ulcer.

ADL = activities of daily living, ULN = upper limit of normal

Longitudinal analysis of the adverse events showed that the proportion of patients reporting adverse events (any grade) varied from 57% at baseline to 77% at 4-6 weeks to 50% at the final time point (24 months). The summary analysis is presented in Table 13. It should be noted, that the small number of patients with follow-up beyond 12 months, increases the uncertainty of these results.

Table 13: Longitudinal analysis of adverse events.

Any grade toxicity present	Baseline	4-6 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
YES	44 (57%)	70 (77%)	52 (69%)	39 (71%)	17 (52%)	11 (69%)	4 (50%)
NO	29 (41%)	19 (21%)	24 (33%)	20 (36%)	14 (42%)	6 (37%)	4 (50%)
N	77	91	75	55	33	16	8

A common indication of impaired liver function, either due to SABR treatment or disease progression is high blood circulating levels of ALT and bilirubin was not observed in this data. Table 14 shows the reported ALT levels at baseline and each follow-up appointment. At baseline the majority of patients (86 %) reported levels within normal range. During follow-up, this proportion dropped and remained to approximately 70%. This indicates that the levels of liver enzymes increase with time which might be the consequence both of the disease progression or long term results of SABR therapy. A similar pattern for ALT is observed in the longitudinal analysis of the bilirubin levels (
Table 15).

Table 14: Summary of ALT blood levels over time.

ALT level	Baseline	4-6 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
Normal	62 (86%)	63 (82%)	56 (85%)	38 (88%)	22 (76%)	10 (77%)	5 (71%)
1 ULN- 3*ULN	10 (14%)	14 (18%)	9 (14%)	4 (9%)	7 (24%)	2 (15%)	2 (29%)
2 >1.5 - 3.0 x ULN	0 (0%)	0 (0%)	1 (2%)	1 (2%)	0 (0%)	1 (8%)	0 (0%)
>3.0 - 10.0 x ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
>10.0 x ULN	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
N	72	77	66	43	29	13	7

Table 15: Summary of bilirubin blood levels over time.

Bilirubin level	Baseline	4-6 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
Normal	63 (86%)	66 (84%)	47 (72%)	36 (84%)	23 (79%)	11 (85%)	6 (86%)
1 Up to 1.5ULN	5 (7%)	7 (9%)	7 (11%)	3(7%)	2(7%)	2 (15%)	0(0%)
2 >1.5 - 3.0 x ULN	3 (4%)	4 (5%)	8 (12%)	3 (7%)	3 (10%)	0 (0%)	1 (14%)
>3.0 - 10.0 x ULN	1 (1%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
>10.0 x ULN	1(1%)	1 (1%)	2 (3%)	1 (2%)	1 (3%)	0 (0%)	0 (0%)
N	73	78	65	43	29	13	7

4.9.8 Patient experience

The results of the patient experience question are in Table 16.

Table 16: Patient Experience

	Number of patients (n=91)		
Patient Experience - How likely are you to recommend our SABR service to friends and family if they needed similar care or treatment?			
	N	Percent	95% CI
Extremely likely	47	64.0%	52.0 to 74.0%
Likely	17	23.0%	14.0 to 34.0%
Neither likely or unlikely	5	6.8%	2.2 to 15%
Extremely unlikely	2	2.7%	0.3 to 9.4%
Don't know	3	4.1%	0.8 to 11%
Total	74		
Missing*	17	18.7%	
*Missing % is based on overall number of patients in the specific category			

4.9.9 Quality of life

The EuroQol-5D-3L (EQ-5D-3L) questionnaire was used to collect QoL outcomes. EQ-5D-3L explores five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and includes a visual analogue scale (VAS) to survey generic health-related quality of life. Each dimension has three possible levels of response: no problems, some problems, and major problems. Due to relatively small number of patients at baseline (N=91) and very small number of patients at the final follow-up point (2 years; N=10) only basic descriptive statistics are provided below.

Data on QoL was available for 88 (97%) patients at baseline. 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. Beyond these findings there was no other trend observed for QoL and this is supported from the analysis of the general state of health (0-100). After transforming the reported values to the index measure the means taken at each follow-up are approximately at the same level (ranging from 0.66 and 0.76).

Table 17: Summary statistics based on responses to the EQ-5D-3L from people with HCC for up to two year follow-up.

Mobility (data in %)	Baseline	4-6 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
1-I have no problems in walking about	41	45	50	41	40	44	63
2-I have some problems in walking about	59	54	47	57	57	50	38
3-I am confirmed to bed	0	1	3	2	3	6	0
Total	88	85	70	54	30	16	8
Self Care (data in %)							
1-I have no problems with self-care	70	68	66	61	57	63	75
2-I have some problems washing or dressing myself	28	31	30	39	40	31	25
3-I am unable to wash or dress myself	1	1	4	0	3	6	0
Total	88	85	70	54	30	16	8
Usual activities (data in %)							
1-I have no problem with performing my usual activities	53	51	56	52	43	50	50
2-I have some problems performing my usual activities	38	42	36	39	43	31	38
3-I am unable to perform my usual activities	9	7	9	9	13	19	13
Total	88	85	70	54	30	16	8
Pain/discomfort (data in %)							
1-I have no pain or discomfort	70	64	77	65	57	75	63
2-I have moderate pain or discomfort	30	36	19	31	40	19	25
3-I have extreme pain or discomfort	0	0	4	4	3	6	13

Total	88	85	70	54	30	16	8
Anxiety depression (data in %)							
1-I am not anxious or depressed	56	67	61	65	50	69	50
2-I am moderately anxious or depressed	41	32	37	31	47	31	50
3-I am extremely anxious or depressed	3	1	1	4	3	0	0
Total	88	85	70	54	30	16	8
Your health today (range 0-100)							
Mean	76	74	73	73	78	76	70
Standard deviation	20	21	73	22	21	15	17
Total	81	78	64	48	29	15	7
EQ5D index							
Mean	0.74	0.76	0.74	0.70	0.66	0.70	0.72
Standard deviation	0.22	0.22	0.29	0.28	0.31	0.35	0.37
Total	88	85	70	54	30	16	8

4.9.10 Pain score

The numeric version of the VAS was used to collect pain control outcomes. The questionnaire asks the respondent to select a number between 0-1 that best reflects the intensity of their pain. The reported pain scores were additionally characterised by subdividing into the classes shown in Figure 4. This resulted in 4 categories of pain from none to severe pain.

Data on pain scores were available for 90 (99%) patients at baseline. According to the summary analysis, the majority of patients (87%) of patients did not report any pain at baseline or during follow-up. There is a notable increase in patients who report severe pain from 1% at baseline, to 9% and 19% at 12 and 18 months, respectively. This finding is in agreement with the analysis of the QoL pain/discomfort dimension that reported a small increase of people reporting worsening symptoms between baseline and last follow-up (from 0% to 6% at 18 months). Table 18 and Table 19 report the mean and standard deviation values for pain scores and the proportion of patients in each pain score category at baseline and during follow-up.

Data completeness decreased slightly over time with approximately 80% of the patients returning their questionnaires at 6 and 12 months, respectively. The analysis assumed that missing data have a random distribution and do not introduce bias.

Figure 4: Classification of pain scores

Table 18: Mean and standard deviation values for pain scores at baseline and during follow-up.

Numeric pain rating scale (0-10)	Baseline	4-6 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
Mean	0.57	0.66	0.65	0.73	1.16	1.75	1.00
Standard deviation	1.55	1.78	1.98	2.21	2.81	3.79	2.83
Total	90	86	74	55	31	16	8

Table 19: Proportion of patients for each pain score category at baseline and during follow-up. Numbers represent proportions.

Numeric pain rating scale (0-10)	Baseline	4-6 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
0	78 (87%)	73 (85%)	65 (88%)	49 (89%)	26 (84%)	13 (81%)	7 (88%)
1	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
2	1 (1%)	2 (2%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
3	3 (3%)	2 (2%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
4	3 (3%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
5	4 (4%)	4 (5%)	2 (3%)	3 (5%)	2 (6%)	0 (0%)	0 (0%)
6	0 (0%)	1 (1%)	1 (1%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
7	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
8	1 (1%)	2 (2%)	1 (1%)	0 (0%)	2 (6%)	1 (6%)	1 (13%)
9	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)
10	0 (0%)	0 (0%)	1 (1%)	1 (2%)	1 (3%)	2 (13%)	0 (0%)
N	90	86	74	55	31	16	8

5 Cost-effectiveness analysis

5.1 Aim and objectives

The objective of the economic evaluation in this study was to determine whether SABR is a cost-effective intervention compared with radiofrequency ablation (RFA) and surgery for patients with resectable HCC. Despite entry criteria for the CtE scheme excluding patients whose HCC was suitable for treatment by surgery or RFA, these interventions, were considered potential alternatives to SABR if the use of SABR is expanded in the future. They were therefore, selected by the data working group as comparators. Data from the CtE scheme on these patients is utilised to estimate outcomes for patients with resectable HCC treated with either surgery or RFA.

5.2 Methods

5.2.1 Population & intervention

The base case for the analysis consisted of a hypothetical cohort of adult patients with HCC who may be candidates for surgery. When entering the model, this patient group will receive an initial treatment of surgery, RFA or SABR. Patients who experience local recurrence[12] after initial treatment may receive retreatment with the same treatment as initially given based on published retreatment rates. Patients who experience distant/regional[13] progression will receive palliative care.

5.2.2 Model structure

In order to compare the total cost and effectiveness of different treatment strategies, a decision analytic model was developed using TreeAge 2014 (TreeAge Software, Williamstown, MA). A Markov process was embedded in the model to simulate patients' possible prognoses after treatments, which are expressed in several mutually exclusive health states. In this model, nine mutually exclusive health states were included (Figure 5). The health state occupied by the patient depended on the patient's cancer progression status (no progression, local progression, or regional/ distant

[12] Local progression or local recurrence is defined as disease progression within the previously treated area. Local progression is reflecting changes associated with the local control outcome of the CtE scheme.
[13] Distant or regional progression is defined as disease progression outside the treated area, either in close proximity anatomically (regional progression) or remote to the previous treated area (distant progression).

progression), the number of treatments that patients received (initial treatment or retreatment), and whether or not patients experienced severe adverse events (SAEs) of treatment, including abscess, wound infection, transient respiratory failure and ileus. The cycle length was one month; which meant that every month, patients either moved from one health state to another, or stayed within their current health state, corresponding to their health status. This model adopted a 5-year time horizon.

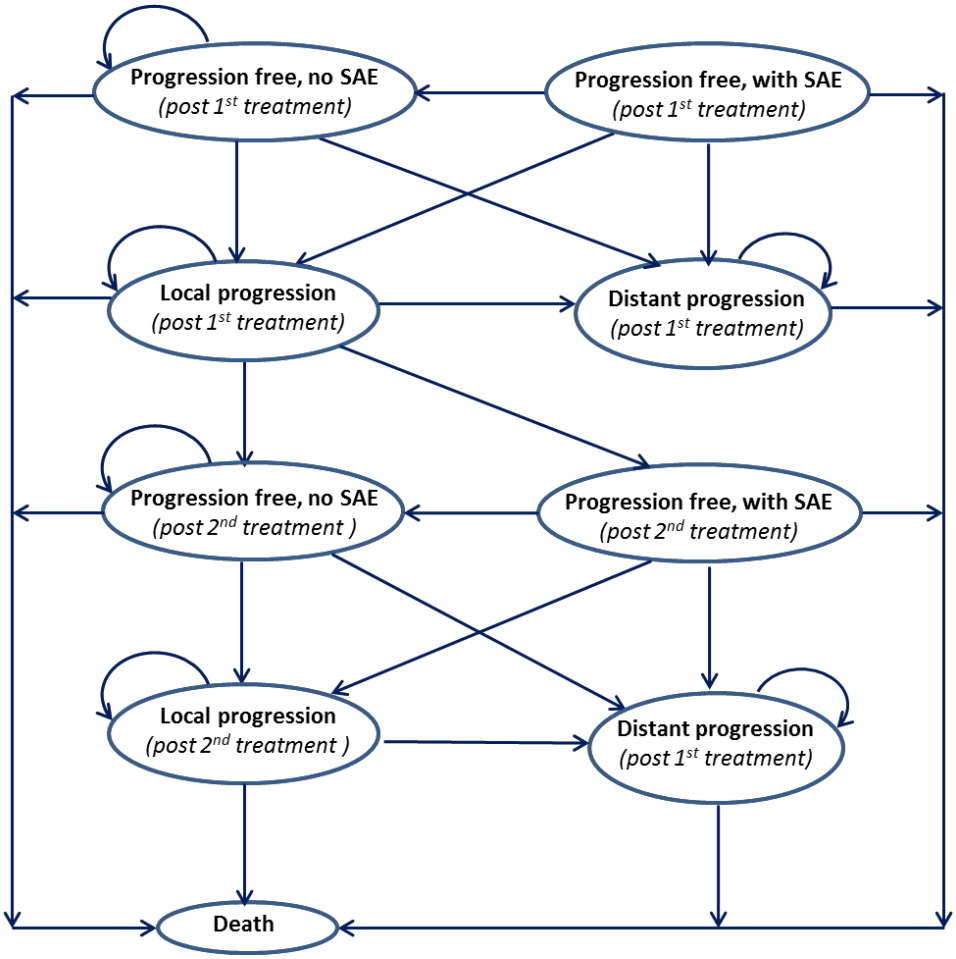


Figure 5: Markov model structure

5.2.3 Cost-effectiveness analysis

Each of the health states in Figure 5 is assigned a cost and outcome that patients accrue while in that state. The costs reflect the treatment that the patient is currently receiving (e.g. surgery, RFA or SABR) and the cost of any other resource use that may be required (e.g. treatment cost for SAEs). The effectiveness is expressed in terms of quality-adjusted life years (QALYs), which is a product of quality of life in a specific health state and duration. For each treatment, the model estimates overall

costs and QALYs as the sum of values accrued in each of the health states over the duration of the simulation (5 years). Following guidance from the National Institute for Health and Care Excellence (NICE) (The National Institute for Health and Care Excellence 2017), costs and benefits were discounted at an annual rate of 3.5%.

5.2.4 Input data

The clinical data used in the model were mainly obtained from published literature and the SABR CtE scheme. An initial search and scoping review of the literature was undertaken to assess the quality and availability of evidence on costs, survival and quality of life of patients receiving either surgery or RFA (where appropriate) for HCC. The following databases were searched: Ovid Medline, Medline ahead of print and in-process, and Embase. The search terms are included in Appendix B. In addition, citations of key references were checked. After de-duplication, the initial database search retrieved 3926 studies for HCC. After initial screening and exclusion of non-relevant studies there were 620 relevant studies for HCC. These studies were supplemented by checking references and citations of relevant studies. The search was updated on 22nd April 2019.

The section below describes the key input data used in the model, including clinical data (section 5.2.4.1), cost and resource use data (section 5.2.4.2), and health-related quality of life (HRQoL) data (section 5.2.4.3). A summary of all parameters used in the model, including their fixed values, ranges, distributions and sources, is reported in Appendix E.

5.2.4.1 Clinical data

This section describes the key clinical data used in the model, including cancer progression, mortality, probability of re-treatment, and probability of SAEs. In the base case analysis, SABR was assumed to confer no advantage for cancer progression or survival, in order to minimise the potential for differences in patient populations across studies to bias the analysis. This assumption was tested in structural sensitivity analysis, using data obtained from the CtE scheme and the best available literature. It should be noted that all probability data reported below are probability per cycle (per month), unless otherwise specified.

5.2.4.2 Cancer progression data

This section describes cancer progression data for patients after treatment, including initial treatment and retreatment. It was assumed that patients would be retreated a maximum of once if local progression occurred after treatment. In the base case analysis, it was assumed that all three interventions of interest (surgery, RFA and SABR) are equally effective in slowing cancer progression;

in other words, the progression rates are the same for all patients, regardless of which intervention they received. The progression data for patients after initial treatment, and after retreatment are presented in Table 20, and briefly described below.

Table 20: Cancer progression rates for treated patients and recurrent patients without retreatment

	Monthly transition rate
No progression to local progression	1.12% [a]
No progression to regional/distant progression	0.16% [a]
Local progression to regional/distant progression	0.90% [a]
a: Calculated from Tabrizian et al. (Tabrizian et al. 2015)	

Cancer progression data – Data obtained from published literature

In order to populate the model, the following transitional probabilities between patients with different progression status are required: from no progression to local progression, from no progression to regional/distant progression, and from local progression to regional/distant progression. A few systematic reviews about the outcomes for patients with HCC have been published (Gluer et al. 2012, Lim et al. 2012, Navadgi et al. 2016, Stevens et al. 2017, Koh et al. 2018, Xu et al. 2018); however, none of them reported the transitional probabilities of interest for the target population. Therefore, progression rates were obtained from a recent study which explored recurrence patterns for 661 patients with HCC undergoing resection (Tabrizian et al. 2015). This study reported that of the 356 patients who had recurrence, 234 of them had intrahepatic recurrence only, 44 had extrahepatic only, and 78 had both intrahepatic and extrahepatic recurrence. Based on the assumption that patients who had both intrahepatic and extrahepatic recurrence developed intrahepatic recurrence first, the cancer progression rates were calculated and are presented in Table 20. It was assumed that the progression rate is the same for patients who are receiving initial and repeated treatment.

In sensitivity analysis, it was assumed that patients who received different interventions have different progression rates. The relative risk (RR) of reoccurrence after RFA versus surgery was obtained from a recently published meta-analysis which compared the effects of RFA and hepatic resection for patients classified as Barcelona Clinic Liver Cancer (BCLC) very early or early stage (Xu

et al. 2018). These patients differed from patients in the CtE scheme for which the eligibility criteria were BCLC stage B or C. The meta-analysis shows that compared to patients treated by surgery, patients treated by RFA had higher overall recurrence (RR, 1.36; 95% CI 1.13 to 1.62) and higher intrahepatic recurrence (RR, 1.42; 95% CI 1.11 to 1.81). The short-term progression rate for patients who received SABR was obtained from the CtE scheme; the long-term progression rate for patients receiving SABR was assumed to be the same as RFA due to the lack of long-term data.

Cancer progression data – data obtained from the CtE scheme

Rates of cancer progression after SABR were estimated from the CtE data. We excluded three patients with no quality of life response data. Data for the remaining 88 patients with HCC was used to estimate parameters on survival and quality of life. Of this cohort, 21 developed local recurrence, and 7 developed regional/distant recurrence. The exponential distribution provided the closest fit to the data for both local and regional/distant progression: from no progression to local recurrence (monthly transition rate=3.00%), and from no progression to regional/distant recurrence (monthly transition rate=1.01%). Due to the small sample size and short observation period, the data obtained from the CtE scheme was not used in the base case analysis and was only tested in the structural sensitivity analysis (Section 5.3).

5.2.4.3 Mortality data

This section describes mortality data for patients after treatment (including initial treatment and retreatment), and recurrent patients without retreatment. The mortality data for both patient groups are presented in Table 21, and briefly described below.

Table 21: Monthly mortality rate for patients with different progression status

	Monthly mortality rate
Patients with no progression	0.26% [a]
Patients with local progression	3.21% [b]
Patients with regional/distant progression	12.65% [c]
a: Calculated based on mortality data for patients with local progression and relative risk of death for patients with and without recurrence as reported by Lee et al. (Lee et al. 2006) b: Calibrated from the median survival time for patients with BCLC stage A (early stage) to B (intermediate stage) reported by Grieco et al. (Grieco et al. 2005) c: Calibrated from the median survival time for patients with BCLC stage C (advanced stage) reported by Grieco et al. (Grieco et al. 2005)	

Mortality data – Data obtained from published literature

In the base case scenario, it was assumed that a patient's mortality only depends on which progression status they are at (no progression, local progression, or regional/distant progression), and does not directly depend on which intervention they received. A few studies have reported survival outcomes for patients with a specific BCLC stage (e.g. Stage A, B or C) (Kao et al. 2015, Sinn et al. 2015, Jun et al. 2017, Kamiyama et al. 2017), however few of them reported survival outcomes for all BCLC stages. Only one study reported survival outcome for patients with BCLC stage A to C (Grieco et al. 2005). The survival outcome reported by this study was used to calibrate mortality data for patients with local or regional/distant progression, based on the assumption that BCLC stage 0-B means the patient has local recurrence, BCLC stage C-D means the patient has regional/distant progression. The mortality data for patients with no progression was calculated based on the mortality rate for patients with local recurrence, and the relative risk of death for patients with and without recurrence (Lee et al. 2006).

In sensitivity analysis, it was assumed that patients who received different interventions have different mortality rates. In order to facilitate comparability with mortality data estimated from the CtE SABR cohort a single mortality rate was applied regardless of progression status, but varying by treatment modality. The monthly mortality rate for patients who received surgery and RFA were calculated based on a recent published meta-analysis (0.37% for surgery and 0.85% for RFA). For patients who received SABR, their short-term mortality data was obtained from the CtE scheme, while their long-term mortality data was assumed the same as RFA due to lack of data.

Mortality data – data obtained from the CtE scheme

Of the 88 patients with HCC included in the economic analysis, 8 died during follow-up and prior to evidence of progression of the disease. The exponential distribution provided the closest fit to the observed mortality data (monthly mortality rate=1.15%). Due to small sample size and short observation period, the mortality data obtained from the CtE scheme was not used in base case analysis and was only tested in structural sensitivity analysis (Section 5.3).

5.2.4.4 Probability of retreatment

This section describes the probabilities of receiving retreatment with the same treatment as initially given for patients who develop local progression after initial treatment (Table 22). The probability of further treatment with surgery was reported to be 25.09% with a range of 10.00% to 50.00% tested in sensitivity analysis (Itamoto et al. 2007). The probability of retreatment with RFA was reported to be 69.46% (Rossi et al. 2011), with a range of 50.00% to 75.00% tested in sensitivity analysis. The probability of retreatment of SABR was assumed the same as RFA.

Table 22: Probability of retreatment according to first treatment

	Probability of retreatment	Source
For patients received surgery	25.09%	Itamoto et al. (2007)
For patients received RFA	69.46%	Rossi et al. (2011)
After patients received SABR	69.46%	Assumed same as RFA

5.2.4.5 Severe adverse events (SAEs)

The probability of developing SAEs for patients who received different treatment is reported in Table 23. The probability of developing SAEs for patients who received RFA was obtained from a recent meta-analysis conducted by Pollom et al. (Pollom et al. 2017): 1.00% was used as the baseline value

while a range 0 to 0.3438 was tested in one-way sensitivity analysis. Several meta-analyses have found that RFA is associated with a lower probability of SAEs compared to surgery (Qi et al. 2014, Wang et al. 2014, Chen et al. 2015), the RR reported by Wang et al. was selected for the model as this is the largest meta-analysis based on 11,873 patients (Wang et al. 2014). The probability of developing SAEs for patients who received SABR was obtained from the CtE scheme (4/88, 4.55%). The probability was calculated after excluding SAEs attributable to ALT/Bilirubin levels.

Table 23: Relative risk and probability of developing SAEs for patients according to first treatment

	Probability of SAEs	Source
Probability of developing SAEs for patients who received RFA	5.56%	Calculated based on probability of developing SAEs for RFA and RR reported by Wang et al. (Wang et al. 2014)
Probability of developing SAEs for patients who received RFA	1.00%	Pollom et al. (Pollom et al. 2017)
Probability of developing SAEs for patients who received SABR	4.55%	CtE scheme

5.2.5 Cost and resource data

The model takes a health perspective. The perspective recommended by NICE includes health and Personal Social Services (PSS), but the latter costs were unavailable (October 2014). The financial year is 2016. The cost components considered in the model include: initial treatment (SABR, RFA or surgery), treatment for SAEs, outpatient follow-up, retreatment, and palliative chemotherapy for patients with regional/distant progression. The unit cost and resource use of each cost component is reported in Table 24. The total costs for patients who received different interventions were estimated by multiplying the unit costs with resources quantities. Unit costs were obtained from the NHS reference costs 2015-16 (Department of Health 2016) or the Unit Costs of Health and Social Care 2016 (Curtis 2016). Where appropriate, costs were uplifted to current values using the Hospital & Community Health Services Index (Curtis 2016). The resource use for patients receiving RFA or surgery were mainly obtained from published literature. The package price for SABR is £3,432 for 3 fractions and £4,856 for 5 fractions (NHS England 2015) The data of CtE scheme showed that of 88 patients with HCC, 3 patients had three fractions, 84 patients had five fractions (the datum was

missing for one patient). Therefore, the weighted cost of one course of SABR was calculated as £4,807 per patient.

Table 24: Unit cost and resource use data

Item	Unit cost	Resource use	Total cost
Surgery			
Surgical procedure	£6,272.87 [a]	1	£6,272.87
Additional bed days	£297 [b]	2.24 [c]	£665.28
		Total	£6,938.15
RFA			
RFA procedure	£3,714.06 [d]	1	£3,714.06
Additional bed-days	£297.00 [b]	4.63 d [e]	£1,375.11
		Total	£5,089.17
SABR			
SABR	£4,807.00 [f]	1	£4,807.00
		Total	£4,807.00
Outpatient follow-up			
Outpatient attendance	£199 [g]	Every 3 months prior to disease progression	£199
Full blood count	£0.55 [h]	As above	£0.55
Liver function tests	£0.42 [h]	As above	£0.42
Carcinoembryonic antigen	£1.91 [h]	As above	£1.91
Abdominal CT	£94.96 [i]	As above	£94.96
		Total	£296.84
SAEs			
Treatment for SAEs	£2,849 [j]	N/A	£2,849
Retreatment			
Retreatment	Assume to be the same as initial treatment		
Palliative care			
Palliative care for patients with regional/distant progression	£166.34 per month [k]	N/A	£166.34 per month

a. NHS Reference Costs 2015–16 (Department of Health 2016), HRG code GA05D: 'Very Major Open, Hepatobiliary or Pancreatic Procedures, with CC Score 0-2', including 4.16 elective inpatient bed days, 7 non-elective long stay bed days and outpatient procedure. The cost for HRG code GA05C 'Very Major Open, Hepatobiliary or Pancreatic Procedures, with CC Score 3+' (£9,337.35) was tested in sensitivity analysis.

b. Additional days are costed at Inpatient excess bed-day cost of £297 per day, based on NHS Reference Costs 2015–16 (Department of Health 2016).

c. Average length of stay for surgically resected patients in the study reported by Kim et al. (Kim et al. 2011) was 13.4 days. Therefore, the number of additional hospital bed days was calculated as: 13.4-4.16 (number of elective inpatient bed days) -7 (number of non-elective long stay bed days) =2.24.

d. Uplifted from Loveman et al. 2014 (Loveman et al. 2014).

e. Meta-analytic evidence shows that patients receiving RFA had 8.77 fewer hospital days compared with patients receiving surgery (Wang et al. 2014). Therefore, the number of hospital days for patients received RFA was calculated as 13.4-8.77=4.63 days.

f. The package price for SABR is £3,432 for 3 fractions and £4,856 for 5 fractions (NHS England 2015). The data of CtE programme showed that of 88 patients with HCC, 3 patients had three fractions and 84 patients had five fractions (the data was missing for one patient). Therefore, the weighted cost was calculated as £4,807.00 per patient.

g. NHS Reference Costs 2015-16 (Department of Health 2016), currency code WF01B, service code 105: 'Hepatobiliary & Pancreatic Surgery Consultant-led: follow-up attendance non-admitted face to face'.

h. Uplifted from Loveman et al. (Loveman et al. 2014).

i. NHS Reference Costs 2015–16 (Department of Health 2016), HRG code RD20A: 'Computerised Tomography Scan of one area, without contrast, 19 years and over'.

j. The cost of treating acute upper gastrointestinal bleeding was used as a proxy for those patients develop SAEs (Campbell et al. 2015).

k. Uplifted from Thompson Coon et al. (Thompson Coon et al. 2008).

5.2.6 Health-related quality of life (HRQoL)

The model estimates quality adjusted life-years (QALYs) as a product of quality of life in each health state and duration in that state. Quality of life or health state utilities are expressed on a scale including 0 (death) and bounded at 1 (perfect health). This model requires health state utilities for

four health states: progression free without SAEs, progression free with SAEs, local progression, and regional/distant progression. Health state utilities applied in the model are reported in Table 25. The utility for patients in the health state 'progression free without SAEs', was obtained from the CtE scheme. The utility for the other three health states were mainly derived from published literature.

Table 25: Health states and their utility weight used in the model

Health state in model	Utility weight	Range	Source
Progression free without SAEs	0.74	0.74-0.92	The CtE scheme, Lim et al. (Lim et al. 2015)
Progression free with SAEs	0.50	0.39-0.60	Oster et al. (Oster et al. 1994), White el al. (White et al. 2012)
Local progression	0.63	0.26-0.86	Cucchetti et al. (Cucchetti et al. 2013)
Regional/distant progression	0.40	0.32-0.48	Hanmer et al. (Hanmer et al. 2006)

5.3 Sensitivity analysis

Three types of sensitivity analyses were conducted: structural sensitivity analysis, one-way sensitivity analysis of parameter uncertainty and probabilistic sensitivity analysis (PSA). Structural sensitivity analysis was undertaken to explore the impact of assumptions on cancer progression rates and mortality. The base case analysis applies cancer progression rates and mortality rates according to progression status but regardless of treatment modality. Three structural sensitivity analyses were undertaken to test the impact of using different cancer progression rates and different mortality rates for patients receiving alternative treatments:

(1) Assuming different cancer progression rates for patients receiving different interventions. The cancer progression rates for patients who received surgery were calibrated from published literature (Table 20). The cancer progression rates for patients who received RFA were calculated based on the RR (RFA vs surgery) reported by a recently published meta-analysis of five trials including 742 patients: 1.42 for local progression and 1.36 for regional/distant progression (Xu et al. 2018). The short-term cancer progression rate for patients who receiving SABR was obtained from the CtE scheme; the long-term cancer

progression rate for patients receiving SABR was assumed the same as RFA due to lack of long-term data.

(2) Assuming different mortality rates for patients receiving different interventions. The monthly mortality rate for patients who received surgery and RFA were calculated based on a recent published meta-analysis (0.37% for surgery and 0.85% for RFA) (Xu et al. 2018). The mortality rates up to 2 years for patients receiving SABR was obtained from the CtE scheme (exponential distribution, monthly mortality rate=1.15%). The mortality rate post two years for patients receiving SABR was assumed to be the same as patients who received RFA. Mortality rates were applied according to treatment modality and regardless of progression status.

(3) Assuming the same mortality rate for RFA and SABR, and a different mortality rate for patients receiving surgery. The monthly mortality rate for patients who received surgery and RFA were calculated based on a recent published meta-analysis (0.37% for surgery and 0.85 for RFA) (Xu et al. 2018). The mortality rate for patients receiving SABR was assumed to be the same as patients receiving RFA.

