KiTEC

Commissioning through Evaluation:

Stereotactic ablative body radiotherapy (SABR) re-irradiation report

KiTEC

Contents

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Work package reference	RX116
Work package name	Commissioning through Evaluation:
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Date report completed	20/6/2019
Version	1.7

Authorship and acknowledgments

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.

Dr Mariusz Grezda 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.

Acknowledgements

KiTEC's centre manager Viktoria McMillan and project managers, Kasia Dylinska and Joanne Boudour, worked on several aspects of project management of the SABR CtE scheme. Viktoria McMillan for also contributing to the development of the active surveillance plan for the SABR CtE scheme.

KiTEC would like to thank all of the staff at the 17 NHS Trusts that took part in the SABR CtE scheme for their hard work in recruiting, treating patients, and collecting patient data.

The authors thank all members of the SABR CtE Data Working Group (appendix G) for ongoing support and advice in relation to study design, data collection, and analysis.

The authors thank the PROPEL database team from University Hospital Birmingham for their hard work on establishing a national database to host the SABR CtE scheme data. We especially thank Libby Zou and Sandy Sahdra for all their efforts during the data collection and data completeness phases of the project.

The authors thank the following individuals from NICE for their contribution to the planning and management of the SABR CtE project: Dr Hannah Patrick, Dr Helen Powell, and Lee Berry. Hannah Patrick and Helen Powell reviewed the draft report and provided comments and feedback.

The authors would like to thank the EuroQol Research Foundation for offering the use of the EQ-5D tool free in the CtE scheme.

Finally, we would like to thank all the patients that took part to the SABR CtE scheme and contributed with their data to this analysis.

Funding sources & conflicts of interest

KiTEC is an EAC for NICE and its work on the SABR CtE scheme was funded entirely through a contract with NICE. The authors report no conflicts of interest.

Abbreviations

ACR	American College of Radiology
ADT	Androgen deprivation therapy
AE	Adverse events
ASTRO	American Society for Radiation Oncology
BED	Biologically equivalent dose
CBCT	Cone beam CT
CC	Cubic centimetre
CI	Confidence interval
CRC	Colorectal cancer
CtE	Commissioning through Evaluation
DOB	Date of birth
EBRT	External beam radiotherapy
fx	Fraction
G	Grade
HES	Hospital Episode Statistics
HRA	Health Research Authority
IGRT	Image-guided radiotherapy
IQR	Inter Quartile Range
ICER	Incremental cost-effectiveness ratio
KCL	King's College London
KiTEC	King's Technology Evaluation Centre
Kv	Kilovoltage
LC	Local control
MDT	Multidisciplinary team
NICE	National Institute for Health and Care Excellence
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
R&D	Research and Development
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Side effects
SA	Sensitivity analysis
SABR	Stereotactic ablative body radiotherapy
SD	Standard deviation
UK	United Kingdom
VCF	Vertebral compression fracture

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 side effects (SEs). Because of these advantages, SABR can be considered a treatment option in cases where cancer recurs within or at the edge of a previously irradiated region; re-irradiation with standard radiotherapy to the spine and pelvis is commonly avoided as the spinal cord or organs of the pelvis such as the bladder or bowel have often received doses considered near normal tissue tolerance[1]. In these cases SABR can be an alternative treatment option because of the ability to limit the volume of normal tissue that is exposed to radiation, potentially minimising toxicity and increasing local control.

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 undergoing re-irradiation of the pelvis and spine (estimated 450 for the duration of the scheme) to access 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 for these patients.

Between 2015 and 2018, the CtE scheme collected outcomes from 203 (185 undergoing pelvic and 18 spinal re-irradiation) patients recruited from 8 centres nationally. From these 149 patients had their data also linked to the Hospital Episode Statistics (HES) and Office for National Statistics (ONS) registries. The median age of patients was 68 and 60 years, respectively, and most (61.1%) were men. The cohort undergoing pelvic re-irradiation was mainly comprised of patients with prostate (39.5%) and colorectal cancer (28.6%). The cohort undergoing spinal re-irradiation was mainly comprised of patients with sarcoma (16.7%) and renal cancer (16.7%). Approximately half of the

[1] Tolerance is defined by the maximum dose of radiation a normal tissue or organ can receive without developing serious adverse events.

patients (49.19%) undergoing pelvic re-irradiation were treated with Cyberknife. Cone beam[2] CT (CBCT) image guidance was the most commonly used technique to assist treatment delivery in this patient cohort. The majority of patients undergoing spinal re-irradiation, were treated with Cyberknife and planar kV images[3] using fiducial markers was the most commonly used image-guidance technique to assist treatment delivery. For both cohorts, most patients were treated with 5 fractions of radiotherapy receiving 30Gy of radiation (median).

The analysis of people treated under the CtE scheme reported median overall survival (OS) >24 months for both cohorts. The 1-year actuarial[4] OS was 92.0% (95%CI 86.0-95.5%) for people undergoing pelvic re-irradiation. For people undergoing spinal re-irradiation it wasn't possible to estimate 1-year OS due to the small number of events (a minimum of 6 deaths was required to provide estimates). The examination of the Kaplan-Meier curves for people undergoing spinal re-irradiation, indicates an 80% 1-year OS with large 95%CIs. Both results were higher than the OS targets proposed[5] at the beginning of the CtE scheme (1-year target = 60% for both cohorts). In addition, the CtE analysis reported a 2-year OS estimate for people undergoing pelvic re-irradiation at 71.9% (95%CI 60.5-80.5%). The examination of the Kaplan-Meier curves for people undergoing spinal re-irradiation, indicates a 70% 2-year OS with large 95%CIs. The literature does not provide an estimate of 2-year OS for pelvic re-irradiation, therefore, the CtE data is the only evidence available.

The findings of the CtE scheme on the effect of SABR in OS of patients undergoing pelvic and spinal re-irradiation, is partially supported by low quality evidence, mainly from retrospective single centre case series. These studies report median OS between 11.5-40 and 10-22.5 months for people undergoing pelvis and spinal re-irradiation respectively.

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[2] Cone beam CT is an imaging technique using CT images to guide the delivery of radiotherapy.

[3] Planar kv image-guidance is a technique using xrays to guide the delivery of radiotherapy.

[4] 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.

[5] Target OS and LC rates were proposed 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.

The CtE data analysis also reported local control (LC) rates at 1-year of 54% (95%CI 26.3-75.2%) and 75.8% (95%CI 66.7-82.7%) for people undergoing spinal and pelvic re-irradiation, respectively. Both results were higher than the local control targets proposed at the beginning of the CtE scheme (1-year target = 50% for both cohorts), however, the 95%CIs for the spinal re-irradiation overlap with the LC targets proposed at the beginning of the CtE scheme. This is probably attributable to the small patient cohort recruited for this indication (n=18 patients). The results are in accordance with the range of LC outcomes reported in the literature for both cohorts. These studies have reported a 1-year local control between 51.4-100% and 66-90% for pelvis and spinal re-irradiation, respectively.

The CtE data analysis reported grade 3[6] toxicity of 3.8% (95%CI: 1.5 to 7.6%) for people undergoing pelvic re-irradiation which is within than the proposed target of 20%. For people undergoing spinal re-irradiation, the CtE analysis reported grade 3 adverse event rate of 5.6% (95%CI: 0.1-27%) which is within the proposed target set of 20%. No grade 4[7] or 5 toxicity was reported for either cohort which is lower than the target set of 5%. The CtE findings are supported from low quality evidence from the literature that reports low rates of grade 3 toxicity and absence of grade 5 events. The combined findings from the CtE and the published literature, provide low quality evidence that SABR can achieve LC and can be delivered without severe toxicity.

Data on quality of life (QoL) were available for 169 (83%) patients at baseline. Due to the low number of people undergoing spinal re-irradiation, both CtE cohorts were analysed together. According to the summary analysis, the majority of patients did not report issues at baseline and during follow-up. Data completeness decreased over time with approximately 50% and 20% of the patients returning their questionnaires at 12 and 24 months, respectively.