One-way sensitivity analysis was undertaken to explore the sensitivity of the results to variation in each of the parameters in the analysis considered singly. PSA was undertaken to capture the impact of joint uncertainty of multiple parameters simultaneously. PSA assigns to each input parameter a specified distribution and, by drawing randomly from those distributions, generates a large number of mean cost and effectiveness estimates that can be used to form an empirical joint distribution of the differences in cost and effectiveness between interventions. In this study, the main results of PSA were re-calculated 5000 times. The ranges and distributions tested in sensitivity analysis are reported in Appendix E.

5.4 Results

5.4.1 Base case and structural sensitivity results

In the base case analysis, it was assumed that:

(1) The cancer progression rates are independent of the intervention patients received.
(2) Mortality depends only on patients' progression status (no progression, local progression, or regional/distant progression), and does not directly depend on which intervention they received.

Therefore, the only difference between different interventions are:

(1) Probability of developing SAEs;
(2) Probability of receiving re-treatment for those patients who developed local recurrence after the initial treatment.

The results of base case analysis show that under the NICE £20,000 willingness-to-pay threshold, SABR is considered the most cost-effective intervention. This is because compared with surgery, SABR is associated with lower intervention cost (£4,807 vs £6,273), lower probability of SAEs (4.55% vs 5.56%), and higher probability of receiving re-treatment after local recurrence (69.46% vs 25.09%). Compared with RFA, SABR results in lower cost and lower QALYs. This is because SABR is associated with lower treatment cost (£4,807 vs £5,089), higher probability of SAEs (4.55% vs 1.00%) and the same probability of receiving re-treatment after local recurrence. However, the incremental cost-effectiveness ratio (ICER) of RFA (£516,974) compared to SABR exceeds the NICE £20,000 willingness-to-pay threshold; SABR is considered to be the most cost-effective intervention.
In structural sensitivity analyses:

- when different cancer progression rates were applied to different interventions, RFA became the most cost-effective intervention (SA1 in Table 26);
- when different mortality rates were applied to different interventions (surgery was associated with the lowest mortality rate), surgery became the most cost-effective intervention (SA2 and SA3 in Table 26).

Table 26: Base case and structural sensitivity analyses

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Base case results							
SABR	10,979	2.8334	–	–	–	1	1
RFA	11,261	2.8340	281	0.0005	516,974	2	2
Surgery	11,571	2.7008	–	–	Dominated	3	3
SA 1: Assuming different cancer progression rates for patients receiving different interventions [1] (base case analysis assumes same progression rate for all three interventions)							
SABR	11,001	2.1486	–	–	–	3	3
RFA	11,500	2.7012	500	0.5526	904	1	1
Surgery	11,571	2.7008	–	–	Dominated	2	2
SA 2: Assuming different mortality rates for patients receiving different interventions [2] (base case analysis assumes same mortality rate for all three interventions)							
SABR	10,529	2.4422	–	–	–	3	3
RFA	11,120	2.5760	591	0.1338	4,421	2	2
Surgery	12,179	2.7417	1,059	0.1658	6,387	1	1
SA 3: Assuming the same mortality rate for RFA and SABR, and a different mortality rate for patients receiving surgery (base case analysis assumes same mortality rate for all three interventions)							
SABR	10,844	2.5754	–	–	–	2	2

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
RFA	11,120	2.5760	–	–	Extendedly dominated	3	3
Surgery	12,179	2.7417	1,335	0.1663	8,026	1	1

Abbreviations:

ICER: Incremental cost-effectiveness ratio; NMB: net monetary benefit; QALY: quality-adjusted life of years; SA: sensitivity analysis; WTP: willingness-to-pay.

Notes:

1. Assuming different cancer progression rates for patients receiving different interventions. The cancer progression rates for patients who received surgery were calibrated from published literature (Table 1). The cancer progression rates for patients who received RFA were calculated based on the RR (RFA vs surgery) reported by a recently published meta-analysis of five trials including 742 patients: 1.42 for local progression and 1.36 for regional/distant progression (Xu et al. 2018). The short-term cancer progression rate for patients who receiving SABR was obtained from the CtE scheme; the long-term cancer progression rate for patients receiving SABR was assumed the same as RFA due to a lack of long-term data.
2. Assuming different mortality rates for patients receiving different interventions. The monthly mortality rate for patients who received surgery and RFA were calculated based on a recent published meta-analysis (0.37% for surgery and 0.85% for RFA) (Xu et al. 2018). The mortality rates up to 2 years for patients receiving SABR was obtained from the CtE scheme (exponential distribution, monthly mortality rate=1.15%). The mortality rate post two years for patients receiving SABR was assumed the same as patients who received RFA.
3. Assuming the same mortality rate for RFA and SABR, and a different mortality rate for patients receiving surgery. The monthly mortality rate for patients who received surgery and RFA were calculated based on a recent published meta-analysis (0.37% for surgery and 0.85 for RFA) (Xu et al. 2018). The mortality rate for patients receiving SABR was assumed the same as patients receiving RFA.

5.4.2 One-way sensitivity analysis results

Forty scenarios were tested using one-way sensitivity analysis (Appendix E). The results showed that under the NICE £20,000 per QALY willingness-to-pay threshold, the base case conclusion (SABR being the most cost-effective intervention) was unchanged in all scenarios tested except the cost of SABR and RFA. A further goal-seeking analysis for these two cost parameters showed that in the following scenarios, RFA became the most cost-effective intervention, as the ICER of SABR exceeded NICE £20,000 per QALY willingness-to-pay threshold:

1) when the cost of SABR is over £5,019 (base case value: £4,807);
2) when the cost of RFA (including inpatient stay) is below £4,877 (base case value: £4,961).

5.4.3 Probabilistic sensitivity analysis

The PSA results are shown in Figure 6. Assuming a willingness-to-pay threshold of £20,000 per QALY, the probability that SABR is the most cost-effective intervention is 50%. Assuming a willingness-to-pay threshold of £30,000 per QALY, the probability that SABR is the most cost-effective treatment is 51%.

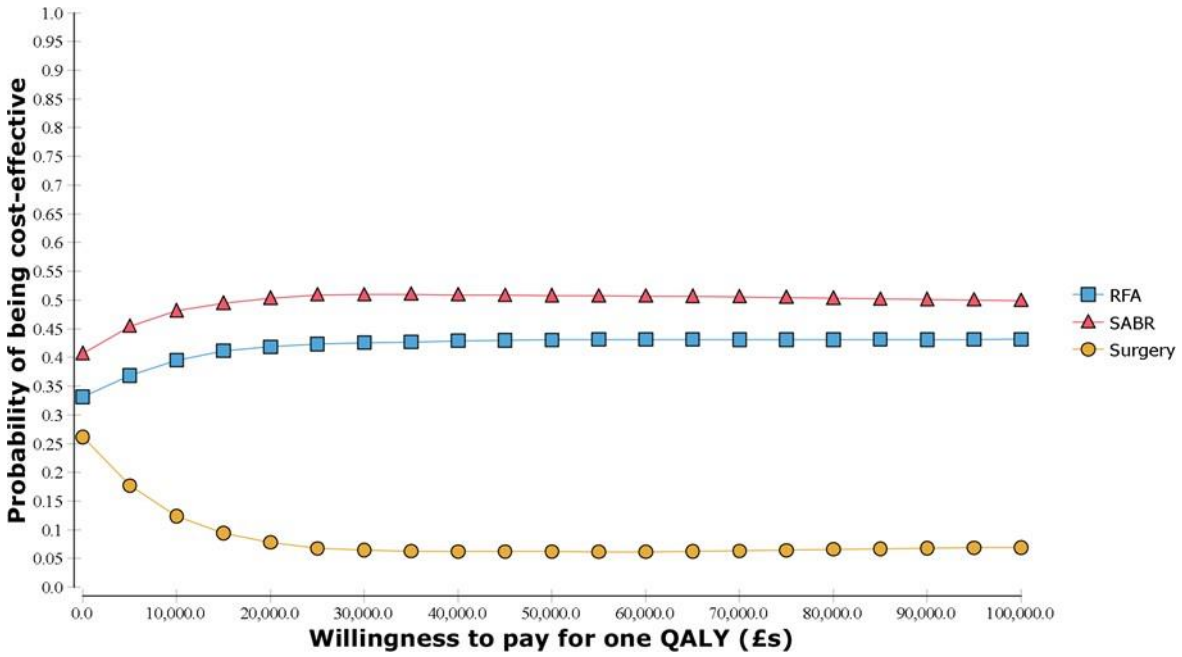


Figure 6: Cost-effectiveness acceptability curve

5.5 Discussion

This section compares our findings with published economic studies (Section 5.6) and discusses the strengths and limitations of our analysis (Section 5.7). The conclusion is presented in Section 5.8.

5.6 Comparison with published studies

The literature search identified a number of economic analyses which compared alternative treatments for HCC. However, of those identified studies:

- The majority of them only covered one of the three interventions of interest (surgery, RFA and SABR) and therefore the conclusions of which cannot be compared with our study;
- Four studies covered two interventions of interest: two studies compared RFA with surgery (Cucchetti et al. 2013, Thein et al. 2017), while another two studies compared RFA with SABR (Pollom et al. 2017, Parikh et al. 2018);
- None of them assessed all three interventions of interest.

Two of the published studies utilised a Markov model (Cucchetti et al. 2013, Pollom et al. 2017). Cucchetti compared the cost-effectiveness of RFA with surgery for patients meeting the Milan criteria[14] in Italy (Cucchetti et al. 2013). The study conducted subgroup analysis by number of lesions in patients presenting with cancer and size of tumour. The findings of this study show that:

- For those patient subgroups in which surgery confers no advantage for cancer progression or survival compared to RFA (e.g. patients with very early HCC), surgery results in higher costs and similar QALYs. Therefore, RFA was considered the most cost-effective intervention.
- For those patient subgroups in which surgery is associated with better overall survival and disease-free survival compared to RFA (e.g. patients with a single HCC lesion of 3–5 cm), surgery results in higher costs and higher QALYs, and the ICER of surgery of €4200 per QALY indicates surgery is cost-effective.

[14] The Milan criteria for liver transplantation require the presence of a single tumour of <5cm in diameter or no more than three tumours <3cm each in diameter.

In short, the above results indicate that surgery is only more cost-effective than RFA if it is associated with a better cancer progression rate and mortality rate. This is consistent with our findings:

- In the base case analysis, when it was assumed that the cancer progression rate and mortality rate is the same for all patients regardless of which interventions they received, RFA dominates surgery.
- In the structural sensitivity analysis, when it was assumed that surgery was associated with better survival outcome, surgery results in higher QALYs and higher cost compared with RFA (SA2 and SA3 of Table 17).

Pollom et al. (2017) compared four possible combinations of RFA and SABR as either first line treatment or treatment for progression (SABR-SABR; SABR-RFA; RFA-RFA; RFA-SABR) (Pollom et al. 2017). The results of this study showed that of the two options assessed in our model (SABR-SABR and RFA-RFA), SABR-SABR results in higher costs ($3,986) and higher QALYs (0.019), which is different from our findings (SABR resulted in lower costs and lower QALYs). This might due to two reasons:

(1) Use of different adverse event data. In our model, the monthly probability of developing SAEs for patients receiving SABR was obtained from the CtE scheme (4.55%) and is higher than the probability used in the model built by Pollom et al. (1.00%). This might have arisen from different definitions of SAEs. Pollom et al. defined SAEs as grade 3 or higher toxicity events that would require hospitalization and/or intervention, such as gastrointestinal bleeding and ulceration, ascites, and radiation-induced liver disease. Pollom et al. did not specify which grading system was used. In our analysis, SAEs were defined as grade 3-4 toxicity events at any site except ALT/bilirubin levels (based on the CTCAE system). This could include adverse events, such as fatigue not relieved by rest, limiting self-care etc. Therefore, it seems likely that the definition of SAEs used in Pollom et al. is broader than the definition that was used in our analysis.

(2) Use of different unit cost. In the model built by Pollom et al., the cost of providing SABR was estimated to be $12,826 per treatment course, which is 2.2 times of the cost of providing RFA ($5,759). In our analysis, the cost of one course of SABR was estimated to be £4,807, which is less than the cost of providing RFA (£5,089, including intervention cost and 2.24 days of hospitalisation). In one-way sensitivity analysis (details in Appendix E, when the cost of SABR was increased to over £5,019, SABR results in higher cost compared to RFA.

The remaining two studies were analyses of administrative data which compared costs and outcomes of RFA with surgery (Thein et al. 2017) or SABR (Parikh et al. 2018). After propensity score matching, Parikh (2018) reported no difference in costs or survival between patients in the SEER-Medicare linked database receiving RFA and those receiving SABR (Parikh et al. 2018). Mean costs in the matched sample were $38,810 and $46,253 (2016USD) for SABR and RFA, respectively. These findings are similar to our own base case in which costs were modestly higher with RFA compared to SABR.

Thein (2017) compared patients in the Ontario cancer registry database receiving surgery, RFA or liver transplantation (Thein et al. 2017). Regression analysis was used to control for differences in casemix after estimating costs and QALYs for patients according to treatment. The authors report that survival was weighted according to quality of life as a function of stage and liver function to estimate QALYs, but no detailed methodology is provided. From the data reported, incremental costs and QALYs of $68,000 and 0.145 can be calculated, generating an ICER of $470,000 (2013USD). These findings indicate a health gain from surgery compared with RFA which is higher than the gain we found in sensitivity analysis in which we assumed different mortality rates for RFA and surgery. The analysis also suggests a much larger increase in costs for surgery relative to RFA which generates the high ICER. Differences in costs between Thein (2017) and our analysis may reflect case-mix or differences in clinical practice between Canada and the UK.

5.7 Strengths and limitations of the analysis

5.7.1 Strengths

There are three strengths of our study:

(1) To our knowledge, this is the first economic analysis which compares all three interventions for people with HCC: surgery, RFA and SABR.

(2) The clinical data were carefully selected from the best evidence sources identified from the literature review, while the clinical data for SABR was obtained from the CtE scheme, with the published SABR data tested in sensitivity analysis. The unit cost and resource use data were obtained from published cost calculations based on reliable UK databases, such as NHS Reference Costs (Department of Health 2016) and PSSRU (Curtis 2016). The utility data were obtained from published studies which reported different utility for patients with different cancer progression status and with/out adverse events, with a wide range of possible values tested in sensitivity analysis.

(3) Extensive sensitivity analyses have been conducted to test the robustness of the base case conclusion under different assumptions and different sets of input data, including structural sensitivity analysis, one-way sensitivity analysis, and PSA.

5.7.2 Limitations

There are a number of limitations of the economic analyses presented here, the majority of which derive from limitations in the evidence base:

(1) The economic analysis compared SABR with surgery and RFA. These were considered potential alternatives to SABR if the use of SABR is expanded, hence they were selected by the data working group at the commencement of the project. The patient eligibility criteria for the CtE scheme precluded patients eligible for surgery as it was considered that there was insufficient evidence to show equivalence of outcomes with SABR and surgery. Consequently, patients in the CtE scheme were different to the population considered in the economic analysis. It seems likely that survival will be lower and cancer progression rates higher after SABR treatment for patients ineligible for surgery compared to patients eligible for surgery. Partly for this reason we chose to ignore evidence of differences in survival and cancer progression across different treatments in the base case analysis. We did include it in sensitivity analysis and hence we might expect that analysis to be biased against SABR.

(2) Lack of clinical studies which directly compare SABR with RFA and surgery. Our analysis was based on data collected prospectively for a single treatment of SABR and compared with the best available data from the literature on the comparator treatments. It is likely that disease severity and other patient characteristics which would affect prognosis differed between the CtE population with HCC and the patient populations in the literature. This is evidenced by the higher mortality rate observed in the CtE cohort compared to the literature (applied in sensitivity analysis). Such differences will have impacted on estimates of mortality and progression rates by treatment modality.

(3) The CtE cohort was relatively small in size (91 patients of whom 88 supplied data for quality of life and survival parameters). This introduces uncertainty in the estimation of parameters such as mortality. Patient follow-up was also limited in time in the CtE cohort which further limited the possibility of using CtE data to estimate parameters for patients who had local or distant progression.

(4) Lack of clinical evidence about the mortality rate for patients with different cancer progression status. As a result, the mortality rates used in the base case analysis were calibrated based on published data.

(5) Lack of data on the cost of SABR. We did not collect data on the cost of provision of SABR and instead applied the tariff agreed by NHS England to remunerate hospitals according to the number of fractions delivered. This tariff may not reflect the true cost of SABR.

However, in this study, the limitation related to parameter uncertainty has been partially mitigated by extensive sensitivity analyses.

5.8 Conclusion

Economic analysis of SABR was undertaken in comparison with surgery and RFA as specified by the data working group at the commencement of the project. The data from the CtE scheme which informed the analysis of SABR was taken from a population in which surgery was not indicated. Survival outcomes in this group of patients are likely to be poorer than in patients for whom surgery is indicated limiting comparison of survival data from the CtE scheme with data on outcomes from surgery in the literature. In the base case we assumed no difference in survival or cancer progression for patients receiving surgery or SABR. This analysis found that for adult patients resectable HCC, SABR is the most cost-effective intervention. In sensitivity analysis in which survival and progression after surgery was taken from literature estimates, surgery was the most cost-effective option. There was considerable uncertainty surrounding these findings and the results were sensitive to assumptions on the cost of SABR and RFA and the impact of treatment modality on mortality. The results are limited by the lack of a control group in the CtE data; it is likely that comparisons with data from the literature on survival and progression rates are confounded by differences in patient characteristics. A randomised trial might provide the robust data required to conclusively assess the cost-effectiveness of treatments for HCC.

6 Evidence from the literature

6.1 Methods

6.1.1 Scope

The aim of the systematic review was to identify published evidence for the efficacy, toxicity, and cost-effectiveness of SABR in patients with HCC.

6.1.2 Search methods

A systematic search was undertaken based on the PICO document, which was formulated in collaboration with NHS England representatives, clinicians involved in the SABR CtE project, and KiTEC. The databases searched included Medline, Medline In-Process, Embase, Cochrane Database of Systematic Reviews (CDSR) and Cochrane Controlled Register of Trials (CENTRAL). The search excluded conference abstracts and was restricted to articles from 2009 to the present. The full details of the search strategy are included in Appendix B. Following de-duplication in EndNote X7, 861 records were assessed for relevance according to the criteria outlined in Table 27.

Table 27: PICO table

Population and Indication	Patients of all ages with localised hepatocellular carcinoma (HCC) with or without low burden metastatic disease who are/ have: • unsuitable for surgery (resection or transplant) • unsuitable for or refractory to radiofrequency ablation • unsuitable for or refractory to transhepatic arterial chemo-embolisation (TACE) • have five or fewer discrete intrahepatic parenchymal foci of HCC • HCC tumour 6 cm or less • Low burden of disease defined as: extrahepatic metastases or malignant lymph nodes that enhance with typical features of HCC <3.0 cm in sum of maximal diameters (e.g. 2 lung lesions <3cm in total diameter). • Child-Pugh Class A only* (Child Pugh scoring system classification).
Intervention	Stereotactic ablative body radiotherapy (10 fractions or fewer)
Comparators	• No treatment or best supportive care • Targeted/ biological agents

	○ Sorafenib ○ Lenvatinib • Thermal ablation (radiofrequency ablation or microwave ablation) • Standard fractionated radiotherapy
Outcomes	• Median overall survival • 1-year overall survival • 2-year overall survival • Local control (i.e. tumour regression/ resolution OR no tumour progression within the lesion treated/ treatment field) • Progression free survival • Quality of life • Adverse events
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2009-2019
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters and editorials
Study design	Case reports, resource utilisation studies Studies with <30 patients
* Studies with a small % of patients with Child Pugh score B were considered eligible for inclusion.	

6.1.3 Data extraction and management

Two reviewers independently screened titles and abstracts of the citations identified by the search strategies. Full-text copies of all potentially relevant publications were obtained and independently assessed by each reviewer to determine whether they met the inclusion/exclusion criteria. Any disagreements were resolved by consensus. The data extracted included information on study design, population characteristics, comparators used, and outcome measures. Microsoft Excel software was used for data collection and management.

6.2 Results

6.2.1 Studies identification and selection

The 861 abstracts identified after deduplication, were first assessed by title and abstract alone. Following the first sift, 127 records were identified as relevant, and the full texts of these articles were retrieved and reviewed. Following a second sift of the full-text articles, 6 fit the inclusion criteria and are included in this review. The sifting process was undertaken by two members of the KiTEC team and the results cross-matched for quality control. The PRISMA flowchart for study identification and selection is listed in Appendix A: Prisma flowchart. Table 28 and Table 29 list the methodological characteristics and quality appraisal of all included studies.
Table 30 presents the methodological characteristics and quality appraisal of the CtE cohort for comparison.

6.2.2 Evidence summary tables

Table 28: Non-comparative studies

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Rim et al (2019) Systematic review and meta-analysis 32 studies (33 cohorts) including 1950 patients with HCC Median tumour size of 3.3cm (ranging from 1.6-8.6cm) Median Equivalent Dose in Gray-2 (EQD2)	A systematic search of PubMed, Medline, Embase and Cochrane was undertaken Inclusion criteria: SABR in <10 fraction at least 10 patients treated with SABR, reporting overall survival or local control No date limits were used (search date was 23-Apr-2018)	Pooled analyses using random effects model Overall survival: 1-yr: 72.6% (95% CI: 65.7–78.6) 2-yr: 57.8% (95% CI: 50.9–64.4) 3-yr: 48.3% (95% CI: 40.3–56.5) Tumour size >5cm significantly associated with 1-yr OS (p<0.001) Under meta-regression tumour size was significantly correlated with 1-, 2-, and 3- year OS ranges	The systematic review methods were well reported and reproducible, although the search strategy used was overly simplistic. The majority (85%) of the included studies were retrospective. The authors report potential publication biases (using Egger's test quantitatively and visual inspections of funnel plots), which could have influenced a number of outcomes. However, the authors presented trimmed results using the Duval and Tweedie method.

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
was 83.3Gy (ranging from 48-114.8Gy) Median CP-A score: 82.3% (ranging from 47.9-100%)		(p < 0.0001, p = 0.0022, and p = 0.0002). Local control: 1-yr: 85.7% (95% CI: 80.1–90.0) 2-yr: 83.6% (95% CI: 77.4–88.3) 3-yr: 83.9% (95% CI: 77.6–88.6) Tumour size >5cm significantly associated with 1-, 2- and 3-yr LC (p<0.001 for all) 1-year LC was also influenced by radiation dose (median EQD2 estimates of 80 Gy10). Adverse events: Grade ≥3 complications GI: 3.9% (95% CI: 2.6-5.6)	Recruitment period suggests that the cohort is more likely to be comparable with current practice. Included studies were mostly retrospective single centre studies with high risk of bias for patient selection and outcomes detection. Complications reported within 3 months after the end of radiotherapy were classified as acute complications, and those reported later than 3 months or described as 'late complication' were classified as late complications.

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
		Grade ≥3 complications hepatic: 4.7% (95% CI: 3.4-6.5) Under meta-regression, CP-A status was a significant factor for hepatic toxicity (p=0.013). Neither tumour size nor dose were significant factors.	
Klein et al (2015) Prospective non-comparative cohort study Single centre, Canada Recruitment period: 2003-2011 205 patients with hepatocellular	Median radiation dose = 37Gy (5.1-60) Radiation dose was unknown in 6 patients of the patients. Maximum follow-up 12 months (median unknown).	QoL: FACT-Hep: Baseline= 137.4 1-month=129.7 3-months=133.4 6-months=133.6 12-months=135.1 QLQ-C30: Baseline=65.8	Prospective, observational study and therefore treatment allocation was not controlled and may be biased due to different clinical factors. The SABR group was heterogeneous including patients with HCC, cholangiocarcinoma, and liver metastases. Some of the patients received low radiation dose (minimum dose 5.1Gy).

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
carcinoma (HCC= 99 patients), liver metastases, or intrahepatic cholangiocarcinoma; tumour size median=133cm. 93% Child-Pugh score A Median age = 67 years, 66% men		1-month=61.7 3-months=62.9 6-months=58.6 12-months=64.5 Higher baseline QoL scores were associated with improved survival.	Multiple imputations were performed on missing data of eligible patients alive at follow-up. Two widely used and validated tools in this population were chosen for concurrent comparison of QoL outcomes: FACT-Hep and the EORTC QLQ-C30. QoL was evaluated at each visit. Maximum follow-up was only 12 months and it is unknown what proportion of patients completed follow-up.
CP; Child-Pugh score, EQD2; Equivalent Dose in Gray-2, Gy; Gray, HR; Hazard ratio PFS; progression free survival, OS; overall survival, LC; local control, PVT; portal vein thrombosis RFA; radiofrequency ablation,			

Table 29: Comparative studies

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Rajyaguru et al (2018) Retrospective comparative cohort study Data from National Cancer Database, USA Recruitment period: 2004-2013 796 patients included in matched analyses (from 3,980 eligible patients) with non-advanced non-	After propensity-score and time-to-treatment matching, 521 received RFA and 275 received SABR (overall 3684 received RFA, 296 received SABR). Following matching, the groups were similar in baseline characteristics. 42% of SABR patients received dose of 40-49Gy; 80% received their dose in 3-5 fractions. Radiation dose was unknown in 14% of the patients. Of those with known	Overall survival: RFA significantly better than SABR (hazard ratio 0.67 [0.55-0.81], p<0.001). 5-yr OS: 29.8% for RFA vs. 19.3% for SABR (p<0.001). Sub-group analysis of the Tumour-Node-Metastases (TNM) classification of malignant tumours (status revealed a similar significant difference in survival between RFA and SABR.	Retrospective, observational study and therefore treatment allocation was not controlled and may be biased due to different clinical factors. The SABR group was heterogeneous in terms of radiation dose and fractionation schedule. As the Child Pugh status was unknown the analysis may also have included patients outside the scope of the review. Although propensity-score was used to match patients' baseline characteristics this

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
metastatic HCC; tumour size ≤5cm. Patients who received surgery or chemotherapy were excluded. 42% of SABR patients received dose of 40-49Gy; 80% received their dose in 3-5fraction.	dose, 26% received lower than standard dosing (< 40 Gy). Median 25.3-month follow-up.		did not include Child-Pugh status a variable associated with OS. 26% of the patients with recorded dose in the SABR cohort were treated with lower than standard radiotherapy dose (either 50-54 Gy in five fractions). A follow-up study that reanalysed the same data only including patients who received standard dose showed no difference in OS between the two cohorts (Shinde et al. 2018)[15]. The long recruitment period means that practice may have changed over the course of the study, which could limit generalisability.

[15] The study was published as a letter to the editor and therefore, not included in this review.

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
			The authors also carried out an inverse probability–weighted analysis, which confirmed the significantly different OS outcomes between the groups.

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Parikh et al (2018) Retrospective comparative cohort study Data from Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database, USA 64 patients included in matched analyses (from 450 eligible patients) with non-metastatic stage I or II	After propensity-score matching, 32 received RFA and 32 received SABR (overall 418 received RFA, 32 received SABR). Following matching, the groups were similar in baseline characteristics. Median follow-up (propensity score matched patients) was 594 days for RFA and 487 days for SABR.	Overall survival: Under propensity score matching, OS showed no significant differences between RFA and SABR (SABR HR 1.28 [95% CI: 0.60-2.72], p=0.53). 90-day hospitalisation: Overall cohort analysis showed no significant differences between the groups.	Retrospective, observational study and therefore treatment allocation was not controlled and may be biased due to different clinical factors. As the Child Pugh status was unknown the analysis may also have included patients outside the scope of the review. The long recruitment period means that practice may have changed over the course of the study, which could limit generalisability. In the overall cohort, 1-yr OS was similar (78.1% SABR, 79.4% RFA), but at 3-years there were significant differences, with SABR on approximately 16% and RFA on 50%* (SABR hazard ratio 1.80 [95% CI:

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
HCC; tumour size not reported Child Pugh status was unknown SABR dose not reported			1.15–2.82], p=0.01). However, the propensity score matched analysis showed no significant differences. It should be noted that although the propensity score matched cohort contained 64 patients compared to 450 patients in the overall cohort, the number treated with SABR was the same in both analyses (n=32). *estimated from Kaplan-Meier graph

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Bettinger et al (2018) Retrospective comparative cohort study Multi-institution, Switzerland and Germany (6 centre Sorafenib, 13 centres SABR) Recruitment period: 2013-2017 1023 patients with primary unresectable HCC, 1-2 intrahepatic lesions, or multifocal HCC (3 or more lesions	Median prescribed SABR dose was 44Gy (range: 21-66) Gy in 3-12 fractions The median BED (BED10) prescribed was 84.4Gy (range: 36-124) After propensity-score matching, 95 received Sorafenib and 95 SABR (overall 901 received Sorafenib, 122 received SABR). Following matching, the groups were similar in baseline characteristics The following variables were included to match the patients: Child-Pugh score, prior surgery, radiofrequency ablation (RFA), transarterial chemoembolization	Median overall survival: 16.0-months SABR vs. 9.6-months Sorafenib (p=0.005). Multivariable analysis showed SABR was a significant prognostic factor for OS (HR 0.53 [95%CI: 0.36-0.77], p=0.001). Higher EQD2 did not significantly influence OS rates. Sub-group extrahepatic lesions, median overall survival: 16.0-months SABR vs. 10.0-months Sorafenib; HR 0.38 [0.17–0.84], p=0.018. Progression free survival:	Retrospective, observational study and therefore treatment allocation was not controlled and may be biased due to different factors such as the intrahepatic tumour burden, liver function, and especially the performance status (PS) of the patient. Recruitment period suggests that the cohort is more likely to be comparable with current practice. The propensity score matched analysis is very clear and the number of matched patients is relatively high. In both groups approximately 1/3 of the patients had CP score B. Also, some patients presented with multifocal disease. Both

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
or diffuse growth pattern) SABR median EQD2 was 84.4Gy (36-124)	(TACE), hepatic tumour burden, portal vein thrombosis (PVT), extrahepatic metastases, and Eastern Cooperative Oncology Group (ECOG) performance status Median follow-up not reported	9.0-months SABR vs. 6.0-months Sorafenib (p=0.004) Toxicity (overall analysis): 1 SABR patient (0.8%) had grade 3 event 73.6% of Sorafenib patients had a grade 1-4 event The most frequent side effects with sorafenib were diarrhoea, hand-foot skin reaction, fatigue, weight loss, and sorafenib-related hypertension. Sorafenib was stopped in 175 patients (19.4%) due to adverse events. Severe side effects associated with SABR were cholangitis,	these characteristics make the population less comparable to the CtE cohort. Some patients in the SABR group received less than the standard radiation dose. 33 patients (27%) of the SABR cohort received additional treatment which could have confounded the OS results. However, the authors excluded those patients and the significant OS advantage for SABR remained. The reporting of the toxicity outcomes is very unclear, and no meaningful comparisons can be drawn. Adverse events were recorded using the CTCAE criteria.

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
		gastric ulcers with bleeding, and necrotic abscess.	

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Wahl et al. 2016 Retrospective comparative cohort study Single centre, USA 224 patients with inoperable, non-metastatic HCC (332 discrete liver tumours) Mean Child-Pugh score: 6.2 SABR, 6.9 RFA SABR median age = 62 years, 85.7% men RFA median age = 60 years, 72.7% men	Patients were identified from a prospective departmental database. RFA was the first choice for tumours smaller than 3 to 4 cm. SABR was first choice for tumours not visualised by ultrasound, abutting a vessel or the luminal GI tract, or after RFA failure. Freedom from local progression (FFLP) and toxicity were retrospectively analysed. SABR median dose: Patients were treated with either three (46%) or five (53%) fractions delivered two to three times per week with median	FFLP -1 year = 97.4% SABR vs. 83.6% RFA -2 year = 83.8% SABR vs. 80.2% RFA Increasing tumour size predicted for FFLP in patients treated with RFA (HR 1.54 per cm; p= 0.006), but not with SABR (HR, 1.21 per cm; P=.617). For tumours ≥2 cm, there was decreased FFLP for RFA compared with SABR (HR, 3.35; P = 0.025). After adjusting for treatment type, tumour size was the only	Non-randomised. Due to the nature of the intervention, blinding was not possible. However, inverse probability of treatment weighting was used to control for differences in baseline characteristics. Although the two treatment populations were well balanced with respect to multiple factors, patients undergoing SABR had, on the average, received more prior treatments, and were less likely to proceed to transplantation. This may have biased the OS results. The two groups were well matched in terms of tumour size (median 1.8 vs. 2.2 cm, RFA and SABR respectively). LC was defined as the absence of progressive disease by the

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
	doses of 30 or 50 Gy with a range of 27 to 60 Gy, Median follow up: SABR 13 months, RFA 20 months.	covariate predictive of LC (HR, 1.36 per cm; p= 0.029. OS 1 year = 74.0% SABR vs. 70.0% RFA 2 years = 46.0% SABR vs. 53.0% RFA Acute grade 3+ complications occurred after 11% and 5% of RFA and SABR treatments, respectively (p= 0.31). Late Grade ≥3 biliary: 1-year=3.3% SABR vs. 2.3% RFA 2-years=3.3% vs. 6.0% RFA -Late Grade ≥3 GI: 1-year=5.4% SABR vs. 3.4% RFA	Response Evaluation Criteria in Solid Tumors (RECIST) criteria within or at the PTV margin for patients receiving SABR and the absence of recurrence within or adjacent to the ablation zone for patients receiving RFA. Adverse events were defined as grade 3+ events according to the CTCAE criteria during the 30 days after treatment (acute) or at all later time points (late biliary and luminal GI toxicity). Follow-up was shorter in the SABR group.

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
		2-years=8.3% SABR vs. 6.4% RFA -Late Grade 5=0 for SABR and RFA. For SABR the toxicities were radiation-induced liver disease (n = 1), GI bleeding (n = 1), and worsening ascites (n = 1). For RFA complications included pneumothorax (n = 1), sepsis (n = 2), duodenal and colonic perforation (n = 2), and bleeding (n = 3) and resulted in two deaths.	
BED; Biologically Equivalent Dose, CP; Child-Pugh score, HR; Hazard ratio PFS; progression free survival, OS; overall survival, LC; local control, PVT; portal vein thrombosis RFA; radiofrequency ablation, 95% CI = 95% confidence interval			

Table 30: CtE Registry

Study Design and Population characteristics	Methodology	Results	Critical Appraisal Summary
SABR CtE cohort Prospective registry Multicentre UK Recruitment period 2015-2018 91 patients with HCC WHO PS 0=30.8%, 1=54.9%, 2=14.3% Median age: 72 Men = 72.5% Most patients had a single lesion	Patients received SABR (40-50Gy in 5 fractions) Median dose was 45 Gy delivered in 3-5 fractions Median 6.96 months follow-up.	Median overall survival 21.96 months Actuarial OS: -1-year = 76.5% (95% CI: 62.4 to 85.9%) -2-year = 41.7% (95% CI: 22.4 to 60.0%) Local control: -1-year = 72.3% (95% CI: 57.9-82.5%) -2-year = 52.4% (95% CI: 25.2-73.9%) Toxicity:	**Appraisal:** Non-comparative cohort – no randomisation, blinding, concealment. Multicentre experience in a UK NHS setting increases the external validity of the results, however, most patients were recruited by a single centre. Small patient cohort. Patients recruited into the CtE scheme were assessed for eligibility by a MDT making sure that both clinical eligibility criteria, but also technical feasibility aspects of the treatment were meet.

Previous chemotherapy: 31.9%		-all grades = 87.9% (95% CI 79.3-93.2%) -grade 3 = 12.1% (95% CI: 6.8-20.7%) -grade 4 = 3.3% (95% CI: 1.1-9.9%) -grade 5: 0% QoL Data on QoL was available for 88 (97%) patients at baseline. The mean EQ5D index did not change significantly between baseline and follow-up ranging from 0.66 and 0.76). Pain Pain scores were available for 99% patients at baseline. The majority of patients (87%) did not report any pain at baseline or during follow-up. There was	LC was assessed qualitatively without using objective lesion size-based measurements. This limits the generalisability of the results and introduces potential detection bias. The study did not include a sample size calculation. CIs are reported for most outcomes The Kaplan-Meier analysis was based on the assumption that there was "no event" unless an event was recorded (for example death). As a result, the analysis relies on data completeness. Events cannot be accounted for patients who are lost to follow-up and we know from the providers' feedback that patients are often lost to follow-up because they become sicker due to disease progression. This increased the risk of detection bias within the CtE

		an increase in the number of patients who report severe pain, from 1% at baseline to 9% and 19% at 12 and 18 months, respectively.	analysis. For OS this limitation is mitigated by the use of HES and ONS databases for data triangulation. Patients in the registry were linked to HES and ONS data, which provided a method to triangulate the mortality event rates, minimising detection outcomes and uncertainty. All centres taking part to the scheme had to undergo a nationally assured training system for SABR treatment, ensuring not only consistency of the intervention across in a multicentre setting but also potentially increasing safety. The analysis of the adverse events results does not take into account the timing of the event. It is therefore, not possible to separate acute and late toxicity. Furthermore, this analysis can

			potentially overestimate the adverse events reported by the CtE scheme in comparison with the published literature.
HES; Hospital episode statistics, HR; Hazard ratio PFS; progression free survival, ONS; Office for National Statistics, OS; overall survival, LC; local control, QoL; quality of life, 95% CI = 95% confidence interval, WHO PS; World Health Organisation performance status,			

6.2.3 Evidence on clinical effectiveness

6.2.3.1.1 Overall survival

Five of the included studies reported results on overall survival. One study was the meta-analysis by Rim et al. (2019) that included 32 observational single-arm studies involving 1950 patients with HCC who underwent SABR. Although the meta-analysis included studies with heterogeneous patient populations and study designs, the pooled result resulted in a patient cohort with similar characteristics to the CtE scheme with a median proportion of patients with Child-Pugh class A of 82.3% (range: 47.9-100) and an overall median tumour size of 3.3 cm (range: 1.6-8.6). Pooled 1-, 2-, and 3-year OS rates were 72.6% (95% CI 65.7-78.6), 57.8% (95% CI 50.9-64.4), and 48.3% (95% CI 40.3-56.5), respectively.

Results of comparative studies

Four retrospective comparative observational studies (Wahl et al. 2016, Bettinger et al. 2018, Parikh et al. 2018, Rajyaguru et al. 2018) compared SABR with RFA or sorafenib. All the included studies performed propensity score matching to account for baseline characteristics imbalances between the two groups.

Wahl et al. (2016) reported OS at 1 and 2 years of 69.6% and 52.9% after RFA and 74.1% and 46.3% after SABR in patients with inoperable and not metastatic HCC, with no significant difference between treatment groups (Wahl et al. 2016). Although the two groups were well balanced with respect to multiple clinical characteristics, patients undergoing SABR had received more prior treatments and were less likely to proceed to transplantation. There was also shorter follow-up in the SABR group, which could obscure late effects.

Parikh et al. (2018) reported their analysis of patients with non-metastatic stage I or II HCC treated with SABR or RFA. In the unmatched cohort, patients undergoing SABR had worse overall survival than RFA-treated patients ($p < 0.001$). The 1-year OS for SABR-treated patients was 78.1% and 79.4% for RFA-treated patients. The 2-year OS was approximately 50% for both groups. However, 3-year survival was significantly longer in the RFA-treated cohort. After propensity-matched scoring, there was no significant difference in survival between SABR-treated and RFA-treated patients ($p = 0.30$) (Parikh et al. 2018).

Rajyaguru et al. (2018) analysed patients' data with inoperable not metastatic HCC using the National Cancer Database, which includes about 70% of all newly diagnosed patients with

cancer in the United States who had undergone SABR or RFA as their primary treatment. In the propensity score matched and time to treatment matched analysis, RFA was associated with a significant OS benefit (HR 0.67; 95% CI 0.55-0.81; p<0.001); the 5-year OS was 29.8% (95% CI 24.5%-35.3%) in the RFA group versus 19.3% (95% CI 13.5%-25.9%) in the SABR group (p<0.001).

With the exception of one study (Rajyaguru et al. 2018), after adjusting for imbalances in the patients' characteristics with propensity matched scoring, SABR and RFA resulted in similar OS rates. In Rajyaguru et al. (2018), although propensity-score was used to match patients' baseline characteristics this did not include CP status, a variable associated with OS. In addition, 36% of the patients in the SABR cohort (n = 296) were treated with lower than standard radiotherapy dose (either 50-54 Gy in five fractions). A follow-up study that re-analysed the same data only including patients who received standard dose showed no difference in OS between the two cohorts (Shinde et al. 2018)[16].

Bettinger et al. (2018) compared OS in patients treated with SABR with patients treated with sorafenib. Median OS in the SABR group was 18.1 (95% CI 10.3-25.9) months compared to 8.8 months (95% CI 8.2-9.5) in the sorafenib group. After propensity-matched scoring adjusting for different baseline characteristics, the OS benefit for patients treated with SABR was still preserved with a median OS of 17.0 (95% CI 10.8-23.2) months compared to 9.6 (95% CI 8.6-10.7) months in patients treated with sorafenib.

Although OS was a primary outcome in most studies, none of them reported a sample size calculation. It is therefore, unknown if they were adequately powered to detect a difference in the effect. In addition, all studies were retrospectively conducted with a high risk of bias. The use of propensity matched scoring can improve the comparability of the two cohorts, however, it largely depends on the available information, and the clinical variables included in the matching.

6.2.3.1.2 Local control

Two of the included studies provided results on local control. The meta-analysis by Rim et al. (2019) reported pooled 1-, 2-, and 3-year LC rates of 85.7% (95% CI 80.1-90.0%), 83.6% (95% CI 77.4-88.3%), and 83.9% (95% CI 77.6-88.6%), respectively. In subgroup analysis based on

[16] The study was published as a letter to the editor and therefore, not included in this review.

tumour size, lesions of less than 5cm diameter, had statistically significant better LC for 1-year, 2-year, and 3-year ($p < 0.001$, 0.001, and 0.001, respectively). In subgroup analysis based on radiation dose (median EQD2 estimates of 80 Gy10), the difference was not statistically significant.

6.2.3.1.2.1 Results of comparative studies

One retrospective comparative cohort study by Wahl et al. (2016) compared the LC rate between SABR and RFA. The 1- and 2-year LC was 83.6% and 80.2% for RFA-treated tumours and 97.4% and 83.8% for tumours treated with SABR. Twenty tumours (8%) treated with RFA showed residual disease after first ablation. Eight of these were re-ablated within 3 months of first treatment and were not counted as local failures. The authors used inverse probability of treatment weighting (IPTW) to adjust for potential imbalances in treatment assignment between the two groups. In IPTW univariate analysis, treatment modality was associated with local progression (HR, 2.63; $p = 0.016$). After adjusting for treatment type, tumour size was the only covariate predictive of local progression (HR, 1.36 per cm; $p = 0.029$).

6.2.3.1.3 Quality of life

One prospective cohort study reported quality of life with SABR (Klein et al. 2015). The study included patients with HCC, intrahepatic cholangiocarcinoma, and liver metastases but presented separate results for the three cohorts. Although the main cohort consisted of patients with Child-Pugh A liver function, a small number of patients with HCC (n=10) with Child-Pugh B liver function were also treated. The EORTC QLQ-C30 and FACT-Hep validated and cancer-specific questionnaires were used to assess QoL. No difference in baseline QoL ($p=0.17$) was seen between the HCC, liver metastases, and intrahepatic cholangiocarcinoma patients. The authors concluded that treatment with SABR in patients with liver cancer temporarily worsened appetite and fatigue at approximately 1 month after treatment but QoL returned to baseline levels at 1-year post treatment. Other QoL domains did not show significant change from baseline after SABR. The study did not report any sample size calculation, therefore, it is unknown if it was adequately powered to detect a difference between the different cohorts of patients. Multiple imputations were performed to account for missing data of eligible patients alive at follow-up. Patient compliance for questionnaire completion fell from 90% at baseline to 60% at 1-year post-treatment.

6.2.4 Evidence on safety

Three of the included studies provided results on toxicity as a secondary outcome. One study was the meta-analysis of observational studies by Rim et al. (2019), one study was a comparative cohort comparing SABR with RFA (Wahl et al. 2016, Bettinger et al 2018) and one comparative cohort study compared SABR with sorafenib (Bettinger et al. 2018). All studies used the CTCAE[17] criteria to record toxicity information. In most cases toxicity outcomes were reported as acute or late toxicity with the definition of the former varying from 1 to 3 months post treatment.

The most commonly reported toxicities were gastrointestinal (GI), haematologic, and hepatic. GI complications included gastric or duodenal ulcer, nausea and vomiting; haematologic complications included abnormalities of white blood cells, platelets, and haemoglobin; and hepatic complications included abnormalities of liver function profile (alanine aminotransferase, aspartate aminotransferase, and bilirubin), albumin abnormalities, and liver decompensation (ascites, encephalopathy, and varices) (Rim et al. 2019).

The meta-analysis reported toxicity rates from 23 of the 33 included cohorts. The most commonly reported grade≥3 complications were GI or hepatic toxicities. For GI toxicities, the grade 3+ event rate were less than 5% in 16 of 17 cohorts (94.1%), it was 15% in one study and was not reported in the other 6 studies. The pooled rate using random effects analysis was 3.9% (95% CI 2.6-5.6%). For hepatic toxicity, the rates of grade 3+events were <10% in 23 of 24 cohorts (95.8%). The pooled rate was 4.7% (95% CI 3.4-6.5%). When tested in subgroup analysis neither tumour size nor radiation dose were found to be statistically significant. Meta-regression analysis showed that CP class was significantly correlated with hepatic complications of grade ≥3 ($p = 0.013$).

The meta-analysis also looked separately at the results of the three studies that reported high rates of grade 3+ toxicity. One study that reported high rates of hepatic toxicity (16.3%), all cases were transient elevations of liver enzymes. The authors assumed that possible risk factors were large tumour size and poor liver function (Scorsetti et al. 2015). Two other studies reported high rates of haematological adverse events (approximately 30% in both

[17] The CTCAE (Common Terminology Criteria for Adverse Events) criteria are a set of standardised criteria used to classify toxicity when a patient is undergoing anticancer treatment.

studies). The study by Kim et al. (2019) reported mostly thrombocytopaenia (patients who experienced this complication had prior haematological problem). The authors concluded that considering the pooled rates of complications and the fact that complications at high rates were mostly transient and possibly caused by chronic liver disease, the use of SABR to treat patients with HCC was safe.

Bettinger et al. (2018) compared the toxicity rates between SABR and sorafenib. Overall, 73.6% of sorafenib-treated patients experienced at least one adverse event at any grade. The most common adverse event was diarrhoea (39.3%), followed by hand-foot skin reaction (31.2%), fatigue (29.3%), weight loss (19.0%) and sorafenib-related hypertension (13.3%). A total of 19.4% of the patients had to stop sorafenib due to adverse events. For the group treated with SABR, 6.5% developed grade 2 adverse events, mostly relating to increases in liver enzymes. Grade 3 toxicity was reported in 10.6% of the SABR-treated patients mainly relating to an increase in liver enzymes, however, there were also 1 case of radiation-induced liver disease, 1 case of cholangitis and 2 cases of hepatic decompensation. Finally, grade 4 toxicity was reported in 2 cases (1.6%) as hepatic decompensation in 1 case and liver abscess in the other.

Wahl et al. 2016 compared the toxicity rates between SABR and RFA. Grade 3+ acute toxicity was 11% and 5% in the RFA and SABR groups respectively (p=0.31). The RFA complications were pneumothorax (n = 1), sepsis (n = 2), duodenal and colonic perforation (n = 2), and bleeding (n = 3) and resulted in two deaths. The SABR complications were radiation-induced liver disease (n = 1), GI bleeding (n = 1), and worsening ascites (n = 1) and there were no toxicity-related deaths. The rates of late grade 3+ biliary toxicity were similar in the RFA and SABR groups at 1 (2.3% v 3.3%; p=0.7) and 2 years (6% v 3.3%; p=0.38). The rates of late grade 3+ GI toxicity were also 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.

Treatment-related toxicity was a secondary outcome in all studies, therefore, it is unknown if any of them was adequately powered to detect a difference relative to a comparator (RFA or sorafenib). In addition, the retrospective design of most studies may lead to detection bias and the inability to accurately capture toxicity events.

6.2.5 Subgroup analyses

The meta-analysis by Rim et al. 2019 performed subgroup analyses based on tumour size and radiotherapy dose. The effect of tumour size (median value of 5 cm) was statistically significant for 1- and 2-year OS rates, and for 1-, 2- and 3-year LC rates. The effect of radiotherapy dose (median EQD2 estimates of 80 Gy10), was not statistically significant for OS or LC. Neither tumour size nor radiation dose had an effect on toxicity rates. The authors attributed the effect of tumour size on LC and OS to the fact that they categorised studies reporting high tumour invasion rates (>30%) into the subgroup of tumour size>5 cm, and the higher tumour vascular invasion (TVI) rate might affect the difference seen in clinical outcomes.

Rajyaguru et al. (2018) performed exploratory subgroup analyses of the matched cohort, using as variables age, sex, tumour size, tumour grade, Charlson-Deyo comorbidity score, and facility type[18]. According to their analyses the overall advantage of RFA over SABR on OS persisted across all subgroups.

Finally, Bettinger et al. (2018) performed subgroup analyses based on the presence of portal vein thrombosis and extrahepatic metastases. In the unmatched cohort, patients with extrahepatic metastases treated with SABR (having SABR treatment of the hepatic tumour only) showed a significantly improved OS compared to patients with sorafenib treatment (16.0 [6.7–25.4] vs. 7.6 [6.2–8.9] months, HR 0.43 [0.22– 0.84], p = 0.014). Also, in the matched cohort, the survival benefit of SABR treatment in metastatic patients was consistent (16.0 [6.6–25.4] vs. 10.0 [5.5-14.5] months, HR 0.38 [0.17-0.84], p = 0.018). Also, patients with portal vein thrombosis treated with SABR had a median OS of 8.0 (4.3-11.7) compared to 6.1 (5.2-6.9) months in sorafenib-treated patients in the unmatched cohort (p = 0.330). After propensity score matching, there was no difference in OS between patients treated in either group (9.0 [2.9-15.1] vs. 6.0 [2.7-9.3] months, p = 0.568).

It should be noted that all subgroup analyses were retrospective and exploratory. Given the heterogeneity of study designs and included populations it is not possible from the current

[18] In the context of this study this facility type included the following characteristics: distance from patient area of residence to treatment facility, case volume in quartiles, and geographic region.

evidence to discern any subgroups of patients who may benefit from SABR more than the wider population.

6.3 Conclusions

Seven studies provide evidence relevant to the scope of this review. All evidence results described above are for an adult population. The most significant evidence is provided by the meta-analysis by Rim et al. (2019) that included 32 observational single-arm studies involving 1950 patients with HCC who underwent SABR. The analysis provides evidence for the clinical efficacy and safety of SABR. Both OS and LC were affected by tumour size, and radiation dose marginally affected LC. LC rates were better for smaller HCC lesions, and moderate efficacy was shown in treatment of tumours >5 cm. Reported rates of severe toxicity were low, and mainly due to hepatic or GI toxicity.

There is also low quality evidence that the clinical efficacy of SABR is similar to that achieved with RFA and that it is better than sorafenib. There is low quality evidence from a single study suggesting that SABR does not significantly affect QoL.

The main limitation of the current evidence (including the analysis of the CtE data) is that the majority of the evidence comes from non-comparative (often retrospective) observational studies. These studies include heterogeneous patient populations, and study designs that limit the generalisability of the results. The evidence from retrospective comparative studies that used propensity score matching to account for baseline differences between SABR and RFA, and SABR and sorafenib, also suffer from the same limitations as the inherent biases of retrospective design, such as patient selection bias, lack of information on important baseline clinical characteristics and toxicity outcomes, cannot be fully addressed by statistical methods.

7 Discussion

7.1 Findings of the CtE scheme in the context of other studies

Between 2015 and 2018, the CtE registry collected outcomes from 91 patients with HCC recruited from 7 centres nationally. The mean age of patients was 72 years, and most (72.5%) were men. The cohort was mainly comprised of patients with a single lesion. The majority of the patients (95%) were treated with a standard linear accelerator. Most

patients were treated with 5 fractions of radiotherapy receiving 45 Gy of radiation in total. Cone beam CT (CBCT) image guidance was the most commonly used technique to assist treatment delivery in this patient cohort.

Median follow-up time for was 0.58 years (IQR 0.35-1.06). The median OS time was 21.96 months. The data analysis also reported OS of 76.5% (95% CI: 62.4-85.9%) at 1 year and 41.7% at 2 years (95% CI: 22.4-60.0%). The 95% confidence interval of the CtE data contains the survival target set at the beginning of the SABR CtE scheme (2-year target = 50%). The findings of the CtE scheme on the effect of SABR on OS of patients with HCC is supported by low quality evidence from the literature. The main evidence comes from a systematic review and meta-analysis (Rim et al. 2019) that included 32 observational single-arm studies involving 1950 patients with HCC who underwent SABR. Pooled 1-, 2-, and 3-year OS rates were 72.6% (95% CI 65.7-78.6%), 57.8% (95% CI 50.9-64.4%), and 48.3% (95% CI 40.3-56.5%), respectively. Although the meta-analysis included studies with heterogeneous patient populations and study designs, the pooled result reflected a patient cohort with similar characteristics to the CtE scheme inclusion criteria. The CtE included patients with Child-Pugh class A and up to 5cm in diameter and the median proportion of patients with Child-Pugh class A was 82.3% and the overall median tumour size was 3.3 cm in the Rim et al. (2019) study).

The CtE data analysis reported a 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 95% confidence interval of the CtE data contains the LC target set at the beginning of the SABR CtE scheme (1-year target = 80%). The findings of the CtE scheme on the effect of SABR on LC is partially supported by the findings of the meta-analysis by Rim et al. (2019). Pooled 1-, 2-, and 3-year LC rates from the meta-analysis were 85.7% (95% CI: 80.1-90.0), 83.6% (95% CI: 77.4-88.3), and 83.9% (95% CI: 77.6-88.6), respectively. Only the 1-year and not the 2-year LC rate of the CtE scheme is within the 95% confidence interval reported by Rim et al. (2019). Contrary, to the rest of the studies, the CtE scheme has not used RECIST to calculate LC, therefore, the results are not easily comparable. Although RECIST is a universal tool commonly used to measure local control, the clinicians participating in the SABR scheme did not feel that they had sufficient resources to use it outside a clinical trial setting and therefore a pragmatic solution was adopted instead.The combined findings from the published literature and the CtE provide low quality evidence that SABR achieves high LC rates. There is further low-quality evidence from the

published literature only, that the LC achieved with SABR is equivalent to that achieved by RFA for small lesions (<3cm) and superior for larger lesions.

The CtE data analysis reported a grade 3 adverse event rate of 12.1% (95% CI 6.8-20.7) and a grade 4 adverse event rate of 3.3% (95% CI 1.1-9.9%), above and within the proposed targets of 15% and 10%, respectively. No grade 5 adverse events were reported.

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. The most frequently reported adverse event was fatigue. Other frequently recorded adverse events were associated with increased blood levels of alanine aminotransferase (ALT) and bilirubin. Longitudinal analysis of these results suggests that the abnormal liver function test results were not treatment related.

The main evidence from the literature for the safety of SABR is provided by the meta-analysis by Rim et al. (2019). The most commonly reported grade 3+ complications were gastrointestinal (GI) or hepatic. For GI toxicities, the grade 3+ event rates were less than 5% in 16 of 17 cohorts (94.1%), it was 15% in one study and were not reported in the other 6 cohorts. The pooled rate using random effect was 3.9% (95% CI 2.6-5.6%). For hepatic toxicity, the rates of grade 3+ complications were <10% in 23 of 24 cohorts (95.8%). The pooled rate was 4.7% (95% CI: 3.4-6.5%). Meta-regression analysis showed that Child-Pugh class was significantly correlated with hepatic complications of grade 3+ ($p = 0.013$). The combined findings from the CtE scheme and the published literature provide low quality evidence that SABR does not result in high rates of severe toxicity in this patient cohort.

Data on QoL were available for 88 (97%) patients at baseline. 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. Beyond these findings there was no other trend observed for QoL and this is supported from the analysis of the general state of health (0-100). After transforming the reported values to the index measure the means taken at each follow-up are approximately at the same level (ranging from 0.66 and 0.76). It should be noted, however, that the small number of patients with follow-up beyond 12 months increases the uncertainty of these results. The CtE results on QoL are supported by 1 observational study that reported no significant impact in most QoL outcomes following

SABR treatment in patients with liver cancer. The combined findings from the CtE scheme and the published literature provide low quality evidence that SABR does not significantly affect QoL in this patient cohort.

Data on pain scores were available for 90 (99%) CtE patients at baseline. According to the summary analysis, the majority of patients (87%) did not report any pain at baseline or during follow-up. There was a notable increase in patients who report severe pain from 1% at baseline, to 9% and 19% at 12 and 18 months, respectively. This finding is in agreement with the analysis of the QoL pain/discomfort dimension that reported a small increase of people reporting worsening symptoms between baseline and last follow-up (from 0% to 6% at 18 months). For both QoL and pain scores, the analysis assumed that missing data have a random distribution and do not introduce bias. Based on the providers' feedback, however, missing data are often associated with a decline in the patient's performance status and clinical condition. There is therefore a lot of uncertainty about the QoL and pain conclusions and the results should be interpreted with caution.

The main limitation of the current evidence (including the analysis of the CtE data) is that the majority of the evidence comes from non-comparative observational studies. These studies include heterogeneous patient populations, and study designs that limit the generalisability of the results. The evidence from retrospective comparative studies even when using propensity score matching to account for baseline differences between SABR and its comparators suffer from the same limitations as the inherent biases of retrospective design, such as patient selection bias, lack of information on important baseline clinical characteristics and toxicity outcomes, which cannot be fully addressed by statistical methods. Finally, the small size of the CtE scheme cohort and the small number of patients with more than 12 months follow-up, increases the uncertainty around any conclusions drawn for this cohort.

There is absence of outcomes in children in the published literature.

7.2 Strengths and limitations

7.2.1 Strengths of available evidence

The CtE registry had several strengths. Firstly, the scheme prospectively recruited and analysed a contemporary cohort of patients with HCC in the NHS, bridging a gap in the literature for available evidence from a UK setting. Patients recruited into the CtE scheme

were assessed for eligibility by a MDT making sure that both clinical eligibility criteria and technical feasibility aspects of the treatment were met. All centres taking part in the scheme had to undergo a national quality assured training system for SABR treatment, ensuring not only consistency of the intervention across in a multicentre setting but also potentially increasing safety. In addition, patients in the registry were linked to HES and ONS data, which provided a method to triangulate the mortality event rates, minimising detection bias and uncertainty.

7.2.2 Limitations of available evidence

Most of the evidence for using SABR to treat people with HCC, including the CtE data, come from non-comparative studies. In addition, most of the published evidence is from retrospective studies. The low reporting quality of most of these studies, the high degree of variability (study design and patient population) among them, and the absence of long-term follow-up means that comparison of the CtE results with these published data is limited. All comparisons between the CtE outcomes and published data on use of sorafenib and RFA should be considered low quality and subject to considerable uncertainty. As a result, no robust conclusions can be reached about the efficacy and safety of SABR against sorafenib or RFA.

Other limitations with the CtE registry include the following:

- The CtE only had a maximum of two years follow-up. Due to the slow recruitment at the start of the scheme, the median follow-up was only 7 months. As a result, the follow-up is too short to allow the evaluation of long-term safety and efficacy of SABR.
- The small size of the cohort and the small number of patients with more than 12 months follow-up, increases the uncertainty around any conclusions drawn for this cohort.
- Although the CtE scheme recruited patients from 7 centres nationally, the majority of the patients were recruited by a single centre (UHB). This can potentially minimise the generalisability of the results across the whole NHS. The presence of a quality assured training system for SABR treatment can potentially minimise this concern.
- It was not possible to ascertain if patients received further treatment after SABR.

- The Kaplan-Meier analysis assumed that there was "no event" unless an event was recorded (for example death). As a result, the analysis relies on data completeness. Events cannot be accounted for patients who are lost to follow-up and we know from the providers' feedback that patients are often lost to follow-up because they become sicker due to disease progression. This increased the risk of detection bias within the CtE analysis. For OS this limitation is mitigated using HES and ONS databases for data triangulation (see strengths above).
- For LC the CtE scheme adopted a qualitative reporting method that was based on the absence or presence of any progression without using objective size measurements. This limits the generalisability of the results and introduces potential detection bias.
- The analysis of the adverse events results does not take into account the timing of the event it is therefore, not possible to separate acute and late toxicity. Furthermore, this analysis can potentially overestimate the adverse events reported by the CtE scheme in comparison with the published literature.

8 Providers' feedback

Participating SABR centres gave feedback about their experiences of implementing SABR in the NHS as a part of the CtE scheme. Telephone interviews were held with available clinicians, radiographers, physicists and data managers at all 17 provider centres included in the SABR CtE scheme. All of the centres treated patients with oligometastatic disease, however, some centres also additionally treated patients with HCC and/or patients undergoing re-irradiation. This report covers the feedback provided for all three of the SABR CtE cohorts (oligometastases, re-irradiation of the pelvis and spine, and HCC), and therefore, some of the comments provided may be less applicable to the HCC cohort.