Data on pain scores were available for 185 (91%) patients at baseline. According to the summary analysis, the majority of patients (70%) of patients did not report any pain at baseline. This proportion remained stable until 18 months of follow-up and decreased in the final follow-up time point (24 months) by approximately 15 points. 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 (9%). Data completeness decreased over time with

[6] Defined as severe or medically significant but not immediately life-threatening toxicity resulting in hospitalisation or prolongation of hospitalisation, may also limit self-care or be disabling.

[7] Defined as toxicity resulting to life-threatening consequences that need urgent intervention.

approximately 50% and 20% of the patients returning their questionnaires at 12 and 24 months, respectively. 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, often missing data are 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.

In the published evidence, pain control rates are reported between 50-100% and 65-81% for pelvis and spinal re-irradiation respectively. The included studies report good safety outcomes with SABR, with crude rates of vertebral body fracture ranging from 4.5%-22% and a symptomatic radiation-induced myelopathy rate of 1.2%. Both these results are comparable with studies using SABR in non-previously irradiated spinal metastases and provide low quality evidence that SABR re-irradiation does not lead to severe toxicity. The results reported have a high degree of variability and there is an absence of comparative data and thorough long-term follow-up. There is absence of quality of life outcomes, and of outcomes in children.

According to the patient experience questionnaire, 93% of CtE people undergoing pelvic re-irradiation and 100% undergoing spinal re-irradiation were extremely likely or likely to recommend the SABR service to their friends and family.

The cost-effectiveness analysis found that for adult patients undergoing pelvic re-irradiation following recurrence of cervical or colorectal cancer, SABR results in more QALY gains and lower cost compared to pelvic exenteration, indicating SABR is the more cost-effective intervention. The finding needs to be interpreted carefully in the light of limitations in the available data on exenteration and the comparability of the cohort undergoing SABR with patients undergoing exenteration in the literature. If, as seems likely, it is reasonable to assume that outcomes in patients amenable to surgical exenteration would be improved, the analysis is likely to be conservative with respect to SABR and would support a role for SABR instead of exenteration for patients in which surgery is feasible.

The main limitation of the current evidence (including the analysis of the CtE data) is that no comparative data exists, therefore, the clinical efficacy and safety of SABR versus standard care is unknown. In addition, contrary to published studies (that reported mainly outcomes in spinal re-irradiation), the CtE SABR scheme treated a low proportion (n=18) of people undergoing spinal re-

irradiation. This difference was mainly attributed to the focus of the CtE scheme to recruit patients with good prognosis, contrary to the literature that often treated patients with palliative intent.

The main implication from the available evidence is that the use of SABR in people undergoing pelvic re-irradiation can lead to increased local control without an increase in severe toxicity. The small size of the spinal re-irradiation cohort and the high heterogeneity in patient prognosis between the CtE and the literature, increases the uncertainty around any conclusions drawn for this cohort.

1 Background

1.1 Stereotactic ablative radiotherapy

Stereotactic Ablative Body Radiotherapy (SABR) is an emerging radiation therapy 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 side effects (SEs). In addition, as the technique uses a smaller number of fractions (fx) (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 Re-irradiation

A variety of primary or secondary tumours may arise in the pelvis or spine. Pelvic tumours are commonly due to colorectal, prostate, and gynaecological cancer, all of which may metastasise to regional lymph nodes. Spinal and para-aortic tumours often present as metastases and can be derived from a wide variety of primary tumours such as breast cancer and prostate cancer.

Tumours in the pelvis, spine, or para-aortic area may be treated with a combination of surgery, radiotherapy, and chemotherapy. When previously irradiated tumours in these regions recur locally, further treatment options are limited due to the accumulated radiation dose to nearby organs at risk (for example the spinal cord and bowel). In these cases, conventional radiotherapy techniques cannot be used. In addition, although in some cases surgery can be an option, in others it may be impossible given the proximity of the recurrence to neuro-vascular structures or because of concerns over the extent of radiation-induced fibrosis in the treated area (Schmidt et al. 2012, Murray et al. 2017). Systemic therapy may be adopted with palliative intent, however, in the absence of widespread disease this may lead to systemic toxicity with low control of the recurrent disease.