8.1 Questions

The following broad, open ended questions were provided as prompts (adapted from the NHS Improvement Lessons Learnt guide):

- What are your thoughts on how successful the project has been?
- What were the key elements that worked well?
- What were barriers to success?
- If the service is routinely commissioned by the NHS, what would be the key learning points?

The following topics of interest were also suggested as topics for feedback: resources, quality assurance (QA), eligibility criteria, consenting, referral and follow up pathways, dose constraint issues, and impact on capacity.

8.2 Feedback

8.2.1 Thoughts on the success of the CtE scheme implementation within the centres

All centres felt that the project had been successful from the clinical perspective, particularly in light of the relatively short timeframe. Some centres suggested that clinical evidence increasingly demonstrated the advantages of SABR and described the CtE scheme as a "lifeline" for patients who would otherwise have not had access to the treatment. The CtE

scheme was seen as beneficial for centres who would otherwise have a low volume of patients for SABR as it provided the opportunity to build the necessary skills and experience within a national framework.

Centres noted that, in general, patients undergoing SABR treatment expressed high satisfaction and would be very likely to recommend the service.

8.2.2 Key elements that facilitated success

Centres mentioned a number of factors as key to the success of the CtE scheme.

8.2.2.1 Multidisciplinary team

All 17 centres highlighted that establishing a strong, specialised multidisciplinary team (MDT) was paramount. The MDT was described as the "nucleus" of a successful service and especially important when setting up and treating new anatomical sites. The MDT should ideally comprise of the following staff:

- Clinical lead
- Clinicians - site specialist oncologists and radiologists
- Dedicated radiographers to provide input for treatment delivery
- Physicists to provide technical input for treatment planning
- Dosimetrists (usually a radiographer or clinical technologist)
- SABR administrative coordinator

The structure of the MDT varied amongst centres. Most centres recruited a larger number of site-specialised staff to carry out SABR treatment as a small part of their role, for example, the lung cancer team would treat lung sites, or the urological team would treat the pelvic area. If resources are available, another option would be to recruit a smaller number of staff where SABR is a significant, specialist part of the role. Future SABR centres may decide on having a more organ-based SABR team or a more SABR treatment-specific team, depending on resources available. Centres suggested that a smaller, dedicated team was likely to be optimal in most situations. A smaller MDT at the outset can build up strong expertise that can be rolled out in the longer term to adapt to developing the service. A smaller, more visible team may also help raise the profile of the service and help develop pathways that are more consistent. The biggest recruitment centre for patients with HCC (UHB) stated that the adoption of SABR as a treatment option by the MDT happened gradually and was mainly

due to two factors: promotion of SABR by a clinical oncologist as a treatment option and a culture of open-mindedness among MDT clinicians. Most centres mentioned that frequent MDT meetings were helpful and held these weekly or fortnightly. In practise, the SABR MDT meeting was sometimes added on to other tumour-specific MDT meetings, but many centres felt that the complexity of SABR would warrant a dedicated group. Many centres discussed the importance of having a dedicated SABR/MDT administrative coordinator to organise the meetings and the additional clinical workload.

MDTs were often mentioned as bringing unanticipated benefits, including closer working ties between the different professions. Centres saw the increased intra-professional discussion about patient eligibility as an opportunity for learning and breaking communication silos. Some centres noted that the scheme had encouraged improvements in image review training for radiographers.

8.2.2.2 Radiotherapy Trial Quality Assurance (RTTQA) approval/input

All centres felt that the RTTQA process was very useful for providing a forum for discussion and advice. The process provided an external peer review and support network that all centres described as beneficial. The accreditation given by the QA process was also viewed positively from the departmental perspective and provided confidence that service standards were being maintained. In addition, it promoted the standardisation of practice for a service with complicated clinical pathways, which in turn helped clinicians manage and distribute their workload.

Centres felt that any newly commissioned service would benefit from new sites having access to a centralised QA service for benchmarking and approval. One centre suggested the service would benefit from having dedicated physicists to contact with technique or patient related queries. Another centre suggested that if not nationally, a similar QA process could be developed regionally with centres working closely in their cancer networks. Another centre mentioned this could involve cascaded training provided by more experienced centres, or a mentoring system.

8.2.2.3 Local education and promotion

Centres stated that it was important that the SABR service was well promoted within its catchment area, that there was a straightforward path for referral and that eligibility criteria were well understood. The methods of promoting the service varied depending on the pre-

existing networks between the SABR site and referring centres but all aimed to ensure that there was adequate engagement with referring centres. Some centres noted that they already had very active and close relationships within their referral network, and little additional engagement was necessary. Other centres highlighted that intensive relationship building was key to the success of the project – this included the SABR team visiting referring centres, carrying out presentations and open days, and sending updates and newsletters. Some centres noted that the referral pathway should be made as simple and efficient as possible, for example using electronic referrals, SABR specific referral proformas and a dedicated email account as keys to engage potential referral centres. Centres also recommended advertising the SABR service at site specific MDTs to make sure all eligible patients are considered.

8.2.3 Key challenges to success

8.2.3.1 Resourcing

Centres spoke about challenges procuring adequate hospital staff and equipment resource during the CtE scheme.

Almost all centres noted the need for dedicated radiologist input at the MDT, in particular for mark-up issues (for example for delineation of treatment field or fiducial marker insertion), and that this was often difficult to procure. If the service was covering oligometastases at different anatomical sites, and therefore required site-specialised radiologists, many centres said they struggled to identify and include specialised radiologists for the MDT. This issue may be less relevant for centres that do not treat people with oligometastases. Centres often mentioned that, in general, clinicians would ask radiologists for advice on an ad hoc basis but were not always able to do so in a timely manner, which sometimes produced delays in the process. Radiology input was particularly crucial at the start of a new service when the MDT was relatively inexperienced, for example, in providing advice on determining the volume and outline of tumours. Centres noted that ongoing training and development of radiology capability would be necessary. As a specific example, the setting up of processes to insert fiducial markers was noted by two centres as a consideration for interventional radiology departments wishing to introduce liver as a new treatment site.

Centres noted that certain anatomical sites also required greater staff resource. A number of centres mentioned particular challenges with liver SABR, which was noted as being harder to image and more challenging to contour than many other sites. In addition, if there were no liver-specialist radiologists then clinician presence was required during treatments. One centre mentioned that their dosimetrist reported it took a long time to plan a liver SABR patient.

Centres described how resourcing requirements changed through the lifecycle of the service. Many centres mentioned that lack of resource (staff and equipment time) were primarily a challenge until the services were better established and staff gained enough experience to streamline processes. For example, one centre said that the mark-up (requiring input from two doctors) would often be a bottleneck in treatment. The centre stated that having a dedicated MDT coordinator and using electronic care pathways now helps manage this process much more efficiently. The centre also noted that initially doctors attended all treatment fractions, which was challenging to organise. With increased experience, the service now has a local on call site-specific clinician available rather than requiring a doctor in attendance during all fractions, with the caveat that this can be an issue with less common SABR sites such as liver. The centre also explained that initially, treatments were carried out first thing in the morning, as this meant fewer distractions, but with more experience the centre is more confident treating throughout the day which has alleviated some logistical issues.

Centres noted that individual SABR treatments are typically longer than conventional radiotherapy, and that this impacted linear accelerator (linac) time, especially as SABR treatments often require extra imaging or discussions. Centres mentioned the need for cooperation and the need for strong relationships between the MDT and the radiotherapy service.

Some centres mentioned that they had encountered resource challenges with MRI access. One centre noted “we're lucky we have our own dedicated MRI. I don't know what other centres would do if they didn't have that facility. MRI capacity needs to be thought about”.

8.2.3.2 Staff training

Some centres discussed the challenges of providing training for enough staff to the required standard, noting that ongoing SABR training would be required to maintain competency. One centre described the necessity to maintain a balance between having a small enough

team to maintain competency and expertise and also have enough flexibility in the system that if demand for treatment grew or staff were depleted due to holiday or sickness it did not impact the service. This may be an ongoing issue if new SABR indications are introduced and staff need to build up experience treating them.

8.2.3.3 The complexity of planning for treatment of multi-metastatic disease

Planning for metastatic tumours was posited as a resource challenge. One centre said that planning techniques to treat multi-metastatic targets often had to be developed "on the fly" to meet the unique technical requirements of individual patients. Despite the significant time expenditure, some centres mentioned that the organ at risk constraints for multi-target treatments often could not be met. The same centres said that while the efficiency of planning treatment for this patient group has improved over time, multi-metastatic disease continues to provide a significant challenge to the planning team and represent a significant increase in complexity when compared to single target treatments.

8.2.3.4 Consent form

A new consent form was developed once the CtE scheme had started. Some patients who had already commenced SABR treatment needed to be reconsented. Many centres expressed dissatisfaction that the consent process was not established at the start and that reconsenting was resource heavy. Centres noted it would be helpful to have all paperwork and databases ready from the outset or a new scheme. Most centres expressed overall satisfaction with the final consent form, however some suggested that changes could be made to enhance its usability. Some centres expressed dissatisfaction with the form, explaining that the consent form is not well designed for patients or staff, recommending that the design of the form would benefit from input from a consent writing workshop or patient information group.

8.2.3.5 Database

Some centres reported challenges with using the SABR CtE database recommending amendments, including the following:

- One centre noted an inability to record patients who are no longer appropriate for follow ups, for example, having gone to palliative care. It suggested an option for this in the database would be helpful to provide more detail.

- A centre mentioned there was a lack of choice for some of the systemic therapy options, suggesting it would be useful if there was an option to select 'other' and enter free text.
- One centre mentioned that a more comprehensive list of drugs would be helpful as the database only allowed a choice of certain drugs.
- A centre suggested that the following additions to the dashboard would be useful: the date that the follow up was carried out, highlighting areas with missing data, increasing drop down options for example, for the Gleason score (addition of 4+5 option) for prostate.
- One centre was concerned about the inability of the database to pick up significant toxicity.

8.2.3.6 Image transfer

Some centres mentioned that now the service is established (as part of the CtE scheme), the main barrier has been receiving all the necessary information and prior imaging for the referred patient. Centres suggested that having an efficient method of transferring this information, imaging in particular, would promote a successful service.

8.2.4 Feedback on other key topics

8.2.4.1 Inclusion criteria

All centres felt that the selection criteria were understandable but could be revised in light of new evidence. The following potential updates were suggested as examples:

- Some centres suggested that systemic treatment could be continued in addition to SABR treatment (the CtE eligibility criteria suggested that there should be no concomitant systemic treatment).
- Inclusion criteria could be further developed by considering efficacy and feasibility of SABR by disease site. The existence of a disease marker, for example in prostate or bowel cancer, was noted as helpful to enhance monitoring and therefore treatment effectiveness. One centre suggested the efficacy of SABR in breast cancer is more variable, however if the disease is restricted to a solitary node some clinicians suggested SABR would be effective. Some centres mentioned there may be a difference in efficacy between visceral versus bone metastases.

- Some centres suggested that it might be helpful to have some more information about lower size limits for tumours (in addition to the existing upper size limits in the criteria), explaining that in their experience, some metastases had been too small to treat (for example, due to difficulties with voluming).
- One centre suggested that if low volume metastases are commissioned then some clear guidelines would be needed on what would be considered a treatable number of lesions.

Most centres suggested expanding the indications from the CtE criteria as more evidence accumulates for the effectiveness of SABR.

Some centres suggested that disease definitions were not always clear within the CtE criteria but that these definitions are not well established more generally in the field. For example, some clinicians mentioned that the lack of clarity around definitions for re-irradiation or oligometastatic disease impacted referrals for SABR treatment.

Some centres strictly adhered to the inclusion criteria during the CtE scheme, and others built in some flexibility in terms of how criteria were applied to patients. For example, some centres noted that the definitions for radical treatment or oligoprogression were open to interpretation and therefore subject to debate at MDTs. Most centres agreed that if SABR was to be routinely commissioned it is important that some flexibility should be allowed for decision making on a patient-by-patient basis. One centre noted that an internal audit showed that concordance with the inclusion criteria increased over time.

8.2.4.2 Referral pathway

At most centres, eligibility was discussed at the tumour site MDT and patients were referred on to the dedicated SABR MDT which then made the final decision about whether to treat (the SABR MDT was described as the gatekeeper for the treatment). Other centres followed a different approach, promoting the SABR treatment more widely both within and outside the trust so individual oncologists and surgeons were able to refer a broader selection of potential patients to the dedicated SABR MDT. If SABR was routinely commissioned, one centre suggested that a patient centred approach should be used as the geography of different centres and the referral pathways for different disease types are likely to be varied.

Most centres agreed that ideally patients would be pre-screened at a tumour specific MDT before referring to the SABR MDT. Centres reported a highly variable rate of patient eligibility at the point of the SABR MDT meeting – from almost 100% to around half being

considered eligible. This was often dependent on whether the patient had been pre-screened and how rigidly the eligibility criteria were adhered to.

Some centres discussed the use of a proforma developed by the SABR MDT. The proforma was provided to referring centres and tumour specific MDTs and was then populated and returned along with imaging. The proforma contained questions to gather information such as what treatment the patient had for the primary disease, when this was carried out, the number, and location of metastases, and patient performance status.

8.2.4.3 Follow up pathway

Most centres agreed that the follow up of patients as part of the CtE scheme was a resource-intensive undertaking. For centres with larger catchment areas this was more challenging as patients typically preferred not to travel back to the centre. Telephone follow ups were common, and centres reported that though these were preferred by patients, they varied in success. Centres felt that the key to success was having strong administrative support to ensure patients were sent reminders, called on time or had their call rescheduled. In some places, follow up was carried out by the referring centre, in collaboration with the SABR centre.

One centre explained that if they wanted the patient to be followed up locally, they would send follow up criteria (using SABR consortium guidelines) which included a list of required investigations, along with a letter to the original carer. The nature of future (non-CtE) follow up depends on how a future service is commissioned and the level of detail required.

Centres said follow up was an intensive process for the CtE scheme. If follow up was required with the same level of detail as CtE, centres felt this was a significant undertaking and would require additional funding.

8.2.4.4 Pathway standardisation

Most centres felt that some flexible standardisation of pathways would be helpful for clinical decision-making.

8.2.4.5 Dose constraint issues

All centres felt that they were able to meet the dose constraints in most cases. Centres reported that the constraints were reasonable but noted that occasional compromises needed to be made. The following specific anatomical areas of uncertainty were mentioned:

- The irradiation of the bladder (uncertainty over what alpha-beta ratio to use)
- Multiple lung metastases
- Bowel
- Heart

Centres described a number of tactics for compromise. One centre said: "During the planning, if we were exceeding a dose constraint we would either compromise the coverage, that was one tactic we had, or sometimes we would drop the dose slightly. Another tactic we had is sometimes we would change the fractionation. For example, for pelvic SABR cases, if they were re-irradiations and they'd had prior prostate radiotherapy it was almost impossible to meet the sacroplexus constraints".

Some centres mentioned that it was helpful that the dose constraints were open to interpretation. One centre explained, for example, that in patients who had already received prostate radiotherapy, some may have already exceeded the tolerances allowed before SABR. It suggested that if dose constraints were applied strictly in these situations then SABR would not be given to any patients who were due to be retreated. Flexibility must be built in so individual MDTs can discuss cases on a patient-by-patient basis.

8.2.4.6 Impact on capacity

Most centres said that capacity had not been a significant issue for them during the CtE scheme. For some centres it was because the SABR service had already been established (SABR was described as already being the standard of care for other indications). In other centres it was because the selection criteria were strictly adhered to and therefore a relatively low number of patients were treated. It was suggested that centres that had been more flexible with the criteria may have experienced more pressure on capacity.

Centres acknowledged that the patient numbers included in the CtE scheme were not necessarily an indication of the numbers of patients who would be treated if the service was commissioned in the future. One centre noted that there were many patients who may have fulfilled the criteria for SABR but were not referred on and suggested that if the service becomes routinely available, the programme would need expanding to more centres to cope with the increase in referrals. Another centre noted that in any further roll out, the issue of service quality would be very important and that there may be a snowballing of consequences beyond treatment capacity.

8.2.4.7 *Future with SABR*

All centres felt that emerging evidence suggests that SABR will be suitable for a wider number of indications and will increasingly become part of standard of care. Commissioning SABR may result in a potential paradigm shift from a palliative to a radical treatment pathway. Centres noted that that this shift would profoundly affect pathways both before SABR treatment and at follow up. Some centres noted that a more effective curative treatment may heighten the need for more intensive screening programmes in patient groups such as breast and lung (as opposed to diseases with established biomarkers such as prostate cancer, for example, which already has an effective screening programme).

Centres agreed that follow up may become more intense with SABR. One centre noted that if the CtE inclusion criteria were widened then some indications may be considered palliative (such as oligoprogressive disease) and some radical. The centre suggested that follow up for people with oligoprogression may be easier due to the likelihood of patients also having systemic treatment. For patients having treatment described as radical, there may be more uncertainty about follow-up time points and more collaboration required with the referring centre.

One centre noted that with the advance of imaging technology, surveillance is likely to become more routine and intensive regardless of the commissioning policy for SABR. Anecdotally they noted that the use of PET had increased with the use of SABR: "If you're going to subject someone to a more radical ablative treatment, be it surgery or radiotherapy, then people have more confidence it is oligometastatic if you do a PET".

Some centres suggested there may be wider cost implications of not treating with SABR. If SABR is shown to be effective, then the treatment may prevent the need for further treatment such as RFA or resection and costs entailed.

8.2.5 Key learning points

- **Staffing resource:** Centres stated it was crucial to have an adequately resourced, dedicated SABR team and this included a SABR administrative coordinator. Some centres suggested an optimal MDT structure (see sections about MDT and resourcing above).
- **Quality assurance:** Centres noted that it was extremely helpful to have contouring and planning approval via a centralised RTTQA but that it was also important to have

local peer review of patient eligibility and treatment plans. Centres suggested that local cancer networks could work together to set up a peer review system. This may be especially important for oligometastases at less common anatomical sites and it may not be possible to have enough clinicians available locally to peer review.

- **Communication network:** The importance of setting up or reinforcing strong lines of communication between referral and treatment centres was noted. It was also important to ensure that site specific MDTs and external referral centres were aware of the SABR service and had an informed and simple process for referral (for example with a single centralised dedicated SABR service email account, and a good quality referral proforma).
- **Radiology:** Access to radiologists was vital. Many centres noted that radiology input was critical to MDT decision making but was often difficult to procure. SABR would also entail training for radiologists for newer processes introduced by SABR.
- **Imaging transfer:** Centres often mentioned that not having timely access to imaging results could delay treatment. A smoothly running service would have an established process of obtaining scans from referring centres.
- **Managing resource implications over time:** The change in resource requirements over the life of a service was discussed. Noting the importance of a successful start to a project, centres stated that significant resource was required upfront in the designing and setting up phase.
- **Peripheral equipment:** Some centres noted that additional equipment may be required as the SABR service develops. In particular, centres mentioned access to/funding for MRI resources especially tailored to radiotherapy and not just standard diagnostic MRI. One centre was considering introducing fluoroscopy to improve their SABR service further.
- **National SABR rollout:** Many centres felt that the SABR service should be rolled out to more centres nationally, with the strong caveat that this needed a framework for training and support, and QA. Centres also noted that treatments are increasingly complex and specialised - any national rollout would need to consider this to ensure adequate efficacy and competence.

9 NHS England CtE Questions

The aim of the SABR CtE scheme was to provide data on the efficacy, safety and cost-effectiveness of SABR in patients with HCC. The following table (Table 31) contains KiTEC's response to the evaluation questions (based on Version 6.3, updated 22 December 2015)

Table 31: NHS England/NICE CtE Evaluation Questions

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's response
What is the 1-year and 2-year survival following treatment with SABR for the indications covered by the CtE scheme (presented as estimates with confidence intervals)? How do these survival estimates compare with the target outcomes, in terms of superiority or non-inferiority?	**Proposed target:** The literature reports a 2-year OS rate of approximately 50%. This is the best defined of the 3 SABR cohorts. In addition, there are numerous systematic reviews and meta-analyses treating patients with HCC with other treatments, such as RFA. Any target outcomes set for this cohort will need to be non-inferior to clinical outcomes provided with these treatments.	The data analysis reported 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 95% confidence interval of the CtE data contains the survival target set at the beginning of the SABR CtE scheme (2-year target = 50%). The small size of the CtE scheme cohort and the small number of patients with more than 12 months follow-up, increases the uncertainty around any conclusions drawn for this outcome. The findings of the CtE scheme on the effect of SABR on OS of patients with HCC is supported by low quality evidence from the literature. The main

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's response
		evidence comes from a systematic review and meta-analysis (Rim et al. 2019) that included 32 observational single-arm studies involving 1950 patients with HCC who underwent SABR. Pooled 1-, 2-, and 3-year OS rates were 72.6% (95% CI 65.7-78.6%), 57.8% (95% CI 50.9-64.4%), and 48.3% (95% CI 40.3-56.5%), respectively. Although the meta-analysis included studies with heterogeneous patient populations and study designs, the pooled result reflected a patient cohort with similar characteristics to the CtE scheme.
Does treatment with SABR for the clinical indications covered within the CtE scheme increase local control?	**Proposed target:** At 1-year 80%. This estimate takes into account both findings reported in the literature, and clinical experts' consensus.	The CtE data analysis reported a 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 95% confidence interval of the CtE data contains the LC target set at the beginning of the SABR CtE scheme (1-year target = 80%). The findings of the CtE scheme on the effect of SABR in LC is partially supported by the findings

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's response
		of the meta-analysis by Rim et al. (2019). Pooled 1-, 2-, and 3-year LC rates from the meta-analysis were 85.7% (95% CI: 80.1-90.0), 83.6% (95% CI: 77.4-88.3), and 83.9% (95% CI: 77.6-88.6), respectively. Only the 1-year and not the 2-year LC rate of the CtE is within the 95% confidence interval reported by Rim et al. (2019). Contrary, to the rest of the studies, the CtE has not used RECIST to calculate LC, therefore, the results are not easily comparable. In addition, the small number of patients with more than 12 months follow-up, increases the uncertainty around any conclusions drawn for the 2-year LC rate. The combined findings from the published literature and the CtE provide low quality evidence that SABR achieves high LC rates. There is further low-quality evidence from the published literature only, that the LC achieved with SABR is equivalent to that achieved by RFA.

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's response
What Adverse Events occur as a result of SABR in the CtE cohort of patients?	**Proposed target:** Based on the published evidence and the accreditation scheme for all the NHS Trusts included in the CtE scheme a target outcome rate for grade 3 adverse events of 15% and for grade 4-5 adverse events of 10% was proposed.	The CtE data analysis reported a grade 3 adverse event rate of 12.1% (95% CI 6.8-20.7) and a grade 4 adverse event rate of 3.3% (95% CI 1.1-9.9%), above and within the proposed targets of 15% and 10%, respectively. No grade 5 adverse events were reported. 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. The most frequently reported adverse event was fatigue. Other frequently recorded adverse events were associated with increased blood levels of alanine aminotransferase (ALT) and bilirubin. Longitudinal analysis of these results suggests that the abnormal liver function test results were not treatment related. The main evidence from the literature for the safety of SABR is provided by the meta-analysis by Rim et

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's response
		al. (2019). The most commonly reported grade 3+ adverse events were GI or hepatic. For GI-related adverse events, the pooled overall rate using random effect model was 3.9% (95% CI: 2.6-5.6%). For hepatic toxicity, the pooled rate was 4.7% (95% CI: 3.4-6.5%). The combined findings from the CtE scheme and the published literature, provide low quality evidence that SABR does not result in high rates of severe toxicity in this patient cohort.
What is the patient experience of treatment with SABR for the clinical indications covered within the CtE programme? The 'friends and family test' (https://www.england.nhs.uk/ourwork/pe/fft/), a short generic instrument, designed to provide some patient experience feedback will be used to collect information for all SABR patients. This test has been widely used in the NHS.	NA	KiTEC report that 87% of CtE patients would be extremely likely/likely to recommend the SABR service to friends and family if they needed similar care or treatment.

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's response
What is the cost-effectiveness of providing SABR in patients with HCC covered within the CtE scheme? Cost-effectiveness will be assessed using a Markov model to synthesise evidence on SABR and from literature on relevant comparators over the time horizons specified. The Markov model will model the following four health states for SABR and comparators: • Progression free survival • Local progression • Systemic progression • Death • Data for survival will be obtained from the SABR dataset and literature for comparators. In the absence of literature estimates distinguishing local and systemic progression, the health states will be combined.	The following subgroup of patients and comparators were selected: Comparators: ○ surgery ○ radiofrequency ablation Time horizon: 3 years	The objective of the economic evaluation in the CtE scheme was to determine whether SABR is a cost-effective intervention compared with radiofrequency ablation (RFA) and surgery for patients with resectable HCC. Despite entry criteria for the CtE scheme excluding patients whose HCC was suitable for treatment by surgery or RFA, these interventions, were considered potential alternatives to SABR if the use of SABR is expanded in the future. They were therefore, selected by the data working group as comparators. The CtE analysis found that for adult patients with 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. The results are limited by the lack of a control group in

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's response
• Utilities will be estimated from the EQ5D of the SABR dataset and from literature for the comparators.		the CtE scheme; it is likely that comparisons with data from the literature on survival and progression rates are confounded by differences in patient characteristics. A randomised trial might provide the robust data required to conclusively assess the cost-effectiveness of treatments for HCC.
What are the outcomes by indication in the CtE cohort of patients?	NA	NA
Are there any factors from the experience of provision within centres participating in the scheme that should be taken into account in terms of future service provision?	NA	The providers' feedback reported that according to their experience, the programme was successfully implemented in their NHS Trusts, however, the centres noted the possible future need to expand the programme in order to cover demand.
Are there any research findings that have become available during the course of the CtE scheme that	NA	No published randomised controlled trials have been identified.

Agreed NICE and EAC evaluation questions	SABR subgroup specific question	KiTEC's response
should be considered alongside the evaluative findings of the CtE scheme?		

10 Conclusions

The available evidence from the literature and the CtE data analysis provide low quality evidence that SABR for adult patients with HCC could be a feasible option resulting in good LC rates. There is also low quality evidence that SABR treatment can result in OS rates of approximately 70-80% at 1 year and 50-60% at 2 years post treatment. Finally, there is low quality evidence that the rate of grade 3 and 4 adverse events is low, and no grade 5 deaths have been reported. There is also low quality evidence that the clinical efficacy of SABR is similar to that achieved with RFA and that it is better than sorafenib. There is low quality evidence suggesting that SABR does not significantly affect QoL. There is considerable uncertainty about these findings as the existing evidence comes from mainly retrospective single-arm studies with high risk of bias for patient selection and outcomes detection. Further prospective adequately powered comparative studies are required to confirm the efficacy and safety of SABR for patients with HCC.

The objective of the economic evaluation in the CtE scheme was to determine whether SABR is a cost-effective intervention compared with radiofrequency ablation (RFA) and surgery for patients with resectable HCC. Despite entry criteria for the CtE scheme excluding patients whose HCC was suitable for treatment by surgery or RFA, these interventions, were considered potential alternatives to SABR if the use of SABR is expanded in the future. They were therefore, selected by the data working group as comparators. For adult patients with 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. The results are limited by the lack of a control group in the CtE data; it is likely that comparisons with data from the literature on survival and progression rates are confounded by differences in patient characteristics. A randomised trial might provide the robust data required to conclusively assess the cost-effectiveness of treatments for HCC. Finally, the programme was successfully implemented in all participating NHS Trusts, however, the centres noted the possible future need to expand the programme in order to meet demand.