Where the recurrence is within or at the edge of the previously irradiated region, re-irradiation with standard radiotherapy is commonly avoided as the spinal cord or organs of the pelvis such as the

bladder and bowel have often received doses considered near normal tissue tolerance[8]. In these cases SABR can be an alternative treatment option because of the ability to limit the volume of normal tissue exposed to radiation, potentially minimising toxicity and increasing local control.

It is estimated that 500 patients would be suitable for SABR re-irradiation to the pelvis and spine annually 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, SABR is currently only commissioned by National Health Service (NHS) England for this indication. In order 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:

- Oligometastatic disease;
- Primary liver tumours (hepatocellular carcinoma);
- Re-irradiation of cancers in the spine and pelvis/para-aortic.

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

[8] Tolerance is defined by the maximum dose of radiation a normal tissue or organ can receive without developing serious adverse events.

1.4 Aim of the project

To evaluate the clinical effectiveness, safety and cost-effectiveness of SABR in people undergoing spinal and pelvic re-irradiation.

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 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 evaluation 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 R&D 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 sites 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 Hospital Birmingham (UHB) was selected as the database provider.

1.7 Scope

The scope for the SABR CtE scheme for re-irradiation evaluation is outlined in Table 1.

Table 1: Project scope

Population	Patients who have locally recurrent and previously irradiated pelvic, spinal or para-aortic tumours (primary or secondary).*
Intervention	Stereotactic ablative body radiotherapy (up to 5 fractions and a total dose of 30Gy).
Comparator	No local treatment. Local treatment of tumour recurrence which may be conventionally fractionated radiotherapy or surgical excision.
Outcomes	• Overall survival • Local control† • Pain control • Quality of life • Adverse events • Cost effectiveness
* Inclusion criteria are listed in section 1.7.1 † 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. ‡Progression free survival (PFS) is the length of time during which the disease does not worsen, or the proportion of patients without worsening disease at a defined follow-up point after beginning treatment. 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.	

1.7.1 Eligibility criteria for re-irradiation of the spine

- Metastatic carcinoma with either a histologically or cytologically proven primary site, carcinoma of unknown primary (CUP) with histology or cytology proven metastasis or a male patient with a PSA>50ng/mL and clinical evidence of prostate cancer.
- WHO performance status ≤2.
- Ambulatory without severe comorbidity.
- Life expectancy of more than 6 months.
- A maximum of two sites of spinal metastatic disease requiring treatment for pain relief or tumour control.

- Assessment by spinal SABR MDT that SABR is the most appropriate modality of treatment.
- No current spinal instability.
- No cord compression.
- No chemotherapy within 28 days. Targeted therapies should be stopped a minimum of 14 days prior to SABR.
- At least 6 months from initial radiotherapy course.
- All patients willing to attend follow up and have details collected on a prospective database.

1.7.2 Eligibility criteria for re-irradiation of the pelvis and para-aortic region

- Patients with pelvic or para-aortic nodal, bony, soft tissue recurrence or positive margin after maximal surgery in the pelvis.
- Life expectancy >6 months.
- No significant toxicity from previous radiation.
- >6 months since initial radiation treatment.
- Histologically confirmed malignancy.
- WHO performance status ≤2.
- Ambulatory without severe comorbidity, particularly no significant bowel disease.
- No chemotherapy within 28 days. Targeted therapies should be stopped a minimum of 14 days prior to SABR (concurrent hormone therapy is permitted).
- Patient availability for follow up to assess radiotherapy related morbidity, pain and functional ability for two years.
- Assessment in specialist SABR and site-specific MDTs.

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 hepatocellular carcinoma), 8 sites were selected by NHS England to provide SABR treatments for patients in the re-irradiation cohort. The participating centres are listed below:

- The Royal Marsden NHS Foundation Trust
- Guys and St Thomas' NHS Foundation Trust

- Mount Vernon Cancer Centre (North and East Hertfordshire NHS Foundation Trust)
- Oxford University Hospital NHS Trust
- Leeds Teaching Hospitals NHS Trust
- Nottingham University Hospitals NHS Trust
- University Hospitals Birmingham NHS Foundation Trust
- Barts Health NHS Trust

2 Commissioning through Evaluation questions

NHS England required the following evaluation 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?
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, 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 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 patient 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[9] 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. This was estimated to be approximately 750 patients per year for the three indications (oligometastatic disease, re-irradiation, and hepatocellular carcinoma). For the total duration of the scheme (3 years), 2,250 people were estimated to undergo SABR treatment for the three indications. Of this number, approximately 150 patients per year (total 450) were expected to undergo spinal or pelvic/para-aortic re-irradiation.

4.3 Database

Data for the CtE were collected on three different instruments:

[9] 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

This instrument was provided by NHS England (see appendix C), and allowed 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. It was developed using MS Access and allowed for data collection at the baseline, 4-6 week, 3-month, 6-month, 18 months 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 interim tool was approved by each site's information governance department.

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 sites. The PROPEL database had ethical approval and was managed by the UHB IT department in compliance with NHS security procedures.

PROPEL database also collected DICOM data as a separate project funded by NHS England. The analysis of DICOM data is 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 fed back 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 (Digital 2018, Digital 2018, Digital 2018) data for 149 CtE patients undergoing re-irradiation who had consented for their identifiable data to be used. The linked HES/ONS data covered the period from 2015 to Oct 2018. To understand inconsistencies between data sources, UHB contacted seven centres, which had date of death (DOD) discrepancies between ONS (last updated 31/10/2018) and PROPEL (last updated 22/01/2019).

To understand inconsistencies between data sources, UHB contacted 7 centres which had date of death (DOD) discrepancies between ONS (last updated 31/10/2018) and PROPEL (last updated 22/01/2019). 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 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 Centres the mandatory field completeness newsletters in May 2018 and continued sending them every two months to Centres. UHB also monitored the completeness of patients being followed up. 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 patient experience questionnaire. Median follow-up time with inter quartile range (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 OS and median local control failure 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 indication and reported only for patients undergoing re-irradiation 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.

There was no single variable in the PROPEL database that clearly distinguished and identified the re-irradiation patients into the spine and pelvic subcategories, therefore KiTEC used a combination of the CAB_REIR/CAB_REG and CAB_TRTAREA_1 variables to categorise these.

To determine date of death, where available the 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 date of death or when the latter 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 of grade 5 adverse events. 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 analyses in this report.

4.8 Proposed target outcomes

Proposed target OS and LC 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 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:** • **Re-irradiation pelvis:** OS rate of 60% at 1 year for SABR (figure derived from the findings of an SR including different radiotherapy techniques which reported a 2-year OS rate ranging from 56 to 78.8% and clinical expertise). • **Re-irradiation spine:** OS rates of 60% at 1-year for SABR (figure derived from findings reported in literature of between 60% and 70% at 1 year and clinical expertise).
Does treatment with SABR for the clinical indications covered within the CtE scheme increase local control?	**Proposed target:** • **Re-irradiation pelvis:** LC rate of 50% at 1 year for SABR • **Re-irradiation spine:** LC rate of 50% at 1 year for SABR
What Adverse Events occur as a result of SABR in the CtE cohort of patients?	• **Re-irradiation pelvis:** a target outcome of grade 3 toxicity of 20% and grade 4-5 toxicity of 5% was set for people undergoing pelvic re-irradiation. • **Re-irradiation spine:** a target outcome of grade 3 toxicity of 20% and grade 4-5 toxicity of 5% was set for people undergoing spinal re-irradiation.
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	NA

be used to collect information for all SABR patients. This test has been widely used in the NHS.	
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.	
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.
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 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 of grade 5 adverse events).
- 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).
- Multiple patients with empty rows of data.

Only patients who contributed to the overall survival following SABR first treatment were included in the analysis in this report. Based on the reasons outlined above, a total of n=21 patients were excluded from the analysis in this report.

4.9.2 Patient Recruitment

Data were collected from 8 centres. Figure 1 shows the flow diagram for patient recruitment in the scheme. It should be noted that because centres screened patients through their MDT meetings, it is unknown how many patients were originally screened for eligibility.