11 Appendix A: Prisma flowchart

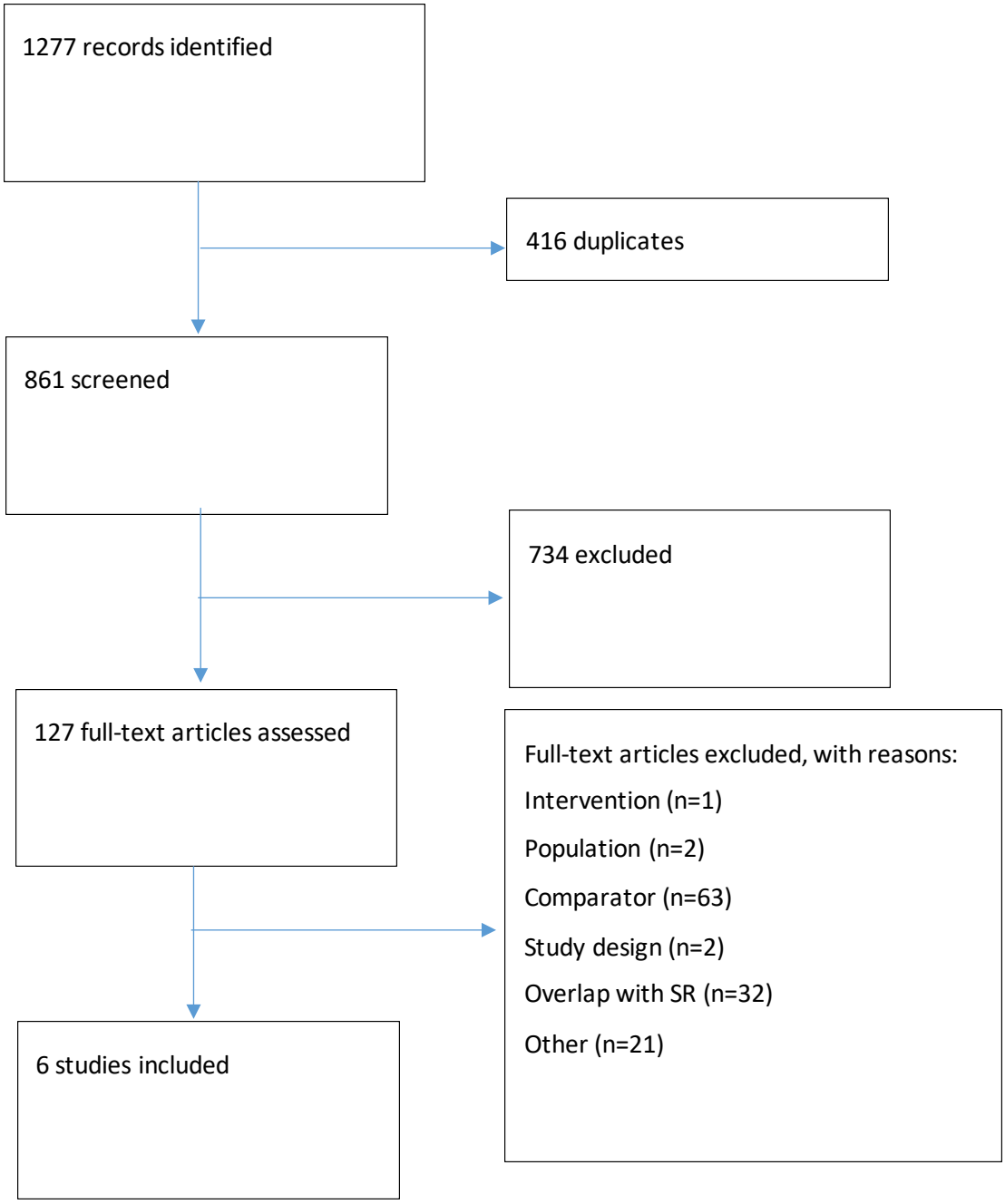


Figure 1: PRISMA table for SABR HCC literature

12 Appendix B: Search strategies

12.1 Search strategy for clinical effectiveness, quality of life, and safety

Total number of references: 1275

Total following de-duplication: 859

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 16, 2019
- 21st May 2019

1	(primary and ((hepatocellular or liver) adj3 (cancer* or carcinoma* or tumour* or mass* or growth* or lesion*))).tw.	17844
2	(Fibrolamellar adj3 (HCC or hepatocell* or carcinoma*)).tw.	558
3	Carcinoma, Hepatocellular/ or HCC.tw. or "hepatocellular carcinoma".kw.	93734
4	or/1-3	102389
5	(SABR or SBRT or SABRT or SRS or stereotactic ablati* or stereotactic body radio* or stereotactic radio*).tw.	17806
6	(arc therap* or vmat).tw.	2923
7	(hypofraction* or hypo-fraction* or hypo fraction*).tw.	3145
8	(cyber knife* or cyberknife* or gamma knife* or gammaknife*).tw.	5518
9	exp Radiosurgery/ or radiosurg*.tw.	18195
10	or/5-9	31828
11	4 and 10	537
12	limit 11 to yr="2009 -Current"	486
13	(editorial or letter or case report or comment or news).pt.	1907311
14	12 not 13	465

- Embase 1974 to 2019 Week 20
- 21st May 2019

1	(primary and ((hepatocellular or liver) adj3 (cancer* or carcinoma* or tumour* or mass* or growth* or lesion*))).tw.	26865
2	(Fibrolamellar adj3 (HCC or hepatocell* or carcinoma*)).tw.	744
3	liver cell carcinoma/ or HCC.tw. or "hepatocellular carcinoma".kw.	153610
4	or/1-3	164347
5	(SABR or SBRT or SABRT or SRS or stereotactic ablati* or stereotactic body radio* or stereotactic radio*).tw.	30875
6	(arc therap* or vmat).tw.	7757
7	(hypofraction* or hypo-fraction* or hypo fraction*).tw.	6716
8	(cyber knife* or cyberknife* or gamma knife* or gammaknife*).tw.	8591
9	gamma knife radiosurgery/ or stereotactic body radiation therapy/ or stereotactic radiosurgery/	23796
10	or/5-9	53120
11	4 and 10	1451
12	limit 11 to yr="2009 -Current"	1386
13	(editorial or letter or case report or comment or news or conference abstract or Conference Paper or Conference Review).pt.	5838065
14	12 not 13	712

- Cochrane (CDSR and CENTRAL)
- 21st May 2019

ID	Search	Hits
#1	(hepatocellular carcinoma) OR (liver NEAR/3 (cancer* OR carcinoma* OR tumour* OR mass* OR growth* OR lesion*))	7334

#2	Fibrolamellar NEAR3 (HCC or hepatocell* or carcinoma*)	7
#3	[mh "Carcinoma, Hepatocellular"] OR HCC OR "hepatocellular carcinoma":kw	3742
#4	{OR #1-#3}	7661
#5	(SABR or SBRT or SABRT or SRS or "stereotactic ablati*" or "stereotactic body radio*" or "stereotactic radio*"):ti,ab,kw	1400
#6	(arc therap* or vmat):ti,ab,kw	816
#7	(hypofraction* or hypo-fraction* or hypo fraction*):ti,ab,kw	833
#8	(cyber knife* or cyberknife* or gamma knife* or gammaknife*):ti,ab,kw	208
#9	[mh "Radiosurgery"] or radiosurg*	789
#10	{OR #5-#9}	3412
#11	#4 and #10 with Cochrane Library publication date from Jan 2009 to present	98

12.2 Search strategies for cost-effectiveness

SABR_HCC_UpdateSR

1. (hepatocellular or liver).tw.
2. (cancer or carcinoma).tw.
3. 1 and 2
4. RFA.tw.
5. radiofrequency ablation.tw.
6. surgery.tw.
7. General surgery/
8. SBRT.tw.
9. SABR.tw.
10. 4 or 5 or 6 or 7 or 8 or 9
11. Survival Analysis/ or Survival/
12. (quality of life or QoL or EQ-5D or EQ5D or utilit$).tw.
13. (cost$ or economic$).tw.
14. (pain control or pain management or toxicity or patient experience).tw.
15. 11 or 12 or 13 or 14
16. 3 and 10 and 15

17. limit 16 to english language

18. limit 17 to yr="2016 -Current"

19. remove duplicates from 18

Medline/Embase : 1291

De duplication : 1286

13Appendix C: CtE analysis plan and data forms

13.1 Statistical Analysis Plan

As per SABR Data Analysis Protocol 17/02/2016 – Version 2.2:

Statistical Analysis

The statistical analysis will address the research questions set out in section 1.2. Descriptive statistics will be presented to characterise the patient populations. This will include demographic and clinical factors.

Estimates of the rates of overall survival and progression-free survival (local control) at 1 year and 2 years following treatment with SABR will be calculated using the Kaplan-Meier method, for each of the three included indications (oligometastatic disease, re-irradiation of pelvis/spine, and hepatocellular carcinoma). A measure of the precision of each estimate will be provided by 95% confidence intervals. Kaplan-Meier graphs will be presented for key outcomes.

Survival estimates will be compared narratively with the 'target outcomes' for each condition (i.e. not using statistical tests), since the target outcomes were informed by a mixture of relevant literature and expert opinion, and therefore there is no appropriate 'sampling error' which can be attributed to these outcomes (a requirement of statistical tests).

The number and percentage of adverse events following treatment with SABR will be presented with 95% confidence intervals, for each of the three indications.

The number and percentage of patients with a positive patient experience of SABR will be presented with 95% confidence intervals, for each of the three indications. Patient experience will be assessed using a single question: "How likely are you to recommend our SABR service to friends and family if they needed similar care or treatment?"

If numbers within subgroups suffice, the results of the above analyses for Oligometastases may be stratified by location or histology.

13.2 CtE monitoring forms- clinical data – initial

Initial clinical data set	
Patient number and initials	
Date of assessment	
Age at treatment	
Primary site	
Treatment for primary	
Date of primary treatment	
Number of metastases	
Site of metastases	
Tumour marker at baseline (if appropriate) and date	
Baseline imaging modality used	
Number of previous lines of systemic therapy (including hormone therapy)	
Current systemic therapy (may be none)	
Previous radiotherapy (date, site)	
WHO performance status at baseline	0 1 2
Relevant past medical history	
Treatment technique and method of image guidance	
Also to complete:	**CTCAE** (site-specific) EQ-5D Visual analogue pain score (if appropriate) Radiotherapy planning details (site-specific)

13.3 CtE monitoring forms- clinical data – follow-up

Follow-up clinical data set	
Patient number and initials	
Date of assessment	
Months after initial treatment	
Patient alive?	Y/N Date of death: Cause of death:
Performance status	
Tumour markers (if relevant)	Date: Value:
Imaging done?	Y/N Type: Date:
Local progression?	Y/N Date:
Distant progression?	Y/N Date: Site(s):
If distant progression, amenable to further SABR?	Y/N
Details of further SABR:	Date given: Site(s) treated:
Systemic therapy status (circle appropriate):	None Change/initiation (describe + date):
Also to complete:	**CTCAE** (site-specific) EQ-5D

Follow-up clinical data set	
	Visual analogue pain score (if appropriate)

13.4 Site-specific CTCAE toxicity scores: Toxicity A

Toxicity A: cervical spine, thorax, lung, mediastinum					
Patient number and initials:			Date:		
	1	2	3	4	5
Pericarditis	Asymptomatic clinical or ECG findings	Symptomatic pericarditis	Pericarditis with physiological consequences	Life-threatening consequences	Death
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic with altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
GI haemorrhage	Mild, intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Upper GI ulcer	Asymptomatic ulcer, intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death

Toxicity A: cervical spine, thorax, lung, mediastinum					
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Fatigue	Relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Pneumonitis	Asymptomatic; clinical or	Symptomatic; medical	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory	Death

Toxicity A: cervical spine, thorax, lung, mediastinum					
	diagnostic observations only; intervention not indicated	intervention indicated; limiting instrumental ADL		compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	

13.5 Site-specific CTCAE toxicity scores: Toxicity B

Toxicity B: Upper lumbar spine, liver, adrenal, kidney, para-aortic region					
Patient number and initials:			Date:		
	1	2	3	4	5
Duodenal/ Gastric ulcer	Asymptomatic ulcer, intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic with altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
GI haemorrhage	Mild, intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Toxicity B: Upper lumbar spine, liver, adrenal, kidney, para-aortic region					
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Fatigue	Relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Fever	38.0-39.0 degrees	39.1-40.0 degrees	>40.0 degrees for <24 hours	>40.0 degrees for >24 hours	Death
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death
Liver enzymes: ALT	ULN- 3*ULN	3*ULN – 5*ULN	>5.0 - 20.0 x ULN; >5 x ULN for >2 weeks	>20 *ULN	Death
Bilirubin	ULN- 1.5* ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	

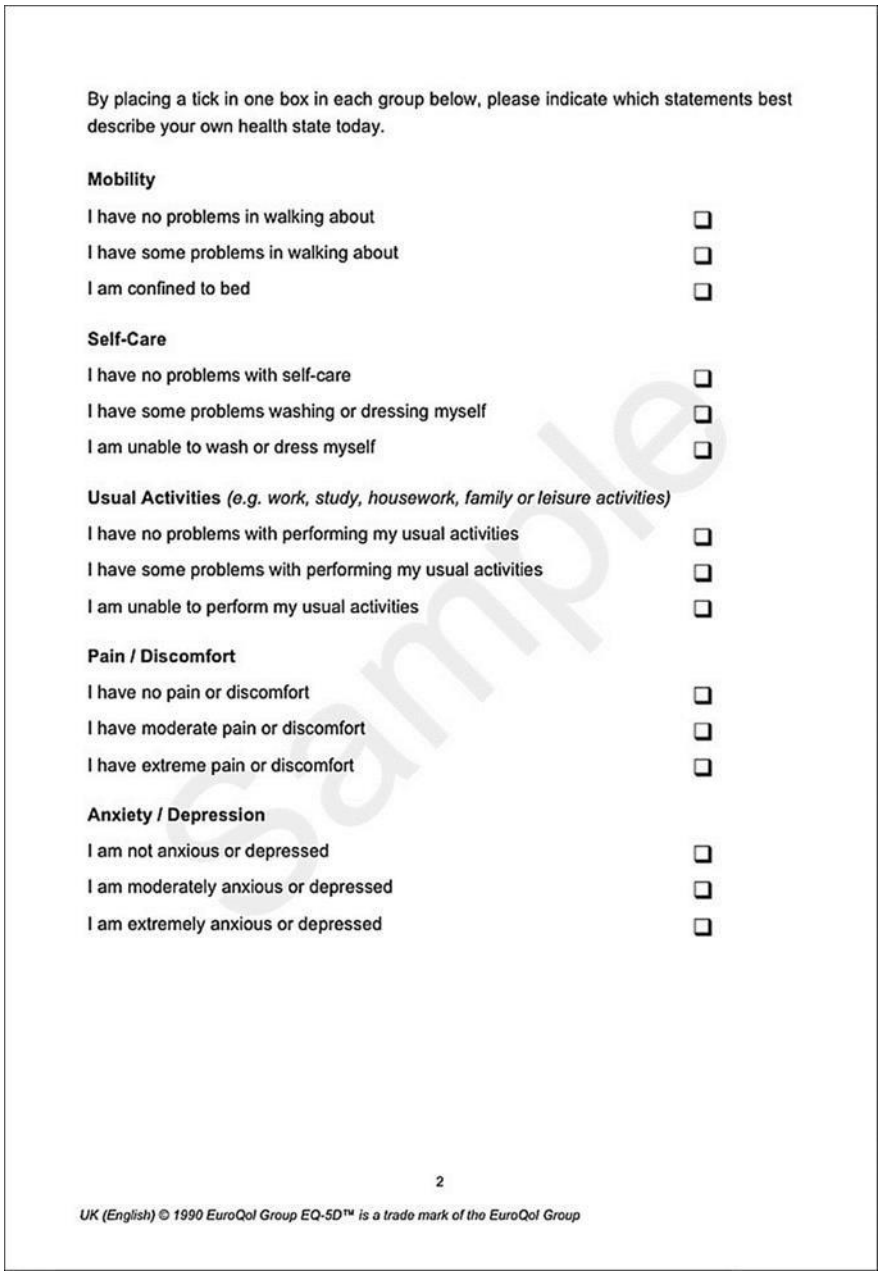
13.6 Site-specific CTCAE toxicity scores: Toxicity C

Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall					
Patient number and initials:			Date:		
	1	2	3	4	5
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Proctitis	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Rectal haemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Haematuria	Asymptomatic; clinical or	Symptomatic; urinary catheter	Gross hematuria; transfusion, IV medications or	Life-threatening consequences; urgent radiologic or operative	Death

Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall					
	diagnostic observations only; intervention not indicated	or bladder irrigation indicated; limiting instrumental ADL	hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	intervention indicated	
Urinary frequency	present	Limiting instrumental ADL; medical management indicated	-	-	-
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental	Severe back pain; hospitalization or intervention	Life-threatening consequences; symptoms associated with neurovascular	Death

Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall					
		ADL	indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	compromise	
Fatigue	Relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

13.7 EQ-5D



By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

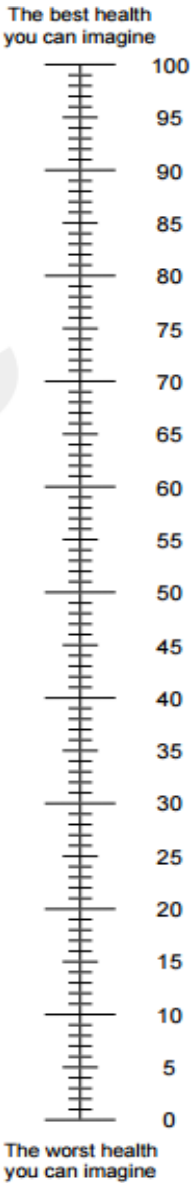
Anxiety / Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

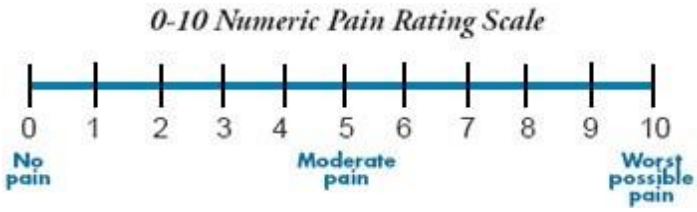
2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



13.8 Visual analogues pain score (Brief Pain Inventory)



STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

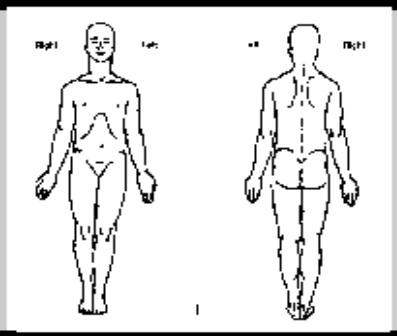
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

14 Appendix D: Data dictionary (UHB)

The following are extracts of the UHB Propel Data Dictionary as provided to KiTEC on the 11th January 2019 in MS-Excel spreadsheets. The spreadsheets consisted of: Time Points, Demographics, Clinical Assessment –Baseline, Clinical Assessment – Follow Up, CTCAE, CTCAE Defn, EQ-5D, Pain Score, Patient Experience, Radiotherapy Planning Details_1, Radiotherapy Planning Details_2, Radiotherapy Planning Details_3, and Death. Please see section 4 and Appendix C for further descriptions of the UHB data dictionary.

TIME POINTS

Forms	Baseline	4-6 Weeks	3 Months	6 Months	12 Months	18 Months	24 Months
Demographics	√						
Clinical Assessment - Baseline	√						
Clinical Assessment - Follow Up	√	√	√	√	√	√	√
EQ-5D	√	√	√	√	√	√	√
CTCAE	√	√	√	√	√	√	√
Pain Score	√	√	√	√	√	√	√
Patient experience		√					
Radiotherapy planning details (Trt 1)	√						
Radiotherapy planning details (Trt 2)	√						
Radiotherapy planning details (Trt 3)	√						
Death		√	√	√	√	√	√

DEMOGRAPHICS

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
DEM_SITE	Site	number	drop down list of sites		√	
DEM_NN	NHS Number	text (10)			√	
DEM_INIT	Initials	text			√	
DEM_DOB	Date of birth	date			√	
DEM_GENDER	Gender	numeric	1-male 2-female		√	
DEM_ETH	Ethnicity	numeric	1-White - British 2-White-Irish 3-White-Any other white background 4-Mixed-White and Black Caribbean 5-Mixed-White and Black African 6-Mixed-White and Asian 7-Mixed-Any other mixed background 8-Asian or Asian British-Indian			Standard NHS ethnicity options

			9-Asian or Asian British-Pakistani 10-Asian or Asian British-Bangladeshi 11-Asian or Asian British-Any other Asian Background 12-Black or Black British-Caribbean 13-Black or Black British-African 14-Black or Black British-Any other Black background 15-Other Ethnic Groups-Chinese 16-Other Ethnic Groups - Any other ethnic group 17-Not stated			
DEM_CF	Consent Form	document			√	Consent form
DEM_CD	Consent Date	date		__/_/_____	√	

Clinical Assessments - Baseline

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_DOA	Date of assessment	date			√	
CAB_IND	CtE Indication	numeric	1-oligomet 2-Hepatocellular carcinoma		√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			3-re-irradiation			
CAB_REIR	Re-irradiation of primary or metastasis	numeric	1-primary 2-metastases	Required if CAB_IND (CtE Indication) is 3 (Re-irradiation)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_PS	Primary site	numeric	1-H&N (include thyroid) 2-lung cancer 3-breast cancer 4-prostate cancer 5-renal cancer 6-colonic cancer 7-oesophageal cancer 8-pancreatic cancer 9-gastrointestinal stromal tumour (GIST) 10-endometrial cancer 11-cervical cancer 12-melanoma 13-sarcoma 14-germ cell tumour 15-gastric cancer 16-bladder cancer 17-rectal cancer 18-anal cancer	Required if CAN_IND (CtE Indication)<>2 (Hepatocellular carcinoma)	√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			19-upper tract (TCC) 20-penile cancer 21-ovarian cancer 22-cholangio cancer 23-vulva cancer 24-urothelial cancer 25-HCC 26-lymphoma [HIDDEN] 27-other			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_OPS	Other primary site	text		Required if CAB_PS (primary site) is 27 (other)		
CAB_PSLAT	Primary site laterality	numeric	1-left 2-right 3-bilateral 4-central	Required if CAB_PS (primary site) is 1 (H&N) or 13 (sarcoma) or 2 (lung cancer) or 3 (breast cancer) or 5 (renal cancer) or 12 (melanoma) or 14 (germ cell tumour)		
CAB_REG	Primary site region	numeric	1-C-spine /Neck 2. Thorax 3-abdomen 4-pelvis 5-Upper limbs 6-Lower limbs	Required if CAB_REIR (reirradiation...) is 1 (primary) and COB_PS (primary site) is 12 (melanoma) or 13 (sarcoma) or 14 (gem cell tumour) or 7 (oesophageal cancer) or 15 (gastric cancer) or 17 (rectal cancer) or 9 (GIST)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_CM_NO	Number of Co-morbidities	numeric	Range (0-6)		√	
	Primary treatment RFA: Radiofrequency ablation RT: Radiotherapy CRT: Chemo-radiation ADT : Androgen Deprivation Therapy Brachy: Brachytherapy HIFU: High intensity	numeric	1-surgery only 2-surgery+ systemic treatment 3-surgery+ radiotherapy 4-surgery + systemic treatment + radiotherapy 5-systemic treatment only 6-Radiotherapy only 7- Systemic Tx + Radiotherapy 8-primary RT [HIDDEN] 9-brachy 10-chemo only 11-RFA 12-ADT 13-ADT+RT 14-ADT+RT+brachy 15-active surveillance [HIDDEN] 16-cryoabalation	Required if CAB_IND (CtE Indication) is 2 (Hepatocellular carcinoma)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
	focused ultrasound Chemo: Chemotherapy		17-HIFU 18-CRT: Chemoradiation			
CAB_DOPT	Date of primary treatment	date	date	Required if CAB_IND (CtE Indication) is 2 (Hepatocellular carcinoma)		
CAB_NOM	Number of metastases	numeric		Range (1,2,3) Required if CAB_IND (CtE Indication) is 1 (oligomet)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
				or CAB_REIR (reirradiation…) is 2 (metastases)		
CAB_TOM	Type of metastases	numeric	1-Synchronous 2-Metachronous			
CAB_TTM	Time to metastases (years)	numeric				Time from initial treatment to development of metastases
CAB_SOM_1	Site of 1st metastases	numeric	1-lung 2-spine 3-bone 4-adrenal 5-renal [HIDDEN] 6-pelvic 7-liver 8-brain [HIDDEN] 9-nodes	Required if CAB_IND (CtE Indication) is 1 (oligomet) or CAB_REIR (reirradiation…) is 2 (metastases)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_SOM_1_LTYP	Type of 1st metastases	numeric	1-Unilateral 2-Bilateral	Required if CAB_SOM_1 (site of 1st metastases) is 1 (lung)		
CAB_ROM_1	Region of 1st metastases	numeric	1-C-spine/neck 2.-Thorax 3-abdomen 4-pelvis 5.-Upper limbs 6-Lower limbs	Required if CAB_SOM_1 (site of 1st metastases) is 2 (spine) or 3 (bone) or 9 (nodes)		
CAB_SOM_2	Site of 2nd metastases	numeric	1-lung 2-spine 3-bone 4-adrenal 5-renal [HIDDEN] 6-pelvic 7-liver 8-brain [HIDDEN] 9-nodes	Required if CAB_NOM(Number of metastases) is two or three		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_SOM_2_LTYP	Type of 2nd metastases	numeric	1-Unilateral 2-Bilateral	Required if CAB_SOM_2 (site of 1st metastases) is 1 (lung)		
CAB_ROM_2	Region of 2nd metastases	numeric	1-C-spine/neck 2.-Thorax 3-abdomen 4-pelvis 5- Upper limbs 6-Lower limbs	Required if CAB_SOM_2 (site of 2nd metastases) is 2 (spine) or 3 (bone) or 9 (nodes)		
CAB_SOM_3	Site of 3rd metastases	numeric	1-lung 2-spine 3-bone 4-adrenal 5-renal [HIDDEN] 6-pelvic 7-liver 8-brain [HIDDEN] 9-nodes	Required if CAB_NOM (Number of metastases) is three		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_SOM_3_LTYP	Type of 2nd metastases	numeric	1-Unilateral 2-Bilateral	Required if CAB_SOM_3 (site of 1st metastases) is 1 (lung)		
CAB_ROM_3	Region of 3rd metastases	numeric	1-C-spine/Neck 2.Thorax 3-abdomen 4-pelvis 5-Upper limbs 6-Lower limbs	Required if CAB_SOM_3 (site of 3rd metastases) is 2 (spine) or 3 (bone) or 9 (nodes)		
CAB_BPML	Biopsy proven [metastatic lesion(s)]	numeric	1-yes 2-no	Required if CAB_IND (CtE Indication) is 2 (Hepatocellular carcinoma)		
CAB_LSIZE	Size of largest lesion (cm)	numeric		Required if CAB_IND (CtE Indication) is 2 (Hepatocellular carcinoma)		
CAB_DSTG	Disease stage	numeric	1-Ia 2-Ib 3-Ic			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			4-IIa 5-IIb 6-IIc 7-IIIa 8-IIIb 9-IIIc 10-IVa 11-IVb 12-IVc			
CAB_HOPT	Histology of primary tumour	numeric	1-HPV P16 +ve 2-HPV P16 -ve 3-EGFR+, ALK- 4-EGFR+, ALK+	Required if CAB_PS (Primary site) is 1 (H&N) Required if CAB_PS (Primary site) is 1 (H&N) Required if CAB_PS(Primary site) is 2 (lung cancer) Required if CAB_PS(Primary site) is 2 (lung cancer)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			5-EGFR-, ALK+	Required if CAB_PS(Primary site) is 2 (lung cancer)		
			6-EGFR-, ALK-	Required if CAB_PS(Primary site) is 2 (lung cancer)		
			7-ER+, PR+, Her2+	Required if CAB_PS (primary site) is 3 (breast cancer)		
			8-ER+, PR-, Her2+	Required if CAB_PS (primary site) is 3 (breast cancer)		
			9-ER-, PR+, Her2+	Required if CAB_PS (primary site) is 3 (breast cancer)		
			10-ER-, PR-, Her2+	Required if CAB_PS (primary site) is 3 (breast cancer)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			11-ER-, PR-, Her2-	Required if CAB_PS (primary site) is 3 (breast cancer)		
			12-ER+, PR+, Her2-	Required if CAB_PS (primary site) is 3 (breast cancer)		
			13-Gleason Score 6 (3+3)	Required if CAB_PS (primary site) is 4 (prostate cancer)		
			14-Gleason Score 7 (3+4)	Required if CAB_PS (primary site) is 4 (prostate cancer)		
			15-Gleason Score 7 (4+3)	Required if CAB_PS (primary site) is 4 (prostate cancer)		
			16-Gleason Score 8 (4+4)	Required if CAB_PS (primary site) is 4 (prostate cancer)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			17-Gleason Score 9 (5+4)	Required if CAB_PS (primary site) is 4 (prostate cancer)		
			18-Gleason Score 10 (5+5)	Required if CAB_PS (primary site) is 4 (prostate cancer)		
			19-AdenoCa (Her 2+ve)	Required if CAB_PS (primary site) is 15 (gastric cancer) or 17 (rectal cancer)		
			20-AdenoCa (Her 2 -ve)	Required if CAB_PS (primary site) is 15 (gastric cancer) or 17 (rectal cancer)		
			21-BRAF +ve	Required if CAB_PS (primary site) is 12 (melanoma)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			22-BRAF-ve	Required if CAB_PS (primary site) is 12 (melanoma)		
			23-NSGCT	Required if CAB_PS (primary site) is 14 (germ cell tumour)		
			24- Seminoma	Required if CAB_PS (primary site) is 14 (germ cell tumour)		
			25-C-Kit+ve	Required if CAB_PS (primary site) is 9 (GIST)		
			26-C-Kit-ve	Required if CAB_PS (primary site) is 9 (GIST)		
			27-DOG1	Required if CAB_PS (primary site) is 9 (GIST)		
			28-ER+, PR-, Her2-	Required if CAB_PS (primary site) is 3 (breast cancer)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			29-ER-, PR+, Her2-	Required if CAB_PS (primary site) is 3 (breast cancer)		
			30-Gleason Score 9 (4+5)	Required if CAB_PS (primary site) is 4 (prostate cancer)		
			31-KRAS +ve	Required if CAB_PS (primary site) is 6 (colonic cancer)		
			32-KRAS -ve	Required if CAB_PS (primary site) is 6 (colonic cancer)		
CAB_HOPT_TNM	Prostate Cancer TNM staging	numeric	1-1 2-2 3-3a 4-3b 5-4	Required if CAB_PS (primary site) is 4 (prostate cancer)		
CAB_TM_1	Tumour marker_1	numeric	1-CEA	Required if CAB_PS (primary site) is 3 (breast		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
				cancer) or 8 (pancreas cancer) or 6 (colon cancer) or 17 (rectal cancer)		
			2-CA153	Required if CAB_PS (primary site) is 3 (breast cancer)		
			3-CA199	Required if CAB_PS (primary site) is 8 (pancreas cancer)		
			4-bHCG	Required if CAB_PS (primary site) is 14 (germ cell tumour)		
			5-AFP	Required if CAB_PS (primary site) is 14 (germ cell tumour)		
			6-LDH	Required if CAB_PS (primary site) is 14 (germ cell tumour)		
			7-PSA			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			8-None performed	Required if CAB_PS (primary site) is 4 (prostate cancer)		
CAB_TMV_1	Tumour marker_1 value			Required if CAB_TM_1 (Tumour marker) is completed		
CAB_TMU_1	Tumour marker_1 unit			Required if CAB_TM_1 (Tumour marker) is completed		
CAB_DOTM_1	Tumour marker_1 date	date		Required if CAB_TM_1 (Tumour marker) is completed		
CAB_TM_2	Tumour marker_2	numeric	1-CEA	Required if CAB_PS (primary site) is 3 (breast cancer) or 8 (pancreas cancer) or 6 (colon cancer) or 17 (rectal cancer)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			2-CA153	Required if CAB_PS (primary site) is 3 (breast cancer)		
			3-CA199	Required if CAB_PS (primary site) is 8 (pancreas cancer)		
			4-bHCG	Required if CAB_PS (primary site) is 14 (germ cell tumour)		
			5-AFP	Required if CAB_PS (primary site) is 14 (germ cell tumour)		
			6-LDH	Required if CAB_PS (primary site) is 14 (germ cell tumour)		
			7-PSA			
			8-None performed	Required if CAB_PS (primary site) is 4 (prostate cancer)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_TMV_2	Tumour marker_2 value			Required if CAB_TM_2 (Tumour marker) is completed		
CAB_TMU_2	Tumour marker_2 unit			Required if CAB_TM_2 (Tumour marker) is completed		
CAB_DOTM_2	Tumour marker_2 date	date		Required if CAB_TM_2 (Tumour marker) is completed		
CAB_TM_3	Tumour marker_3	numeric	1-CEA 2-CA153	Required if CAB_PS (primary site) is 3 (breast cancer) or 8 (pancreas cancer) or 6 (colon cancer) or 17 (rectal cancer) Required if CAB_PS (primary site) is 3 (breast cancer)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			3-CA199 4-bHCG 5-AFP 6-LDH 7-PSA 8-None performed	Required if CAB_PS (primary site) is 8 (pancreas cancer) Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 4 (prostate cancer)		
CAB_TMV_3	Tumour marker_3 value			Required if CAB_TM_3 (Tumour marker) is completed		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_TMU_3	Tumour marker_3 unit			Required if CAB_TM_3 (Tumour marker) is completed		
CAB_DOTM_3	Tumour marker date_3	date		Required if CAB_TM_3 (Tumour marker) is completed		
CAB_IM	Imaging modality	numeric	1-CT CAP 2-CT 3-Bone Scan 4-CT/FDG-PET 5-CT/Choline-PET 6-MRI 12-CT CAP and Bone Scan		√	
CAB_PSR	Prior systemic therapy INT	numeric	1-yes 2-no		√	
CAB_NOLPSR	Number of lines of prior	numeric		Range (0,1,2,3,4,5,6)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
	systemic review					
CAB_TOPSR	Type of prior systemic treatment	numeric	1-hormonal treatment 2-chemotherapy 3-targeted treatment 4-hormonal and chemotherapy treatment	Required if CAB_NOLPSR (Number of lines of prior systemic review) between 1 and 6 inclusive (yes)		
CAB_CST	Current systemic therapy	numeric	1-yes 2-no		√	
CAB_TOCSTT_2	Type(s) of current systemic therapy	numeric	prostate cancer(CAB_PS=4) 1-ADT 2-MAB 3-Arbiraterone 4-Enzalutamide 5-Docetaxel breast cancer(CAB_PS=3)	Required if CAB_CST (Current systemic therapy) is 1 (yes); Options restricted by values CAB_PS (Primary Site).		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			6-Tamoxifen 7-Ai-LHRH 8-Ais 9-FEC-T-heceptin 10-FEC only 11-Docetaxel-hecptin 12-Heceptin 13-Docetaxel 14-Capecitabine 15-Vinorelbine 16-Eribulin lung cancer(CAB_PS=2) 17-erlotinib 18-gefitinib 19-crizotinib 20-Gem/carbo 21-Cis/pem 22-Carbo/pem 23-Doxetaxel			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			24-Cis/Vinorelbine 25-Cis/Etope 26-Carbo/Etope bladder cancer(CAB_PS=16) 27-Gem/Cis 28-Gem/Carbo 29-Vinflunine 30-Cis/5FU 31-gemcitabine 32-mitomycin/5FU gem cell tumour(CAB_PS=14) 33-BEP 34-EP 35-TIP 36-C/BOP/BEP 37-Transplant H+N(CAB_PS=1) 38-Cis/5FU			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			39-carbo/5FU 40-Cetuximab 41-Paclitaxel 87-Radio-iodine 42-Cisplatin 43-Carboplatin 44-Cetuximab HCC(CAB_PS=25) 45-Sorafenib Lymphoma(CAB_PS=26) 46-R-CHOP Colorectal(CAB_PS=6) 47-FOLFOX 48-FOIFIRI 49-XELOXA 50-CapOX 51-Cetuximab-FOLFOX 52-Bavacizumab 53-capcitabine			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			Kidney(CAB_PS=5) 54-sunitinib 55-pazopanib 56-sorafenib Oesophagus(CAB_PS=7)/Gastric(CAB_PS=15) 57-Cis/5FU 58-ECF/ECX/EOX/EOF 59-TC 60-Cis/5FU 61-Capecitabine/Cetuximab Pancreas(CAB_PS=8) 62-Gem 63-FOLFIRINOX 64-Gem/CAP 65-Capecitabine 66-Gemcitabine endometrial(CAB_PS=10)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			67-megase 68-tamoxifen 69-Pac/carbo 70-Carbo 71-Cisplatin 72-Carboplatin Cervix(CAB_PS=11) 73-Cis/5FU 74-Pac/Carbo 75-Cisplatin Sarcoma(CAB_PS=13) 76-Antracycline based chemo 77-Trabectedin 78-Imatinib Melanoma(CAB_PS=12) 79-venumafenib 80-dabrafenib 81-Ipilimumab 82-Ipilimimab Combi			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			83-Nivolumab GIST(CAB_PS=9) 84-Imatinib 85-Sunitinib 86-regorafeni Vulva (CAB_PS=23) 88-Cis/5FU Penile (CAB_PS=20) 89-Cis/5FU 90-Cis Ovarian (CAB_PS=21) 91-Carboplatin 92-Pac/Carbo Cholangio (CAB_PS=22) 93-Gem/Cis Anal (CAB_PS=18) 94-Mitomycin/5FU 95-Cis/5FU Urothelial (CAB_PS=24)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			96-Gem/Cis 97-Gem/Carbo 98-Vinflunine 99-Cis/5FU 100-Gemcitabine 101-Mitomycin/5FU Rectal Cancer (CAB_PS=17) 102-5FU 103-Irinotecan 104-Oxaliplatin 105-Capecitabine 106-Leucovorin 107-5FU/Leucovorin/Oxaliplatin 108-Capecitabine/Oxaliplatin 109-5FU/Leucovorin 110-Capecitabine monotherapy			
CAB_CTT	Therapy to continue	numeric	1-yes 2-no	Required if CAB_CST(Current systemic therapy) is 1 (yes)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
	through treatment					
CAB_LDA	Last date of administration	date		Required if CAB_CTT (Therapy to continue through treatment) is 1 (no)		
CAB_PR	Previous radiotherapy	numeric	1-yes 2-no		v	
CAB_SOPR	Site of previous radiotherapy	numeric	1-H&N (include thyroid) 2-lung cancer 3-breast cancer 4-prostate cancer 5-renal cancer 6-colonic cancer 7-oesophageal cancer 8-pancreatic cancer	Required if CAB_PR (Previous radiotherapy) is 1 (yes)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			9-gastrointestinal stromal tumour (GIST) 10-endometrial cancer 11-cervical cancer 12-melanoma 13-sarcoma 14-germ cell tumour 15-gastric cancer 16-bladder cancer 17-rectal cancer 18-anal cancer 19-upper tract (TCC) 20-penile cancer 21-ovarian cancer 22-cholangio cancer 23-vulva cancer 24-urothelial cancer 25-HCC 26-lymphoma [HIDDEN]			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			27-other			
CAB_OSPR	Other site of previous radiotherapy	text		Required if CAB_SOPR (site of previous radiotherapy) is 27 (other) and CAB_PR (previous radiotherapy) is 1		
CAB_PR_LAT	Previous radiotherapy laterality	numeric	1-left 2-right 3-bilateral 4-central	Required if CAB_SOPR (Previous radiotherapy) is 1 (H&N (include thyroid)) or 13 (sarcoma) or 12 (melanoma) or 14 (germ cell tumour) or 5 (renal cancer) or 2 (lung cancer) or 3 (breast cancer) and CAB_PR (Previous radiotherapy) is 1 (yes)		
CAB_PR_LATDET	Previous radiotherapy laterality detail	text		Required if CAB_SOPR (Previous radiotherapy) is 1 (H&N (include thyroid)) or		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
				13 (sarcoma) or 12 (melanoma) or 14 (germ cell tumour) or 5 (renal cancer) or 2 (lung cancer) or 3 (breast cancer) and CAB_PR (Previous radiotherapy) is 1 (yes)		
CAB_FOPTF	Fractionation of previous RT: Fractions	numeric		Required if CAB_PR (Previous radiotherapy) is 1 (yes); Range (1-100)		
CAB_FOPTD	Fractionation of previous RT: Dose	numeric		Required if CAB_PR (Previous radiotherapy) is 1 (yes); Range (1-100)		
CAB_DOCPR	Date of completion of previous radiotherapy	date		Required if CAB_PR (Previous radiotherapy) is 1 (yes)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_WHO_PST	WHO performance status	numeric	0-Fully active, able to carry on all pre-disease performance without restriction 1-Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work 2-Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours		√	
CAB_SABR_TRTS	How many SABR treatments were done	numeric	Range (1-3)		√	
CAB_TRTDTE_1	Start date of first SABR treatment	date			√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_COMPDTE_1	Completion date of first SABR treatment	date			√	
CAF_TRTAREA_1	First SABR treatment area	date			√	
CAB_TRT_1	Platform for first SABR treatment	numeric	1-Elekta 2-Varian 3-Cyberknife 4-Tomotherapy		√	
CAB_IGRT_TECH_1	IGRT technique for first SABR treatment	numeric	1-CBCT (soft tissue) 2-CBCT (fiducial)	Required if CAB_TRT (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAB_TRT (Treatment option) is 1 (Elekta) or 2 (Varian)	√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			3-kV planar (fiducial) 4-kV planar (spine) 5-kV planar (cranial) 6-kV planar (lung) 7-MVCT	Required if CAB_TRT (Treatment option) is 3 (Cyberknife) Required if CAB_TRT (Treatment option) is 3 (Cyberknife) Required if CAB_TRT (Treatment option) is 3 (Cyberknife) Required if CAB_TRT (Treatment option) is 3 (Cyberknife) Required if CAB_TRT (Treatment option) is 4 (Tomotherapy)		
CAB_IDF_SBRT_1	Intended dose fractionation for first SBRT treatment	text			√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_PDOSE_1	Prescribed dose for first SABR treatment	numeric			√	
CAB_NFRAC_1	Number of fractions for first SABR treatment	numeric			√	
CAB_RSENSI_1	Radiosensitivity (a/b) for first SABR treatment			User to add 0 if the input in N/A	√	
CAB_BED_1	Biological effective dose (100Gy as cutoff) for first SABR treatment	numeric		User to add 0 if the input in N/A	√	BED=nd[1+(d/(a/b))] where n is CAB_PDOSE (Prescribed dose) and d is CAB_NFRAC (Number of fractions)

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_TRTDTE_2	Start date of second SABR treatment	text				
CAB_COMPDTE_2	Completion date of second SABR treatment	date				
CAB_TRTAREA_2	Second SABR treatment area	date				
CAB_TRT_2	Platform for second SABR treatment	numeric	1-Elekta 2-Varian 3-Cyberknife 4-Tomotherapy			
CAB_IGRT_TECH_2	IGRT technique for second SABR treatment	numeric	1-CBCT (soft tissue)	Required if CAB_TRT (Treatment option) is 1 (Elekta) or 2 (Varian)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			2-CBCT (fiducial)	Required if CAB_TRT (Treatment option) is 1 (Elekta) or 2 (Varian)		
			3-kV planar (fiducial)	Required if CAB_TRT (Treatment option) is 3 (Cyberknife)		
			4-kV planar (spine)	Required if CAB_TRT (Treatment option) is 3 (Cyberknife)		
			5-kV planar (cranial)	Required if CAB_TRT (Treatment option) is 3 (Cyberknife)		
			6-kV planar (lung)	Required if CAB_TRT (Treatment option) is 3 (Cyberknife)		
			7-MVCT	Required if CAB_TRT (Treatment option) is 4 (Tomotherapy)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_IDF_SBRT_2	Intended dose fractionation for second SBRT treatment	text				
CAB_PDOSE_2	Prescribed dose for second SABR treatment	numeric				
CAB_NFRAC_2	Number of fractions for second SABR treatment	numeric				
CAB_RSENSI_2	Radiosensitivity (a/b) for second SABR treatment					

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_BED_2	Biological effective dose (100Gy as cutoff) for second SABR treatment	numeric				BED=nd[1+(d/(a/b))] where n is CAB_PDOSE (Prescribed dose) and d is CAB_NFRAC (Number of fractions)
CAB_TRTDTE_3	Start date of third SABR treatment	text				
CAB_COMPDTE_3	Completion date of third SABR treatment	date				
CAB_TRTAREA_3	Third SABR treatment area	date				
CAB_TRT_3	Platform for third SABR treatment	numeric	1-Elekta 2-Varian			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			3-Cyberknife 4-Tomotherapy			
CAB_IGRT_TECH_3	IGRT technique for third SABR treatment	numeric	1-CBCT (soft tissue) 2-CBCT (fiducial) 3-kV planar (fiducial) 4-kV planar (spine) 5-kV planar (cranial)	Required if CAB_TRT (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAB_TRT (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAB_TRT (Treatment option) is 3 (Cyberknife) Required if CAB_TRT (Treatment option) is 3 (Cyberknife) Required if CAB_TRT (Treatment option) is 3 (Cyberknife)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			6-kV planar (lung) 7-MVCT	Required if CAB_TRT (Treatment option) is 3 (Cyberknife) Required if CAB_TRT (Treatment option) is 4 (Tomotherapy)		
CAB_IDF_SBRT_3	Intended dose fractionation for third SBRT treatment	text				
CAB_PDOSE_3	Prescribed dose for third SABR treatment	numeric				
CAB_NFRAC_3	Number of fractions for third SABR treatment	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_RSENSI_3	Radiosensitivity (a/b) for third SABR treatment					
CAB_BED_3	Biological effective dose (100Gy as cutoff) for third SABR treatment	numeric				BED=nd[1+(d/(a/b))] where n is CAB_PDOSE (Prescribed dose) and d is CAB_NFRAC (Number of fractions)

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_DOA	Date of assessment	date			√		
CAF_WHO_ST	WHO performance status	numeric	1-Fully active, able to carry on all pre-disease performance without restriction 2-Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work 3-Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours 4-Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours		√		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			5-Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair				
CAF_TM_1	Tumour marker_1	numeric	1-CEA 2-CA153 3-CA199 4-bHCG	Required if CAB_PS (primary site) is 3 (breast cancer) or 8 (pancreas cancer) or 6 (colon cancer) Required if CAB_PS (primary site) is 3 (breast cancer) Required if CAB_PS (primary site) is 8 (pancreas cancer) Required if CAB_PS (primary site) is 14 (germ cell tumour)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			5-AFP	Required if CAB_PS (primary site) is 14 (germ cell tumour)			
			6-LDH	Required if CAB_PS (primary site) is 14 (germ cell tumour)			
			7-PSA	Required if CAB_PS (primary site) is 4 (prostate cancer)			
CAF_TMV_1	Tumour marker_1 value			Required if CAF_TM_1 (Tumour marker) is completed			
CAF_TMU_1	Tumour marker_1 unit			Required if CAF_TM_1 (Tumour marker) is completed			
CAF_DOTM_1	Tumour marker_1 date	date		Required if CAF_TM_1 (Tumour marker) is completed			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_TM_2	Tumour marker_2	numeric	1-CEA 2-CA153 3-CA199 4-bHCG 5-AFP	Required if CAB_PS (primary site) is 3 (breast cancer) or 8 (pancreas cancer) or 6 (colon cancer) Required if CAB_PS (primary site) is 3 (breast cancer) Required if CAB_PS (primary site) is 8 (pancreas cancer) Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 14 (germ cell tumour)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			6-LDH 7-PSA	Required if CAB_PS (primary site) is 14 (germ cell tumour) Required if CAB_PS (primary site) is 4 (prostate cancer)			
CAF_DOTM_2	Tumour marker_2 date	date		Required if CAF_TM_2 (Tumour marker) is completed			
CAF_TMV_2	Tumour marker_2 value			Required if CAF_TM_2 (Tumour marker) is completed			
CAG_TMU_2	Tumour marker_2 unit			Required if CAF_TM_2 (Tumour marker) is completed			
CAF_TM_3	Tumour marker_3	numeric	1-CEA	Required if CAB_PS (primary site) is 3 (breast cancer) or 8			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
				(pancreas cancer) or 6 (colon cancer)			
			2-CA153	Required if CAB_PS (primary site) is 3 (breast cancer)			
			3-CA199	Required if CAB_PS (primary site) is 8 (pancreas cancer)			
			4-bHCG	Required if CAB_PS (primary site) is 14 (germ cell tumour)			
			5-AFP	Required if CAB_PS (primary site) is 14 (germ cell tumour)			
			6-LDH	Required if CAB_PS (primary site) is 14 (germ cell tumour)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			7-PSA	Required if CAB_PS (primary site) is 4 (prostate cancer)			
CAF_TMV_3	Tumour marker_3 value			Required if CAF_TM_3 (Tumour marker) is completed			
CAG_TMU_3	Tumour marker_3 unit			Required if CAF_TM_3 (Tumour marker) is completed			
CAF_DOTM_3	Tumour marker_3 date	date		Required if CAF_TM_3 (Tumour marker) is completed			
CAF_ITR	Is there imaging to interpret	numeric	1-yes 2-no		√		
CAF_NOI	How many imaging modality	numeric		Required if CAF_ITR(Imaging to report) is 1 (yes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_TOIR	Type of imaging to report	numeric	1-CT CAP 2-CT 3-Bone Scan 4-CT/FDG-PET 5-CT/Choline-PET 6-MRI Pelvis 7-Whole Body MRI 8-Whole Body fMRI 9-MRI spine 10-MRI liver 11-MRI soft tissue 12-other	Required if CAF_ITR(Imaging to report) is 1 (yes)			
CAF_OTIR	Other type of imaging to report	text		Required if CAF_TOIR (Type of imaging to report) is 12 (Other) and CAF_ITR(Imaging to report) is 1 (yes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_DOI	Date of image (s)	date		Required if CAF_ITR(Imaging to report) is 1 (yes)	√		?Is the Mandatory field conditional or unconditional on CAF_ITR (Line40)
CAF_ADIMG	Additional imaging to be done	numeric	1-yes 2-no	Required if CAF_ITR(Imaging to report) is 1 (yes)			
CAF_ADTOIR	Type of additional imaging to report	numeric	1-CT CAP 2-CT 3-Bone Scan 4-CT/FDG-PET 5-CT/Choline-PET 6-MRI Pelvis	Required if CAF_ADIMG(Imaging to report) is 1 (yes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			7-Whole Body MRI 8-Whole Body fMRI 9-MRI spine 10-MRI liver 11-MRI soft tissue 12-other				
CAF_ADOTIR	Other type of imaging to report	text		Required if CAF_ADTOIR (Type of imaging to report) is 12 (Other) and CAF_ITR(Imaging to report) is 1 (yes)			
CAF_LP_TRTDTE_1	Start date of first treatment at baseline	date				Cannot be modified. This is read from the baseline form.	
CAF_LP_COMPDTE_1	Completion date of first	date				Cannot be modified.	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
	treatment at baseline					This is read from the baseline form.	
CAF_LP_TRTAREA_1	First treated area at baseline	text				Cannot be modified. This is read from the baseline form.	
CAF_LP_STATUS_1	Is the first treated area at baseline stable/reduced in size/disappeared	numeric	1-yes (local control) 2-uncertain/equivocal (either discuss at MDT and consider requesting complementary imaging - e.g. PET to	Required if CAF_ITR(Imaging to report) is 1 (yes)	√		?Is the Mandatory field conditional or unconditional on CAF_ITR(Line)

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			clarify- or repeat the same image sequence in 3 months) 3-no (in field progression)				
CAF_LP_MS_1	Is there any evidence of metastatic disease in the first organ treated at baseline or next echelon lymph nodes	numeric	1-yes (loco-regional progression) 2-no	Required if CAF_ITR(Imaging to report) is 1 (yes)	√		?Is the Mandatory field conditional or unconditional on CAF_ITR(Line)
CAF_LP_TRTDTE_2	Start date of second treatment at baseline	date				Cannot be modified. This is read from the baseline form.	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_LP_COMPDTE_2	Completion date of second treatment at baseline	date				Cannot be modified. This is read from the baseline form.	
CAF_LP_TRTAREA_2	Second treated area at baseline	text				Cannot be modified. This is read from the baseline form.	
CAF_LP_STATUS_2	Is the second treated area at baseline stable/reduced in size/disappeared	numeric	1-yes (local control)	Required if CAF_ITR(Imaging to report) is 1 (yes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			2-uncertain/equivocal (either discuss at MDT and consider requesting complementary imaging - e.g. PET to clarify- or repeat the same image sequence in 3 months) 3-no (in field progression)				
CAF_LP_MS_2	Is there any evidence of metastatic disease in the second organ treated at baseline or next echelon lymph nodes	numeric	1-yes (loco-regional progression) 2-no	Required if CAF_ITR(Imaging to report) is 1 (yes)			
CAF_LP_TRTDTE_3	Start date of third treatment at baseline	date				Cannot be modified. This is read	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
						from the baseline form.	
CAF_LP_COMPDTE_3	Completion date of third treatment at baseline	date				Cannot be modified. This is read from the baseline form.	
CAF_LP_TRTAREA_3	Third treated area	text				Cannot be modified. This is read from the baseline form.	
CAF_LP_STATUS_3	Is the third treated area stable/reduced	numeric	1-yes (local control)	Required if CAF_ITR(Imaging to report) is 1 (yes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
	in size/disappeared		2-uncertain/equivocal (either discuss at MDT and consider requesting complementary imaging - e.g. PET to clarify- or repeat the same image sequence in 3 months) 3-no (in field progression)				
CAF_LP_MS_3	Is there any evidence of metastatic disease in the third organ treated or next echelon lymph nodes	numeric	1-yes (loco-regional progression) 2-no	Required if CAF_ITR(Imaging to report) is 1 (yes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_DP_STATUS	Is there any evidence of metastatic disease in other organs	numeric	1-yes (distant progression - metastatic disease) 2-no	Required if CAF_ITR(Imaging to report) is 1 (yes)	√		?Is the Mandatory field conditional or unconditional on CAF_ITR(Line40)
CAF_DP_OP	Are there less than 3 areas of new disease	numeric	1-yes (oligometastatic progression) 2-no	Required if CAF_ITR(Imaging to report) is 1 (yes)			
CAF_PROG_SABR	Progression amenable to further SABR	numeric	1-yes 2-no	Required if CAF_LP_STATUS_(1,2,3), CAF_LP_MS_(1,2,3) (Local progression), CAF_DP_STATUS or CAF_DP_OP (Distant progression) is 1 (yes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_FUTH_SABR	Number of sites for further SABR treatment	numeric	Range(0,1,2,3)		√		
CAF_ST_1	Site of 1st metastases treated	numeric	1-lung 2-spine 3-bone 4-adrenal 5-renal [Hidden] 6-pelvic 7-liver 8-brain [Hidden] 9-nodes	Required if CAF_FUTH_SABR(Details of further SABR treatment) is 1			
CAF_TYP_1	Type of 1st metastases	numeric	1-Unilateral 2-Bilateral	Required if CAF_ST_1 (site of 1st metastases) is 1 (lung)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_ROM_1	Region of 1st metastases	numeric	1-C spine/Neck 2-Thorax 3-Abdomen 4-Pelvis 5-Upper limbs 6-Lower limbs	Required if CAF_ST_1 (site of 1st metastases) is 2 (spine) or 3 (bone) or 9 (nodes)			
CAF_ST_2	Site of 2nd metastases treated	numeric	1-lung 2-spine 3-bone 4-adrenal 5-renal 6-pelvic 7-liver	Required if CAF_FUTH_SABR(Details of further SABR treatment) is 2			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			8-brain 9-nodes				
CAF_TYP_2	Type of 2nd metastases	numeric	1-Unilateral 2-Bilateral	Required if CAB_ST_2 (site of 2nd metastases) is 1 (lung)			
CAF_ROM_2	Region of 2nd metastases	numeric	1-C spine/Neck 2-Thorax 3-Abdomen 4-Pelvis 5-Upper limbs 6-Lower limbs	Required if CAB_ST_2 (site of 2nd metastases) is 2 (spine) or 3 (bone) or 9 (nodes)			
CAF_ST_3	Site of 3rd metastases treated	numeric	1-lung	Required if CAF_FUTH_SABR(Details of further SABR treatment) is 3			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			2-spine 3-bone 4-adrenal 5-renal 6-pelvic 7-liver 8-brain 9-nodes				
CAF_TYP_3	Type of 3rd metastases	numeric	1-Unilateral 2-Bilateral	Required if CAB_ST_3 (site of 3rd metastases) is 1 (lung)			
CAF_ROM_3	Region of 3rd metastases	numeric	1-C spine/Neck 2-Thorax 3-Abdomen 4-Pelvis 5-Upper limbs 6-Lower limbs	Required if CAB_ST_3 (site of 3rd metastases) is 2 (spine) or 3 (bone) or 9 (nodes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_FSABR_TRTS	Number of further SABR treatments	numeric		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_TRTDTE_1	Start date of first further SABR treatment	date		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_COMPDTE_1	Completion date of first further SABR treatment	date		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_TRTAREA_1	Treatment area for first further SABR treatment	date		Required if CAF_FUTH_SABR(Details of further SABR			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
				treatment) is larger than 0			
CAF_TRT_1	Platform for first further SABR treatment	numeric	1-Elekta 2-Varian 3-Cyberknife 4-Tomotherapy	Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_IGRT_TECH_1	IGRT technique for first further SABR treatment	numeric	1-CBCT (soft tissue) 2-CBCT (fiducial) 3-kV planar (fiducial)	Required if CAF_TRT_1 (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAF_TRT_1 (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAF_TRT_1 (Treatment option) is 3 (Cyberknife)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			4-kV planar (spine) 5-kV planar (cranial) 6-kV planar (lung) 7-MVCT	Required if CAF_TRT_1 (Treatment option) is 3 (Cyberknife) Required if CAF_TRT_1 (Treatment option) is 3 (Cyberknife) Required if CAF_TRT_1 (Treatment option) is 3 (Cyberknife) Required if CAF_TRT_1 (Treatment option) is 4 (Tomotherapy)			
CAF_IDF_SBRT_1	Intended dose fractionation for first further SBRT treatment	text		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_PDOSE_1	Prescribed dose for first further SABR treatment	numeric		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_NFRAC_1	Number of fractions for first further SABR treatment	numeric		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_RSENSI_1	Radiosensitivity (a/b) for first further SABR treatment			Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_BED_1	Biological effective dose (100Gy as cutoff)	numeric		Required if CAF_FUTH_SABR(Details of further SABR		BED=nd[1+(d/(a/b))] where n is CAF_PDOS	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
	for first further SABR treatment			treatment) is larger than 0		E_1 (Prescribed dose) and d is CAF_NFRAC_1 (Number of fractions)	
CAF_TRTDTE_2	Start date of second further SABR treatment	date					
CAF_COMPDTE_2	Completion date of second further SABR treatment	date		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_TRTAREA_2	Treatment area for second	text					

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
	further SABR treatment						
CAF_TRT_2	Platform for second further SABR treatment	numeric	1-Elekta 2-Varian 3-Cyberknife 4-Tomotherapy				
CAF_IGRT_TECH_2	IGRT technique for second further SABR treatment	numeric	1-CBCT (soft tissue) 2-CBCT (fiducial) 3-kV planar (fiducial) 4-kV planar (spine)	Required if CAF_TRT_2 (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAF_TRT_2 (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAF_TRT_2 (Treatment option) is 3 (Cyberknife) Required if CAF_TRT_2 (Treatment option) is 3 (Cyberknife)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			5-kV planar (cranial) 6-kV planar (lung) 7-MVCT	Required if CAF_TRT_2 (Treatment option) is 3 (Cyberknife) Required if CAF_TRT_2 (Treatment option) is 3 (Cyberknife) Required if CAF_TRT_2 (Treatment option) is 4 (Tomotherapy)			
CAF_IDF_SBRT_2	Intended dose fractionation for second further SBRT treatment	text					
CAF_PDOSE_2	Prescribed dose for second further SABR treatment	numeric					
CAF_NFRAC_2	Number of fractions for	numeric					

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
	second further SABR treatment						
CAF_RSENSI_2	Radiosensitivity (a/b) for second further SABR treatment						
CAF_BED_2	Biological effective dose (100Gy as cutoff) for second further SABR treatment	numeric				BED=nd[1+(d/(a/b))] where n is CAF_PDOSE_2 (Prescribed dose) and d is CAF_NFRAC_2 (Number of fractions)	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_TRTDTE_3	Start date of third further SABR treatment	date					
CAF_COMPDTE_3	Completion date of third further SABR treatment	date		Required if CAF_FUTH_SABR(Details of further SABR treatment) is larger than 0			
CAF_TRTAREA_3	Treatment area for third further SABR treatment	text					
CAF_TRT_3	Platform for third further SABR treatment	numeric	1-Elekta 2-Varian 3-Cyberknife 4-Tomotherapy				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_IGRT_TECH_3	IGRT technique for third further SABR treatment	numeric	1-CBCT (soft tissue)	Required if CAF_TRT_3 (Treatment option) is 1 (Elekta) or 2 (Varian)			
			2-CBCT (fiducial)	Required if CAF_TRT_3 (Treatment option) is 1 (Elekta) or 2 (Varian)			
			3-kV planar (fiducial)	Required if CAF_TRT_3 (Treatment option) is 3 (Cyberknife)			
			4-kV planar (spine)	Required if CAF_TRT_3 (Treatment option) is 3 (Cyberknife)			
			5-kV planar (cranial)	Required if CAF_TRT_3 (Treatment option) is 3 (Cyberknife)			
			6-kV planar (lung)	Required if CAF_TRT_3 (Treatment option) is 3 (Cyberknife)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			7-MVCT	Required if CAF_TRT_3 (Treatment option) is 4 (Tomotherapy)			
CAF_IDF_SBRT_3	Intended dose fractionation for third further SBRT treatment	text					
CAF_PDOSE_3	Prescribed dose for third further SABR treatment	numeric					
CAF_NFRAC_3	Number of fractions for third further SABR treatment	numeric					
CAF_RSENSI_3	Radiosensitivity (a/b) for third further SABR treatment						

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_BED_3	Biological effective dose (100Gy as cutoff) for third further SABR treatment	numeric				BED=nd[1+(d/(a/b))] where n is CAF_PDOSE_3 (Prescribed dose) and d is CAF_NFRAC_3 (Number of fractions)	
CAF_CST	Has there been a change in systemic therapy since last assessment	numeric	1-yes 2-no		√		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_CST_WHT	What change has there been	numeric	1-re-start 2-stop 3-change	Required if CAF_CST (Has there been a change in...) is 1 (yes)			
CAF_TCSTT	Type(s) of current systemic therapy	numeric	prostate cancer(CAB_PS=4) 1-ADT 2-MAB 3-Arbiraterone 4-Enzalutamide 5-Docetaxel breast cancer(CAB_PS=3) 6-Tamoxifen 7-Ai-LHRH 8-Ais 9-FEC-T-heceptin 10-FEC only	Required if CAF_CST_WHT (What change...) is 1 (start) or 3 (change); Options restricted by values in CAB_PS (Primary Site)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			11-Docetaxel-hecptin 12-Heceptin 13-Docetaxel 14-Capecitabine 15-Vinorelbine 16-Eribulin lung cancer(CAB_PS=2) 17-erlotinib 18-gefitinib 19-crizotinib 20-Gem/carbo 21-Cis/pem 22-Carbo/pem 23-Doxetaxel 24-Cis/Vinorelbine 25-Cis/Etope 26-Carbo/Etope bladder cancer(CAB_PS=16) 27-Gem/Cis				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			28-Gem/Carbo 29-Vinflunine 30-Cis/5FU 31-gemcitabine 32-mitomycin/5FU gem cell tumour(CAB_PS=14) 33-BEP 34-EP 35-TIP 36-C/BOP/BEP 37-Transplant H+N(CAB_PS=1) 38-Cis/5FU 39-carbo/5FU 40-Cetuximab 41-Paclitaxel 87-Radio-iodine 42-Cisplatin 43-Carboplatin				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			44-Cetuximab HCC(CAB_PS=25) 45-Sorafenib Lymphoma(CAB_PS=26) 46-R-CHOP Colorectal(CAB_PS=6) 47-FOLFOX 48-FOIFIRI 49-XELOXA 50-CapOX 51-Cetuximab-FOLFOX 52-Bavacizumab 53-capcitabine Kidney(CAB_PS=5) 54-sunitinib 55-pazopanib 56-sorafenib Oesophagus(CAB_PS=7)/Gastric(CAB_PS=15)				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			57-Cis/5FU 58-ECF/ECX/EOX/EOF 59-TC 60-Cis/5FU 61-Capecitabine/Cetuximab Pancreas(CAB_PS=8) 62-Gem 63-FOLFIRINOX 64-Gem/CAP 65-Capecitabine 66-Gemcitabine endometrial(CAB_PS=10) 67-megase 68-tamoxifen endometrial(CAB_PS=10) 69-Pac/carbo 70-Carbo 71-Cisplatin 72-Carboplatin				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			Cervix(CAB_PS=11) 73-Cis/5FU 74-Pac/Carbo 75-Cisplatin Sarcoma(CAB_PS=13) 76-Antracycline based chemo 77-Trabectedin 78-Imatinib Melanoma(CAB_PS=12) 79-venumafenib 80-dabrafenib 81-Ipilimumab 82-Ipilimimab Combi 83-Nivolumab GIST(CAB_PS=9) 84-Imatinib 85-Sunitinib 86-regorafeni Vulva (CAB_PS=23)				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			88-Cis/5FU Penile (CAB_PS=20) 89-Cis/5FU 90-Cis Ovarian (21) 91-Carboplatin 92-Pac/Carbo Cholangio (22) 93-Gem/Cis Anal (18) 94-Mitomycin/5FU 95-Cis/5FU Urothelial (CAB_PS=24) 96-Gem/Cis 97-Gem/Carbo 98-Vinflunine 99-Cis/5FU 100-Gemcitabine 101-Mitomycin/5FU				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			Rectal Cancer (CAB_PS=17) 102-5FU 103-Irinotecan 104-Oxaliplatin 105-Capecitabine 106-Leucovorin 107-5FU/Leucovorin/Oxaliplatin 108-Capecitabine/Oxaliplatin 109-5FU/Leucovorin 110-Capecitabine monotherapy				
CAF_DOCIST	Date of change/initiation of new therapy	date		Required if CAF_CST (Current systemic therapy) is 1 'yes'			

CTCAE

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_ANY	Any toxicities?	numeric	1 - Yes 2-No		√	
CTCAE_TD	Toxicity date	date		Required if CTCAE_ANY (Any toxicities)=1 (yes)		
CTCAE_TS_1	Toxicity site 1	numeric	1-Toxicity A: cervical spine, thorax, lung, mediastinum 2-Toxicity B: Upper lumbar spine, liver, adrenal, kidney, para-aortic 3-Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall	Required if CTCAE_ANY (Any toxicities)=1 (yes)		
CTCAE_TS_2	Toxicity site 2	numeric	1-Toxicity A: cervical spine, thorax, lung, mediastinum 2-Toxicity B: Upper lumbar spine, liver, adrenal, kidney, para-aortic 3-Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall	Required if CTCAE_ANY (Any toxicities)=1 (yes)		
CTCAE_TS_3	Toxicity site 3	numeric	1-Toxicity A: cervical spine, thorax, lung, mediastinum	Required if CTCAE_ANY (Any toxicities)=1 (yes)		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
			2-Toxicity B: Upper lumbar spine, liver, adrenal, kidney, para-aortic 3-Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall			
CTCAE_PERI	Pericarditis	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1		Grades definitions are on CTCAE-Defn tab
CTCAE_DYSP	Dysphagia	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 2		
CTCAE_GIHA	GI haemorrhage	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 2		
CTCAE_GAST	Gastritis	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 2		
CTCAE_UGIU	Upper GI Ulcer	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_NAUS	Nausea	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 2		
CTCAE_VOMI	Vomiting	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1		
CTCAE_FATI	Fatigue	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 2 or 3		
CTCAE_SFRA	Spinal fracture	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 2 or 3		
CTCAE_MYEL	Myelitis	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1 or 3		
CTCAE_COUG	Cough	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_PNEU	Pneumonitis	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1		
CTCAE_DGUL	Duodenal/Gastric ulcer	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=2		
CTCAE_FEVE	Fever	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=2		
CTCAE_LALT	Liver enzymes : ALT	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=2		
CTCAE_BILI	Bilirubin	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=2		
CTCAE_DIAR	Diarrhoea	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_PROC	Proctitis	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		
CTCAE_RHAE	Rectal Haemorrhage	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		
CTCAE_HAEM	Haematuria	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		
CTCAE_UFRE	Urinary frequency	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		
CTCAE_UINC	Urinary incontinence	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		
CTCAE_URET	Urinary retention	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_UURG	Urinary urgency	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=3		
CTCAE_ULCE	Ulcer	numeric	Grade (1-6)			CTCAE grade definition depends on type of Ulcer
CTCAE_ULCE_LOC	Ulcer location	text		Required if CTCAE_ULCE_LOC (Ulcer) is larger than 0		
CTCAE_FIST	Fistula	numeric	Grade (1-6)			CTCAE grade definition depends on type of Fistula
CTCAE_FIST_LOC	Fistula location	text		Required if CTCAE_FIST_LOC (Fistula) is larger than 0		
CTCAE_PERF	Perforation	numeric	Grade (1-6)			CTCAE grade definition depends on type of Perforation

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_PERF_LOC	Perforation location	text		Required if CTCAE_PERF_LOC (Perforation) is larger than 0		
CTCAE_BPAI	Bone pain	numeric	Grade (1-6)			
CTCAE_BPAI_LOC	Bone pain location	text		Required if CTCAE_BPAI_LOC (Bone pain) is larger than 0		
CTCAE_FRAC	Fracture	numeric	Grade (1-6)			
CTCAE_FRAC_LOC	Fracture location	text		Required if CTCAE_FRAC_LOC (Fracture) is larger than 0		

CTCAE Definitions (XXXXXXXXX)

Note: Grade 0 not applicable.

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
1	PERI	Pericarditis	Asymptomatic clinical or ECG findings	Symptomatic pericarditis	Pericarditis with physiological consequences	Life-threatening consequences	Death	No Toxicities
1,2	DYSP	Dysphagia	Symptomatic, able to eat regular diet	Symptomatic with altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities
1,2	GIHA	GI haemorrhage	Mild, intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
1,2	GAST	Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death	No Toxicities
1	UGIU	Upper GI ulcer	Asymptomatic ulcer, intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death	No Toxicities
1,2	NAUS	Nausea		Oral intake decreased without	Inadequate oral caloric or fluid	-	-	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
			Loss of appetite without alteration in eating habits	significant weight loss, dehydration or malnutrition	intake; tube feeding, TPN, or hospitalization indicated			
1	VOMI	Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities
1,2,3	FATI	Fatigue	Relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-	No Toxicities
1,2,3	SFRA	Spinal fracture	Mild back pain; nonprescription analgesics	Moderate back pain; prescription analgesics	Severe back pain; hospitalization or intervention	Life-threatening consequences; symptoms	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
			indicated	indicated; limiting instrumental ADL	indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	associated with neurovascular compromise		
1,3	MYEL	Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities
1	COUG	Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	No Toxicities
1	PNEU	Pneumonitis	Asymptomatic; clinical or	Symptomatic; medical	Severe symptoms; limiting self	Life-threatening respiratory	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
			diagnostic observations only; intervention not indicated	intervention indicated; limiting instrumental ADL	care ADL; oxygen indicated	compromise; urgent intervention indicated (e.g., tracheotomy or intubation)		
2	DGUL	Duodenal/ Gastric ulcer	Asymptomatic ulcer, intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic	Life-threatening consequences; urgent operative intervention	Death	No Toxicities
					intervention indicated; limiting self care ADL; disabling	indicated		
2	FEVE	Fever	38.0-39.0 degrees	39.1-40.0	>40.0 degrees for <24 hours	>40.0 degrees for >24 hours	Death	No Toxicities
2	LALT	Liver enzymes: ALT	ULN- 3*ULN	3*ULN – 5*ULN	>5.0 - 20.0 x ULN; >5 x ULN	>20 *ULN	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
					for >2 weeks			
2	BILI	Bilirubin	ULN- 1.5* ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN		No Toxicities
3	DIAR	Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities
3	PROC	Proctitis	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention	Severe symptoms; faecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
				indicated; limiting instrumental ADL				
3	RHAE	Rectal haemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities
3	HAEM	Haematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross haematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
					intervention indicated; limiting self care ADL			
3	UFRE	Urinary frequency	present	Limiting instrumental ADL; medical management indicated	-	-	-	No Toxicities
3	UINC	Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention	-	-	No Toxicities
					indicated; limiting self care ADL			
3	URET	Urinary retention	Urinary, suprapubic or	Placement of urinary,	Elective operative or	Life-threatening	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
			intermittent catheter placement not indicated; able to void with some residual	suprapubic or intermittent catheter placement indicated; medication indicated	radiologic intervention indicated; substantial loss of affected kidney function or mass	consequences; organ failure; urgent operative intervention indicated		
3	UURG	Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-	No Toxicities
	BPAI	Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	No Toxicities
	FRAC	Fracture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; disabling;	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities

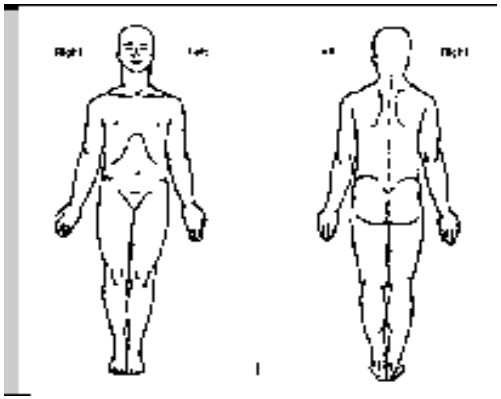
CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
					operative intervention indicated			

EQ-5D

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
EQ5D_0	Mobility	numeric	1-I have no problems in walking about 2-I have some problems in walking about 3-I am confirmed to bed	Range (1-3)	√	
EQ5D_1	Self-care	numeric	1-I have no problems with self-care 2-I have some problems washing or dressing myself 3-I am unable to wash or dress myself	Range (1-3)	√	
EQ5D_2	Usual activities	numeric	1-I have no problem with performing my usual activities 2-I have some problems performing my usual activities 3-I am unable to perform my usual activities	Range (1-3)	√	
EQ5D_3	Pain/discomfort	numeric	1-I have no pain or discomfort 2-I have moderate pain or discomfort 3-I have extreme pain or discomfort	Range (1-3)	√	
EQ5D_4	Anxiety/depression	numeric	1-I am not anxious or depressed 2-I am moderately anxious or depressed 3-I am extremely anxious or depressed	Range (1-3)	√	
EQ5D_5	Your health today	numeric		Range (1-100)	√	

Pain Score (Brief Pain Inventory)

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
BPI_NPRS	Numeric pain rating scale	numeric		Range (0-10)	√	0 - no pain; 5 - moderate pain; 10-worst possible pain
BPI_Related	Is this pain related to current diagnosis (oligomets, recurrence, mets for re-treatment) or related to recent SABR treatment?	numeric	1-Yes 2-No		Required if BPI_NPRS (Numeric pain rating scale)>0	
BPI_1	1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?				Required if BPI_NPRS (Numeric pain rating scale)>0	
BPI_2	2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.	1-Thorax front 2-Thorax back 3-Abdomen front 4-Abdomen back 5-Left arm 6-Right arm 7-Left leg 8-Right leg			Required if BPI_NPRS (Numeric pain rating scale)>0	This will have to be digitized. Such that if there is an X on the right side of the head it will be 1, etc..

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
		9-Right leg 10-Head				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
BPI_3	3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.	numeric		Range (0-10)	Required if BPI_NPRS (Numeric pain rating scale)>0	0-no pain; 10-pain as bad as you can imagine)
BPI_4	4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.	numeric		Range (0-10)	Required if BPI_NPRS (Numeric pain rating scale)>0	0-no pain; 10-pain as bad as you can imagine)
BPI_5	5. Please rate your pain by circling the one number that best describes your pain on average.	numeric		Range (0-10)	Required if BPI_NPRS (Numeric pain rating scale)>0	0-no pain; 10-pain as bad as you can imagine)
BPI_6	6. Please rate your pain by circling the one number that tells how much pain you have right now.	numeric		Range (0-10)	Required if BPI_NPRS (Numeric pain rating scale)>0	0-no pain; 10-pain as bad as you can imagine)

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CONSENT						
PE_1	How likely are you to recommend our SABR service to friends and family if they needed similar care or treatment?	Numeric	1-Extremely likely 2-Likely 3-Neither likely or unlikely 4-Extremely likely 5-Don't know		√	

Radiotherapy Planning Details_1

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_TRTAREA_1	First treatment area at baseline	text				Cannot be modified. This is read from the baseline form.
RPD_STDTE_1	Start date of first SABR treatment at baseline	date			√	
RPD_SPDTE_1	Completion date of first SABR treatment at baseline	date			√	
RPD_PCON_1	Were all planning constraints met?	numeric	1-yes 2-no		√	At least one site to be chosen
RPD_PTVC_1	Was PTV coverage >95% achieved?	numeric	1-yes 2-no		√	
RPD_SITE_THO_1	Thorax treated for first SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_UABM_1	Upper Abdomen treated for first SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_LABM_1	Lower Abdomen treated for first SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_ULMB_1	Upper Limb treated for first SABR treatment	numeric	-1-yes 0-no			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_SITE_LLMB_1	Lower Limb treated for first SABR treatment	numeric	-1-yes 0-no			
THORAX (C SPINE, T SPINE, LUNG, MEDIASTINUM)						
RPD_THO_TDOS_1	Total dose of radiotherapy administered	numeric				
RPD_THO_TDOS_FRAC_1	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_THO_TDOS_DAYS_1	Total dose of radiotherapy administered: Number of days	numeric				
RPD_THO_PISO_1	Prescription isodose	numeric				
RPD_THO_SC_DM01_1	Spinal Canal: DMax (0.1cc)	numeric				
RPD_THO_SC_D12_1	Spinal canal: D1.2cc	numeric				
RPD_THO_OG_DM05_1	Oesophagus: DMax (0.5cc)	numeric				
RPD_THO_LG_V20_1	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_THO_LG_V125_1	Normal Lungs (Lungs-GTV): V12.5Gy	numeric				
RPD_THO_HR_DM05_1	Heart: DMax (0.5cc)	numeric				
RPD_THO_SK_DM05_1	Skin: DMax (0.5cc)	numeric				
RPD_THO_SK_D10_1	Skin: D10cc	numeric				
RPD_THO_ST_DM05_1	Stomach: DMax (0.5cc)	numeric				
RPD_THO_ST_D55_1	Stomach: D5cc	numeric				
RPD_THO_ST_D10_1	Stomach: D10cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_THO_ST_D50_1	Stomach: D50cc	numeric				
RPD_THO_LV_V10_1	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_THO_LV_MLD_1	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_THO_LV_D50PT_1	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_THO_LV_D700_1	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_THO_CW_DM05_1	Chest Wall: DMax (0.5cc)	numeric				
RPD_THO_CW_D30_1	Chest Wall: D30cc	numeric				
RPD_THO_GV_DM05_1	Great Vessels: DMax (0.5cc)	numeric				
RPD_THO_BP_D05_1	Brachial Plexus: Dmax (0.5cc)	numeric				
RPD_THO_TB_D05_1	Trachea and bronchus: Dmax (0.5cc)	numeric				
RPD_THO_TTMIN_1	Treatment time (mins)	numeric				
RPD_THO_PPMIN_1	Physics time to plan (mins)	numeric				
UPPER ABDOMEN						
RPD_UA_TDOS_1	Total dose of radiotherapy administered	numeric				
RPD_UA_TDOS_FRAC_1	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_UA_TDOS_DAYS_1	Total dose of radiotherapy administered: Number of days	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_PISO_1	Prescription isodose	numeric				
RPD_UA_SC_D01_1	Spinal Canal : DMax (0.1cc)	numeric				
RPD_UA_SC_D12_1	Spinal Canal: D1.2cc	numeric				
RPD_UA_OG_D05_1	Oesophagus: DMax (0.5cc)	numeric				
RPD_UA_CE_D01_1	Cauda Equina: DMax (0.1cc)	numeric				
RPD_UA_CE_D5_1	Cauda Equina: D5cc	numeric				
RPD_UA_LG_V20_1	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_UA_LG_V125_1	Normal Lungs (Lungs-GTV): V12.5Gy	numeric				
RPD_UA_HR_D05_1	Heart: DMax (0.5cc)	numeric				
RPD_UA_SK_D05_1	Skin: DMax (0.5cc)	numeric				
RPD_UA_SK_D10_1	Skin: D10cc	numeric				
RPD_UA_ST_D05_1	Stomach: DMax (0.5cc)	numeric				
RPD_UA_ST_D5_1	Stomach: D5cc	numeric				
RPD_UA_ST_D10_1	Stomach: D10cc	numeric				
RPD_UA_ST_D50_1	Stomach: D50cc	numeric				
RPD_UA_DD_D05_1	Duodenum: DMax (0.5cc)	numeric				
RPD_UA_DD_D1_1	Duodenum: D1cc	numeric				
RPD_UA_DD_D5_1	Duodenum: D5cc	numeric				
RPD_UA_DD_D9_1	Duodenum: D9cc	numeric				
RPD_UA_DD_D10_1	Duodenum: D10cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_SB_D05_1	Small bowel: DMax (0.5cc)	numeric				
RPD_UA_SB_D5_1	Small bowel: D5cc	numeric				
RPD_UA_SB_D10_1	Small bowel: D10cc	numeric				
RPD_UA_LB_D05_1	Large bowel: DMax (0.5cc)	numeric				
RPD_UA_KD_MKD_1	Kidneys (individual and combined): Mean kidney dose	numeric				
RPD_UA_KD_D700_1	Kidneys (individual and combined): Dose to >=700	numeric				
RPD_UA_SKD_D10_1	If solitary kidney or if one kidney mean dose >10Gy	numeric				
RPD_UA_LV_V10_1	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_UA_LV_MLD_1	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_UA_LV_D50_1	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_UA_LV_D700_1	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_UA_TTMIN_1	Treatment time (mins)	numeric				
RPD_UA_PPMIN_1	Physics time to plan (mins)	numeric				
LOWER ABDOMEN						
RPD_LA_TDOS_1	Total dose of radiotherapy administered	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_TDOS_FRAC_1	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_LA_TDOS_DAYS_1	Total dose of radiotherapy administered: Number of days	numeric				
RPD_LA_PISO_1	Prescription isodose	numeric				
RPD_LA_SC_D01_1	Spinal Canal: DMax (0.1cc)	numeric				
RPD_LA_SC_D12_1	Spinal Canal: D1.2cc	numeric				
RPD_LA_CE_D01_1	Cauda Equina: Dmax (0.1cc)	numeric				
RPD_LA_CE_D5_1	Cauda Equina: D5cc	numeric				
RPD_LA_SK_D05_1	Skin: DMax (0.5cc)	numeric				
RPD_LA_SK_D10_1	Skin: D10cc	numeric				
RPD_LA_DD_D05_1	Duodenum: DMax (0.5cc)	numeric				
RPD_LA_DD_D1_1	Duodenum: D1cc	numeric				
RPD_LA_DD_D5_1	Duodenum: D5cc	numeric				
RPD_LA_DD_D9_1	Duodenum: D9cc	numeric				
RPD_LA_DD_D10_1	Duodenum: D10cc	numeric				
RPD_LA_SB_D05_1	Small bowel: DMax (0.5cc)	numeric				
RPD_LA_SB_D5_1	Small bowel: D5cc	numeric				
RPD_LA_SB_D10_1	Small bowel: D10cc	numeric				
RPD_LA_LB_D05_1	Large bowel: DMax (0.5cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_LB_D20_1	Large bowel: Dose to 20cc	numeric				
RPD_LA_BL_D15_1	Bladder: D15cc	numeric				
RPD_LA_BL_D05_1	Bladder: DMax (0.5cc)	numeric				
RPD_LA_FHL_D10_1	Femoral heads - Left: D10cc	numeric				
RPD_LA_FHR_D10_1	Femoral heads - Right: D10cc	numeric				
RPD_LA_KD_MKD_1	Kidneys (individual and combined): Mean kidney dose	numeric				
RPD_LA_KD_D700_1	Kidneys (individual and combined): Dose to >=700	numeric				
RPD_LA_SKD_D10_1	If solitary kidney or if one kidney mean dose >10Gy	numeric				
RPD_LA_LV_V10_1	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_LA_LV_MLD_1	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_LA_LV_D50_1	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_LA_LV_D700_1	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_LA_S_D01_1	Sacral plexus: DMax (0.1cc)	numeric				
RPD_LA_S_D5_1	Sacral plexus: D5cc	numeric				
RPD_LA_PB_D3_1	Penile Bulb: D3cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_PB_D05_1	Penile Bulb: DMax (0.5cc)	numeric				
RPD_LA_UR_D05_1	Ureter: DMax (0.5cc)	numeric				
RPD_LA_TTMIN_1	Treatment time (mins)	numeric				
RPD_LA_PPMIN_1	Physics time to plan (mins)	numeric				
UPPER LIMBS						
RPD_UL_TDOS_1	Total dose of radiotherapy administered	numeric				
RPD_UL_TDOS_FRAC_1	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_UL_TDOS_DAYS_1	Total dose of radiotherapy administered: Number of days	numeric				
RPD_UL_PISO_1	Prescription isodose	numeric				
RPD_UL_LG_V20_1	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_UL_LG_V125_1	Normal Lungs (Lungs-GTV):V12.5Gy	numeric				
RPD_UL_SK_D05_1	Skin: DMax (0.5cc)	numeric				
RPD_UL_SK_D10_1	Skin: D10cc	numeric				
RPD_UL_HR_D05_1	Heart: DMax (0.5cc)	numeric				
RPD_UL_TTMIN_1	Treatment time (mins)	numeric				
RPD_UL_PPMIN_1	Physics time to plan (mins)	numeric				
LOWER LIMBS						
RPD_LL_TDOS_1	Total dose of radiotherapy administered	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LL_TDOS_FRAC_1	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_LL_TDOS_DAYS_1	Total dose of radiotherapy administered: Number of days	numeric				
RPD_LL_PISO_1	Prescription isodose	numeric				
RPD_LL_BL_D15_1	Bladder: D15cc	numeric				
RPD_LL_BL_D05_1	Bladder: DMax (0.5cc)	numeric				
RPD_LL_PB_D3_1	Penile Bulb: D3cc	numeric				
RPD_LL_PB_D05_1	Penile Bulb: DMax (0.5cc)	numeric				
RPD_LL_UR_D05_1	Ureter: DMax (0.5cc)	numeric				
RPD_LL_SK_D05_1	Skin: DMax (0.5cc)	numeric				
RPD_LL_SK_D10_1	Skin: D10cc	numeric				
RPD_LL_TTMIN_1	Treatment time (mins)	numeric				
RPD_LL_PPMIN_1	Physics time to plan (mins)	numeric				

Radiotherapy Planning Details_2

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_TRTAREA_2	Second treatment area at baseline	text				Cannot be modified. This is read from the baseline form.
RPD_STDTE_2	Start date of second SABR treatment at baseline	date			√	
RPD_SPDTE_2	Completion date of second SABR treatment at baseline	date			√	
RPD_PCON_2	Were all planning constraints met?	numeric	1-yes 2-no		√	At least one site to be chosen
RPD_PTVC_2	Was PTV coverage >95% achieved?	numeric	1-yes 2-no		√	
RPD_SITE_THO_2	Thorax treated for second SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_UABM_2	Upper Abdomen treated for second SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_LABM_2	Lower Abdomen treated for second SABR treatment	numeric	-1-yes			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			0-no			
RPD_SITE_ULMB_2	Upper Limb treated for second SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_LLMB_2	Lower Limb treated for second SABR treatment	numeric	-1-yes 0-no			
THORAX (C SPINE, T SPINE, LUNG, MEDIASTINUM)						
RPD_THO_TDOS_2	Total dose of radiotherapy administered	numeric				
RPD_THO_TDOS_FRAC_2	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_THO_TDOS_DAYS_2	Total dose of radiotherapy administered: Number of days	numeric				
RPD_THO_PISO_2	Prescription isodose	numeric				
RPD_THO_SC_DM01_2	Spinal Canal: DMax (0.1cc)	numeric				
RPD_THO_SC_D12_2	Spinal canal: D1.2cc	numeric				
RPD_THO_OG_DM05_2	Oesophagus: DMax (0.5cc)	numeric				
RPD_THO_LG_V20_2	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_THO_LG_V125_2	Normal Lungs (Lungs-GTV): V12.5Gy	numeric				
RPD_THO_HR_DM05_2	Heart: DMax (0.5cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_THO_SK_DM05_2	Skin: DMax (0.5cc)	numeric				
RPD_THO_SK_D10_2	Skin: D10cc	numeric				
RPD_THO_ST_DM05_2	Stomach: DMax (0.5cc)	numeric				
RPD_THO_ST_D55_2	Stomach: D5cc	numeric				
RPD_THO_ST_D10_2	Stomach: D10cc	numeric				
RPD_THO_ST_D50_2	Stomach: D50cc	numeric				
RPD_THO_LV_V10_2	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_THO_LV_MLD_2	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_THO_LV_D50PT_2	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_THO_LV_D700_2	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_THO_CW_DM05_2	Chest Wall: DMax (0.5cc)	numeric				
RPD_THO_CW_D30_2	Chest Wall: D30cc	numeric				
RPD_THO_GV_DM05_2	Great Vessels: DMax (0.5cc)	numeric				
RPD_THO_BP_D05_2	Brachial Plexus: Dmax (0.5cc)	numeric				
RPD_THO_TB_D05_2	Trachea and bronchus: Dmax (0.5cc)	numeric				
RPD_THO_TTMIN_2	Treatment time (mins)	numeric				
RPD_THO_PPMIN_2	Physics time to plan (mins)	numeric				
UPPER ABDOMEN						

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_TDOS_2	Total dose of radiotherapy administered	numeric				
RPD_UA_TDOS_FRAC_2	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_UA_TDOS_DAYS_2	Total dose of radiotherapy administered: Number of days	numeric				
RPD_UA_PISO_2	Prescription isodose	numeric				
RPD_UA_SC_D01_2	Spinal Canal : DMax (0.1cc)	numeric				
RPD_UA_SC_D12_2	Spinal Canal: D1.2cc	numeric				
RPD_UA_OG_D05_2	Oesophagus: DMax (0.5cc)	numeric				
RPD_UA_CE_D01_2	Cauda Equina: DMax (0.1cc)	numeric				
RPD_UA_CE_D5_2	Cauda Equina: D5cc	numeric				
RPD_UA_LG_V20_2	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_UA_LG_V125_2	Normal Lungs (Lungs-GTV): V12.5Gy	numeric				
RPD_UA_HR_D05_2	Heart: DMax (0.5cc)	numeric				
RPD_UA_SK_D05_2	Skin: DMax (0.5cc)	numeric				
RPD_UA_SK_D10_2	Skin: D10cc	numeric				
RPD_UA_ST_D05_2	Stomach: DMax (0.5cc)	numeric				
RPD_UA_ST_D5_2	Stomach: D5cc	numeric				
RPD_UA_ST_D10_2	Stomach: D10cc	numeric				
RPD_UA_ST_D50_2	Stomach: D50cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_DD_D05_2	Duodenum: DMax (0.5cc)	numeric				
RPD_UA_DD_D1_2	Duodenum: D1cc	numeric				
RPD_UA_DD_D5_2	Duodenum: D5cc	numeric				
RPD_UA_DD_D9_2	Duodenum: D9cc	numeric				
RPD_UA_DD_D10_2	Duodenum: D10cc	numeric				
RPD_UA_SB_D05_2	Small bowel: DMax (0.5cc)	numeric				
RPD_UA_SB_D5_2	Small bowel: D5cc	numeric				
RPD_UA_SB_D10_2	Small bowel: D10cc	numeric				
RPD_UA_LB_D05_2	Large bowel: DMax (0.5cc)	numeric				
RPD_UA_KD_MKD_2	Kidneys (individual and combined): Mean kidney dose	numeric				
RPD_UA_KD_D700_2	Kidneys (individual and combined): Dose to >=700	numeric				
RPD_UA_SKD_D10_2	If solitary kidney or if one kidney mean dose >10Gy	numeric				
RPD_UA_LV_V10_2	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_UA_LV_MLD_2	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_UA_LV_D50_2	Normal Liver (Liver minus GTV): D50%	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_LV_D700_2	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_UA_TTMIN_2	Treatment time (mins)	numeric				
RPD_UA_PPMIN_2	Physics time to plan (mins)	numeric				
LOWER ABDOMEN						
RPD_LA_TDOS_2	Total dose of radiotherapy administered	numeric				
RPD_LA_TDOS_FRAC_2	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_LA_TDOS_DAYS_2	Total dose of radiotherapy administered: Number of days	numeric				
RPD_LA_PISO_2	Prescription isodose	numeric				
RPD_LA_SC_D01_2	Spinal Canal: DMax (0.1cc)	numeric				
RPD_LA_SC_D12_2	Spinal Canal: D1.2cc	numeric				
RPD_LA_CE_D01_2	Cauda Equina: Dmax (0.1cc)	numeric				
RPD_LA_CE_D5_2	Cauda Equina: D5cc	numeric				
RPD_LA_SK_D05_2	Skin: DMax (0.5cc)	numeric				
RPD_LA_SK_D10_2	Skin: D10cc	numeric				
RPD_LA_DD_D05_2	Duodenum: DMax (0.5cc)	numeric				
RPD_LA_DD_D1_2	Duodenum: D1cc	numeric				
RPD_LA_DD_D5_2	Duodenum: D5cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_DD_D9_2	Duodenum: D9cc	numeric				
RPD_LA_DD_D10_2	Duodenum: D10cc	numeric				
RPD_LA_SB_D05_2	Small bowel: DMax (0.5cc)	numeric				
RPD_LA_SB_D5_2	Small bowel: D5cc	numeric				
RPD_LA_SB_D10_2	Small bowel: D10cc	numeric				
RPD_LA_LB_D05_2	Large bowel: DMax (0.5cc)	numeric				
RPD_LA_LB_D20_2	Large bowel: Dose to 20cc	numeric				
RPD_LA_BL_D15_2	Bladder: D15cc	numeric				
RPD_LA_BL_D05_2	Bladder: DMax (0.5cc)	numeric				
RPD_LA_FHL_D10_2	Femoral heads - Left: D10cc	numeric				
RPD_LA_FHR_D10_2	Femoral heads - Right: D10cc	numeric				
RPD_LA_KD_MKD_2	Kidneys (individual and combined): Mean kidney dose	numeric				
RPD_LA_KD_D700_2	Kidneys (individual and combined): Dose to >=700	numeric				
RPD_LA_SKD_D10_2	If solitary kidney or if one kidney mean dose >10Gy	numeric				
RPD_LA_LV_V10_2	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_LA_LV_MLD_2	Normal Liver (Liver minus GTV): mean liver dose	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_LV_D50_2	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_LA_LV_D700_2	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_LA_S_D01_2	Sacral plexus: DMax (0.1cc)	numeric				
RPD_LA_S_D5_2	Sacral plexus: D5cc	numeric				
RPD_LA_PB_D3_2	Penile Bulb: D3cc	numeric				
RPD_LA_PB_D05_2	Penile Bulb: DMax (0.5cc)	numeric				
RPD_LA_UR_D05_2	Ureter: DMax (0.5cc)	numeric				
RPD_LA_TTMIN_2	Treatment time (mins)	numeric				
RPD_LA_PPMIN_2	Physics time to plan (mins)	numeric				
UPPER LIMBS						
RPD_UL_TDOS_2	Total dose of radiotherapy administered	numeric				
RPD_UL_TDOS_FRAC_2	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_UL_TDOS_DAYS_2	Total dose of radiotherapy administered: Number of days	numeric				
RPD_UL_PISO_2	Prescription isodose	numeric				
RPD_UL_LG_V20_2	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_UL_LG_V125_2	Normal Lungs (Lungs-GTV):V12.5Gy	numeric				
RPD_UL_SK_D05_2	Skin: DMax (0.5cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UL_SK_D10_2	Skin: D10cc	numeric				
RPD_UL_HR_D05_2	Heart: DMax (0.5cc)	numeric				
RPD_UL_TTMIN_2	Treatment time (mins)	numeric				
RPD_UL_PPMIN_2	Physics time to plan (mins)	numeric				
LOWER LIMBS						
RPD_LL_TDOS_2	Total dose of radiotherapy administered	numeric				
RPD_LL_TDOS_FRAC_2	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_LL_TDOS_DAYS_2	Total dose of radiotherapy administered: Number of days	numeric				
RPD_LL_PISO_2	Prescription isodose	numeric				
RPD_LL_BL_D15_2	Bladder: D15cc	numeric				
RPD_LL_BL_D05_2	Bladder: DMax (0.5cc)	numeric				
RPD_LL_PB_D3_2	Penile Bulb: D3cc	numeric				
RPD_LL_PB_D05_2	Penile Bulb: DMax (0.5cc)	numeric				
RPD_LL_UR_D05_2	Ureter: DMax (0.5cc)	numeric				
RPD_LL_SK_D05_2	Skin: DMax (0.5cc)	numeric				
RPD_LL_SK_D10_2	Skin: D10cc	numeric				
RPD_LL_TTMIN_2	Treatment time (mins)	numeric				
RPD_LL_PPMIN_2	Physics time to plan (mins)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_TRTAREA_3	Third treatment area at baseline	text				Cannot be modified. This is read from the baseline form.
RPD_STDTE_3	Start date of third SABR treatment at baseline	date			√	
RPD_SPDTE_3	Completion date of third SABR treatment at baseline	date			√	
RPD_PCON_3	Were all planning constraints met?	numeric	1-yes 2-no		√	At least one site to be chosen
RPD_PTVC_3	Was PTV coverage >95% achieved?	numeric	1-yes 2-no		√	
RPD_SITE_THO_3	Thorax treated for third SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_UABM_3	Upper Abdomen treated for third SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_LABM_3	Lower Abdomen treated for third SABR treatment	numeric	-1-yes 0-no			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_SITE_ULMB_3	Upper Limb treated for third SABR treatment	numeric	-1-yes 0-no			
RPD_SITE_LLMB_3	Lower Limb treated for third SABR treatment	numeric	-1-yes 0-no			
THORAX (C SPINE, T SPINE, LUNG, MEDIASTINUM)						
RPD_THO_TDOS_3	Total dose of radiotherapy administered	numeric				
RPD_THO_TDOS_FRAC_3	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_THO_TDOS_DAYS_3	Total dose of radiotherapy administered: Number of days	numeric				
RPD_THO_PISO_3	Prescription isodose	numeric				
RPD_THO_SC_DM01_3	Spinal Canal: DMax (0.1cc)	numeric				
RPD_THO_SC_D12_3	Spinal canal: D1.2cc	numeric				
RPD_THO_OG_DM05_3	Oesophagus: DMax (0.5cc)	numeric				
RPD_THO_LG_V20_3	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_THO_LG_V125_3	Normal Lungs (Lungs-GTV): V12.5Gy	numeric				
RPD_THO_HR_DM05_3	Heart: DMax (0.5cc)	numeric				
RPD_THO_SK_DM05_3	Skin: DMax (0.5cc)	numeric				
RPD_THO_SK_D10_3	Skin: D10cc	numeric				
RPD_THO_ST_DM05_3	Stomach: DMax (0.5cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_THO_ST_D55_3	Stomach: D5cc	numeric				
RPD_THO_ST_D10_3	Stomach: D10cc	numeric				
RPD_THO_ST_D50_3	Stomach: D50cc	numeric				
RPD_THO_LV_V10_3	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_THO_LV_MLD_3	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_THO_LV_D50PT_3	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_THO_LV_D700_3	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_THO_CW_DM05_3	Chest Wall: DMax (0.5cc)	numeric				
RPD_THO_CW_D30_3	Chest Wall: D30cc	numeric				
RPD_THO_GV_DM05_3	Great Vessels: DMax (0.5cc)	numeric				
RPD_THO_BP_D05_3	Brachial Plexus: Dmax (0.5cc)	numeric				
RPD_THO_TB_D05_3	Trachea and bronchus: Dmax (0.5cc)	numeric				
RPD_THO_TTMIN_3	Treatment time (mins)	numeric				
RPD_THO_PPMIN_3	Physics time to plan (mins)	numeric				
UPPER ABDOMEN						
RPD_UA_TDOS_3	Total dose of radiotherapy administered	numeric				
RPD_UA_TDOS_FRAC_3	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_UA_TDOS_DAYS_3	Total dose of radiotherapy administered: Number of days	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_PISO_3	Prescription isodose	numeric				
RPD_UA_SC_D01_3	Spinal Canal : DMax (0.1cc)	numeric				
RPD_UA_SC_D12_3	Spinal Canal: D1.2cc	numeric				
RPD_UA_OG_D05_3	Oesophagus: DMax (0.5cc)	numeric				
RPD_UA_CE_D01_3	Cauda Equina: DMax (0.1cc)	numeric				
RPD_UA_CE_D5_3	Cauda Equina: D5cc	numeric				
RPD_UA_LG_V20_3	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_UA_LG_V125_3	Normal Lungs (Lungs-GTV): V12.5Gy	numeric				
RPD_UA_HR_D05_3	Heart: DMax (0.5cc)	numeric				
RPD_UA_SK_D05_3	Skin: DMax (0.5cc)	numeric				
RPD_UA_SK_D10_3	Skin: D10cc	numeric				
RPD_UA_ST_D05_3	Stomach: DMax (0.5cc)	numeric				
RPD_UA_ST_D5_3	Stomach: D5cc	numeric				
RPD_UA_ST_D10_3	Stomach: D10cc	numeric				
RPD_UA_ST_D50_3	Stomach: D50cc	numeric				
RPD_UA_DD_D05_3	Duodenum: DMax (0.5cc)	numeric				
RPD_UA_DD_D1_3	Duodenum: D1cc	numeric				
RPD_UA_DD_D5_3	Duodenum: D5cc	numeric				
RPD_UA_DD_D9_3	Duodenum: D9cc	numeric				
RPD_UA_DD_D10_3	Duodenum: D10cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UA_SB_D05_3	Small bowel: DMax (0.5cc)	numeric				
RPD_UA_SB_D5_3	Small bowel: D5cc	numeric				
RPD_UA_SB_D10_3	Small bowel: D10cc	numeric				
RPD_UA_LB_D05_3	Large bowel: DMax (0.5cc)	numeric				
RPD_UA_KD_MKD_3	Kidneys (individual and combined): Mean kidney dose	numeric				
RPD_UA_KD_D700_3	Kidneys (individual and combined): Dose to >=700	numeric				
RPD_UA_SKD_D10_3	If solitary kidney or if one kidney mean dose >10Gy	numeric				
RPD_UA_LV_V10_3	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_UA_LV_MLD_3	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_UA_LV_D50_3	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_UA_LV_D700_3	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_UA_TTMIN_3	Treatment time (mins)	numeric				
RPD_UA_PPMIN_3	Physics time to plan (mins)	numeric				
LOWER ABDOMEN						
RPD_LA_TDOS_3	Total dose of radiotherapy administered	numeric				
RPD_LA_TDOS_FRAC_3	Total dose of radiotherapy administered: Number of fractions	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_TDOS_DAYS_3	Total dose of radiotherapy administered: Number of days	numeric				
RPD_LA_PISO_3	Prescription isodose	numeric				
RPD_LA_SC_D01_3	Spinal Canal: DMax (0.1cc)	numeric				
RPD_LA_SC_D12_3	Spinal Canal: D1.2cc	numeric				
RPD_LA_CE_D01_3	Cauda Equina: Dmax (0.1cc)	numeric				
RPD_LA_CE_D5_3	Cauda Equina: D5cc	numeric				
RPD_LA_SK_D05_3	Skin: DMax (0.5cc)	numeric				
RPD_LA_SK_D10_3	Skin: D10cc	numeric				
RPD_LA_DD_D05_3	Duodenum: DMax (0.5cc)	numeric				
RPD_LA_DD_D1_3	Duodenum: D1cc	numeric				
RPD_LA_DD_D5_3	Duodenum: D5cc	numeric				
RPD_LA_DD_D9_3	Duodenum: D9cc	numeric				
RPD_LA_DD_D10_3	Duodenum: D10cc	numeric				
RPD_LA_SB_D05_3	Small bowel: DMax (0.5cc)	numeric				
RPD_LA_SB_D5_3	Small bowel: D5cc	numeric				
RPD_LA_SB_D10_3	Small bowel: D10cc	numeric				
RPD_LA_LB_D05_3	Large bowel: DMax (0.5cc)	numeric				
RPD_LA_LB_D20_3	Large bowel: Dose to 20cc	numeric				
RPD_LA_BL_D15_3	Bladder: D15cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_BL_D05_3	Bladder: DMax (0.5cc)	numeric				
RPD_LA_FHL_D10_3	Femoral heads - Left: D10cc	numeric				
RPD_LA_FHR_D10_3	Femoral heads - Right: D10cc	numeric				
RPD_LA_KD_MKD_3	Kidneys (individual and combined): Mean kidney dose	numeric				
RPD_LA_KD_D700_3	Kidneys (individual and combined): Dose to >=700	numeric				
RPD_LA_SKD_D10_3	If solitary kidney or if one kidney mean dose >10Gy	numeric				
RPD_LA_LV_V10_3	Normal Liver (Liver minus GTV): V10Gy	numeric				
RPD_LA_LV_MLD_3	Normal Liver (Liver minus GTV): mean liver dose	numeric				
RPD_LA_LV_D50_3	Normal Liver (Liver minus GTV): D50%	numeric				
RPD_LA_LV_D700_3	Normal Liver (Liver minus GTV): Dose to >=700cc	numeric				
RPD_LA_S_D01_3	Sacral plexus: DMax (0.1cc)	numeric				
RPD_LA_S_D5_3	Sacral plexus: D5cc	numeric				
RPD_LA_PB_D3_3	Penile Bulb: D3cc	numeric				
RPD_LA_PB_D05_3	Penile Bulb: DMax (0.5cc)	numeric				
RPD_LA_UR_D05_3	Ureter: DMax (0.5cc)	numeric				
RPD_LA_TTMIN_3	Treatment time (mins)	numeric				
RPD_LA_PPMIN_3	Physics time to plan (mins)	numeric				
UPPER LIMBS						

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_UL_TDOS_3	Total dose of radiotherapy administered	numeric				
RPD_UL_TDOS_FRAC_3	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_UL_TDOS_DAYS_3	Total dose of radiotherapy administered: Number of days	numeric				
RPD_UL_PISO_3	Prescription isodose	numeric				
RPD_UL_LG_V20_3	Normal Lungs (Lungs-GTV): V20Gy	numeric				
RPD_UL_LG_V125_3	Normal Lungs (Lungs-GTV):V12.5Gy	numeric				
RPD_UL_SK_D05_3	Skin: DMax (0.5cc)	numeric				
RPD_UL_SK_D10_3	Skin: D10cc	numeric				
RPD_UL_HR_D05_3	Heart: DMax (0.5cc)	numeric				
RPD_UL_TTMIN_3	Treatment time (mins)	numeric				
RPD_UL_PPMIN_3	Physics time to plan (mins)	numeric				
LOWER LIMBS						
RPD_LL_TDOS_3	Total dose of radiotherapy administered	numeric				
RPD_LL_TDOS_FRAC_3	Total dose of radiotherapy administered: Number of fractions	numeric				
RPD_LL_TDOS_DAYS_3	Total dose of radiotherapy administered: Number of days	numeric				
RPD_LL_PISO_3	Prescription isodose	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LL_BL_D15_3	Bladder: D15cc	numeric				
RPD_LL_BL_D05_3	Bladder: DMax (0.5cc)	numeric				
RPD_LL_PB_D3_3	Penile Bulb: D3cc	numeric				
RPD_LL_PB_D05_3	Penile Bulb: DMax (0.5cc)	numeric				
RPD_LL_UR_D05_3	Ureter: DMax (0.5cc)	numeric				
RPD_LL_SK_D05_3	Skin: DMax (0.5cc)	numeric				
RPD_LL_SK_D10_3	Skin: D10cc	numeric				
RPD_LL_TTMIN_3	Treatment time (mins)	numeric				
RPD_LL_PPMIN_3	Physics time to plan (mins)	numeric				

Death

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
DT_DEAD	Patient deceased	numeric	1-yes 2-no		√	
DT_DOD	Date of death	date		Required if DT_DEAD (Patient deceased) is 1 (yes)	√	
DT_COD	Cause of death	text?		Required if DT_DEAD (Patient deceased) is 1 (yes)		
DT_CRD	Cancer related death	numeric	1-yes 2-no	Required if DT_DEAD (Patient deceased) is 1 (yes)		

15 Appendix E: Health economics appendices

Summary of parameters used in model: baseline deterministic values, range used in one-way and multi-way sensitivity analysis, distribution used in probabilistic sensitivity analyses, and references.

Interventions	Base-line value	Standard error	Range	Distribution	Source
Cancer progression rate (monthly)					
No progression to local progression	1.12%	Not reported	1-5%	Beta (α=7.40; β=653.60)	Calibrated from Tabrizian et al. (Tabrizian et al. 2015)
No progression to regional/distant progression	0.16%	Not reported	1-3%	Beta (α=1.06; β=659.94)	As above
Local progression to regional/distant progression	0.90%	Not reported	1-5%	Beta (α=5.95; β=655.05)	As above
Mortality rate (monthly)					
Patients with no progression	0.26%	Not reported	0-1%	Beta (α=0.08, β=31.92)	Calibrated from Lee et al. (Lee et al. 2006)

Interventions	Base-line value	Standard error	Range	Distribution	Source
Patients with local progression	3.21%	Not reported	1-5%	Beta (α=8.25, β=248.75)	Calibrated from Grieco et al. (Grieco et al. 2005)
Patients with regional/distant progression	12.65%	Not reported	5-20%	Beta (α=1.39, β=9.61)	As above
Probability of retreatment (monthly)					
Probability of retreatment for patients receiving surgery	25.09%	0.16%	10-50%	Beta (α=70, β=209)	(Itamoto et al. 2007)
Probability of retreatment for patients receiving RFA	69.46%	0.10%	50-75%	Beta (α=323, β=142)	(Rossi et al. 2011)
Probability of retreatment for patients receiving SABR	As above	As above	As above	As above	As above
SAEs (monthly)					
RR of SAEs (RFA vs surgery)	0.18	0.12	0.1-1.0	Lognormal	Calculated based on probability of developing SAEs for RFA and RR reported by Wang

Interventions	Base-line value	Standard error	Range	Distribution	Source
					et al. (Wang et al. 2014)
Probability of SAEs after RFA	1.00%	0.22%	0-5%	Beta	(Pollom et al. 2017)
Probability of SAEs after SABR	4.55%	Not reported	0-5%	Beta (α=4, β=84)	CtE programme
Cost of interventions					
Cost of surgery	£6,272.87	Assumed 30% of mean value	£5,000-£8,000	Gamma	NHS reference cost 2015-16 (Department of Health 2016)
Cost of retreatment with surgery	As above	As above	As above	As above	As above
Cost of RFA	£5,089.17	Assumed 30% of mean value	£3,000-£6,000	Gamma	Uplifted from Loveman et al. (Loveman et al. 2014) and adjusted for days of additional hospital

Interventions	Base-line value	Standard error	Range	Distribution	Source
					stay (Wang et al. 2014)
Cost of retreatment with RFA	As above	As above	As above	As above	As above
Cost for SABR	£4,807.00	Assumed 30% of mean value	£2,000-£6,000	Gamma	(Solutions for Public Health 2015)
Cost of retreatment with SABR	As above	As above	As above	As above	As above
Cost of treating SAEs					
Cost of treating SAEs	£2,849	Assumed 30% of mean value	£1,000-£4,000	Gamma	(Campbell et al. 2015)
Other cost data					
Outpatient follow-up	£296.84	Assumed 30% of mean value	Assumed fixed	Gamma	(Department of Health 2016)
Palliative care (per month)	£166.34	As above	Assumed fixed	Gamma	Uplifted from Thompson Coon et

Interventions	Base-line value	Standard error	Range	Distribution	Source
					al. (Thompson Coon et al. 2008)
Utility					
Progression free without SAEs	0.74	0.22	0.74-0.92	Beta	The CtE program, Lim et al. (Lim et al. 2015)
Progression free with SAEs	0.50	0.05	0.39-0.60	Beta	(Oster et al. 1994, White et al. 2012)
Local progression	0.63	0.15	0.26-0.86	Beta	(Cucchetti et al. 2013)
Regional/distant progression	**0.40**	**0.04**	**0.32-0.48**	**Beta**	**(Hanmer et al. 2006)**

One-way sensitivity analysis results

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Base case analysis results							
SABR	10,979	2.8334	–	–	–	1	1
RFA	11,261	2.8340	281	0.0005	516,974	2	2
Surgery	11,571	2.7008	–	–	Dominated	3	3
Set transitional rate from no progression to local progression to 1% (base case value: 1.12%)							
SABR	10,895	2.8566	–	–	–	1	1
RFA	11,172	2.8571	277	0.0005	524,092	2	2
Surgery	11,558	2.7329	–	–	Dominated	3	3
Set transitional rate from no progression to local progression to 5% (base case value: 1.12%)							
SABR	11,731	2.1459	318	0.1485	2,141	1	1
RFA	12,069	2.1467	338	0.0007	458,345	2	2
Surgery	11,414	1.9974	–	–	–	3	3
Set transitional rate from no progression to regional/distant progression to 1% (base case value: 0.16%)							
SABR	10,399	2.3626	–	–	–	1	1
RFA	10,672	2.3631	273	0.0005	535,019	2	2

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Surgery	11,147	2.2745	–	–	Dominated	3	3
Set transitional rate from no progression to regional/distant progression to 3% (base case value: 0.16%)							
SABR	9,407	1.6469	–	–	–	1	1
RFA	9,667	1.6474	260	0.0005	567,467	2	2
Surgery	10,403	1.6183	–	–	Dominated	3	3
Set transitional rate from local progression to regional/distant progression to 1% (base case value: 0.90%)							
SABR	10,980	2.8323	–	–	–	1	1
RFA	11,261	2.8329	281	0.0005	516,974	2	2
Surgery	11,572	2.6982	–	–	Dominated	3	3
Set transitional rate from local progression to regional/distant progression to 5% (base case value: 0.90%)							
SABR	10,986	2.8034	–	–	–	1	1
RFA	11,267	2.8040	281	0.0005	516,974	2	2
Surgery	11,587	2.6273	–	–	Dominated	3	3

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Set mortality rate for patients with no progression to 0% (base case value: 0.26%)							
SABR	11,409	3.0354	–	–	–	1	1
RFA	11,693	3.0360	285	0.0006	511,244	2	2
Surgery	11,921	2.8834	–	–	Dominated	3	3
Set mortality rate for patients with no progression to 1% (base case value: 0.26%)							
SABR	9,953	2.3514	–	–	–	1	1
RFA	10,227	2.3520	273	0.0005	531,931	2	2
Surgery	10,730	2.2631	–	–	Dominated	3	3
Set mortality rate for patients with local progression to 1% (base case value: 3.21%)							
SABR	11,150	2.8982	–	–	–	1	1
RFA	11,432	2.8988	283	0.0005	514,974	2	2
Surgery	11,836	2.8197	–	–	Dominated	3	3
Set mortality rate for patients with local progression to 5% (base case value: 3.21%)							
SABR	10,876	2.7969	–	–	–	1	1

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
RFA	11,157	2.7975	281	0.0005	518,618	2	2
Surgery	11,430	2.6395	–	–	Dominated	3	3
Set mortality rate for patients with regional/distant progression to 5% (base case value: 12.65%)							
SABR	11,181	2.8587	–	–	–	1	1
RFA	11,462	2.8593	281	0.0005	516,974	2	2
Surgery	11,777	2.7268	–	–	Dominated	3	3
Set mortality rate for patients with regional/distant progression to 20% (base case value: 12.65%)							
SABR	10,909	2.8246	–	–	–	1	1
RFA	11,191	2.8251	281	0.0005	516,974	2	2
Surgery	11,500	2.6919	–	–	Dominated	3	3
Set probability of receiving retreatment for patients who developed local recurrence after initial treatment of surgery to 10% (base case value: 25.09%)							
SABR	10,979	2.8334	–	–	–	1	1
RFA	11,261	2.8340	281	0.0005	516,974	2	2

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Surgery	11,130	2.6558	–	–	Dominated	3	3
Set probability of receiving retreatment for patients who developed local recurrence after initial treatment of surgery to 50% (base case value: 25.09%)							
SABR	10,979	2.8334	–	–	–	1	1
RFA	11,261	2.8340	281	0.0005	516,974	2	2
Surgery	12,298	2.7752	–	–	Dominated	3	3
Set probability of receiving retreatment for patients who developed local recurrence after initial treatment of RFA or SABR to 50.00% (base case value: 69.46%)							
SABR	10,525	2.7753	–	–	–	1	1
RFA	10,793	2.7758	267	0.0005	544,384	2	2
Surgery	11,571	2.7008	–	–	Dominated	3	3
Set probability of receiving retreatment for patients who developed local recurrence after initial treatment of RFA or SABR to 75.00% (base case value: 69.46%)							
SABR	11,109	2.8500	–	–	–	1	1

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
RFA	11,394	2.8505	285	0.0006	510,121	2	2
Surgery	11,571	2.7008	–	–	Dominated	3	3
Set RR of developed SAEs (RFA vs surgery) to 0.10 (base case value: 0.18)							
SABR	10,979	2.8334	–	–	–	1	1
RFA	11,261	2.8340	281	0.0005	516,974	2	2
Surgery	11,646	2.7003	–	–	Dominated	3	3
Set RR of developed SAEs (RFA vs surgery) to 1.00 (base case value: 0.18)							
SABR	10,979	2.8334	–	–	–	1	1
RFA	11,261	2.8340	281	0.0005	516,974	2	2
Surgery	11,493	2.7014	–	–	Dominated	3	3
Set probability of developed SAEs after RFA to 0% (base case value: 1.00%)							
SABR	10,979	2.8334	–	–	–	1	1
RFA	11,239	2.8341	260	0.0007	372,046	2	2

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Surgery	11,476	2.7015	–	–	Dominated	3	3
Set probability of developed SAEs after RFA to 5% (base case value: 1.00%)							
SABR	10,979	2.8334	–	–	Dominating	1	1
RFA	11,348	2.8333	–	–	Dominated	2	2
Surgery	11,948	2.6982	–	–	Dominated	3	3
Set probability of developed SAEs after SABR to 0% (base case value: 4.55%)							
SABR	10,880	2.8341	–	–	Dominating	1	1
RFA	11,261	2.8340	–	–	Dominated	2	2
Surgery	11,571	2.7008	–	–	Dominated	3	3
Set probability of developed SAEs after SABR to 10% (base case value: 4.55%)							

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
SABR	11,098	2.8326	–	–	–	1	1
RFA	11,261	2.8340	162	0.0014	117,656	2	2
Surgery	11,571	2.7008	–	–	Dominated	3	3
Set cost of surgery to £5,000 (base case value: £6,272.87)							
SABR	10,979	2.8334	807	0.1326	6,085	1	1
RFA	11,261	2.8340	281	0.0005	516,974	2	2
Surgery	10,173	2.7008	–	–	–	3	3
Set cost of surgery to £8,000 (base case value: £6,272.87)							
SABR	10,979	2.8334	–	–	–	1	1
RFA	11,261	2.8340	281	0.0005	516,974	2	2
Surgery	13,468	2.7008	–	–	Dominated	3	3
Set cost of RFA to £3,000 (base case value: £4,961.46)							
SABR	10,979	2.8334	–	–	Dominated	2	2

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
RFA	8,603	2.8340	–	–	Dominating	1	1
Surgery	11,571	2.7008	–	–	Dominated	3	3
Set cost of RFA to £6,000 (base case value: £5,089.17)							
SABR	10,979	2.8334	–	–	–	1	1
RFA	12,420	2.8340	1,440	0.0005	2,645,560	2	2
Surgery	11,571	2.7008	–	–	Dominated	3	3
Set cost of SABR to £2,000 (base case value: £4,807.00)							
SABR	7,408	2.8334	–	–	–	1	1
RFA	11,261	2.8340	3,853	0.0005	7,076,860	2	2
Surgery	11,571	2.7008	–	–	Dominated	3	3
Set cost of SABR to £6,000 (base case value: £4,807.00)							
SABR	12,497	2.8334	–	–	Dominated	2	2

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
RFA	11,261	2.8340	–	–	Dominating	1	1
Surgery	11,571	2.7008	–	–	Dominated	3	3
Set cost of treating SAEs to £1,000 (base case value: £2,849)							
SABR	10,915	2.8334	–	–	–	1	1
RFA	11,247	2.8340	332	0.0005	609,424	2	2
Surgery	11,509	2.7008	–	–	Dominated	3	3
Set cost of treating SAEs to £4,000 (base case value: £2,849)							
SABR	11,019	2.8334	–	–	–	1	1
RFA	11,270	2.8340	250	0.0005	459,424	2	2
Surgery	11,609	2.7008	–	–	Dominated	3	3
Set utility for 'progression free without SAEs' = 0.92 (base case value: 0.74)							
SABR	10,979	3.4770	–	–	–	1	1
RFA	11,261	3.4779	281	0.0010	295,414	2	2

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Surgery	11,571	3.2815	–	–	Dominated	3	3
Set utility for 'Progression free with SAEs' = 0.39 (base case value: 0.50)							
SABR	10,979	2.8331	–	–	–	1	1
RFA	11,261	2.8339	281	0.0008	354,496	2	2
Surgery	11,571	2.7005	–	–	Dominated	3	3
Set utility for 'Progression free with SAEs' = 0.60 (base case value: 0.50)							
SABR	10,979	2.8337	–	–	–	1	1
RFA	11,261	2.8340	281	0.0003	886,241	2	2
Surgery	11,571	2.7011	–	–	Dominated	3	3
Set utility for 'Local progression' = 0.26 (base case value: 0.63)							
SABR	10,979	2.7400	–	–	–	1	1
RFA	11,261	2.7405	281	0.0005	516,974	2	2
Surgery	11,571	2.5333	–	–	Dominated	3	3

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Set utility for 'Local progression' = 0.86 (base case value: 0.63)							
SABR	10,979	2.8915	–	–	–	1	1
RFA	11,261	2.8920	281	0.0005	516,974	2	2
Surgery	11,571	2.8049	–	–	Dominated	3	3
Set utility for 'Regional/distant progression' = 0.32 (base case value: 0.40)							
SABR	10,979	2.8280	–	–	–	1	1
RFA	11,261	2.8285	281	0.0005	516,974	2	2
Surgery	11,571	2.6954	–	–	Dominated	3	3
Set utility for 'Regional/distant progression' = 0.48 (base case value: 0.40)							
SABR	10,979	2.8388	–	–	–	1	1
RFA	11,261	2.8394	281	0.0005	516,974	2	2
Surgery	11,571	2.7062	–	–	Dominated	3	3

16 Appendix F: Adverse events data quality checks

KiTEC note that there were n=17 CTCAE grade 5 adverse events amongst n=17 patients (corresponding to death) reported in PROPEL across all three CtE indications. Of these, three patients were also recorded as having died as defined by the date of death (variable DT_DOD). One of these patients had a CTCAE grade 5 '*Urinary Retention*' death adverse event occurring (according to the Adverse Event form) five months before the DT_DOD reported date of death. One of these patients had a CTCAE grade 5 '*Spinal Fracture*' death adverse event occurring (according to the Adverse Event form) almost two years before the DT_DOD and HES/ONS reported date of death. KiTEC have used the DT_DOD date of death in the analysis in this report in these two instances. One of these patients had a CTCAE grade 5 '*Pneumonitis*' death adverse event (according to the Adverse Event form) with no recorded adverse event date, therefore KiTEC have used the DT_DOD variable as date of death.

KiTEC note that the remaining n=14 adverse events amongst 14 patients recorded as a CTCAE grade 5 (i.e. death) did not have death recorded as an outcome in either the PROPEL database designated field or in the HES/ONS national registries. These adverse event/deaths were therefore, considered errors, and were not included as events in the survival analyses.

As part of data quality checks, KiTEC requested the database provider to contact all centres and verify the presence or not of grade 5 events. All centres verified that no grade 5 events occurred in these 17 patients and that the recording of those events in PROPEL was due to wrong data entries.

17Appendix G: Data working group membership

Angela Baker, Radiotherapy Trials Quality Assurance (RTTQA)

Lee Berry, NICE

Kim Fell, NHS England

Dr Matthew Hatton, Chair of UK SABR Consortium

Professor Maria Hawkins, Oxford University Hospital Trust

Dr Ann Henry, Leeds Teaching Hospitals

Jonathan Lee, Radiotherapy Trials Quality Assurance (RTTQA)

Rushil Patel, Radiotherapy Trials Quality Assurance (RTTQA)

Dr Hannah Patrick, NICE

Dr Helen Powell, NICE

Sandy Sahdra, PROPEL database University Hospital Birmingham

Professor Nick Slevin, NHS England/The Christie

Dr Nicholas Van As, The Royal Marsden NHS Foundation Trust

Gareth Webster, PROPEL database University Hospital Birmingham

Libby Zou, PROPEL database University Hospital Birmingham

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