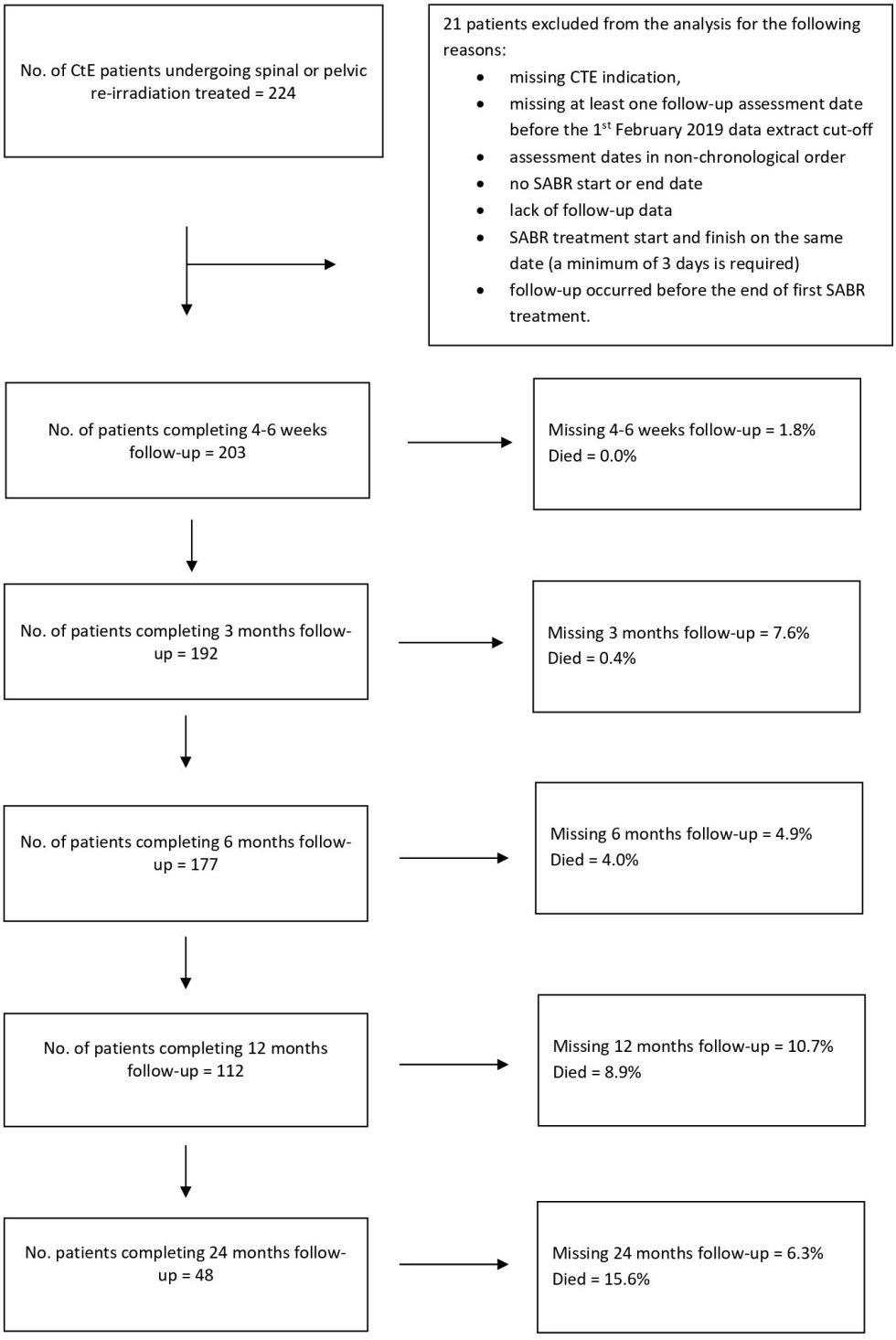


Figure 1: Patient recruitment flow chart.

4.10 Pelvic re-irradiation

4.10.1 Demographics – pelvic re-irradiation

Baseline demographics and clinical characteristics of patients undergoing pelvic re-irradiation are in Table 5 and Table 6.

Table 5: Cohort demographics

	(n=185)	
Age		
Age - N (%)	185	100%
Age - Median (years; IQR)	68	(59 to 74)
Sex		
Male - N (%)	113	61.1%
Female - N (%)	72	38.9%
Ethnicity - N (%)		
White - British	134	81.2%
White - Irish	2	1.2%
White - Any other white background	6	3.6%
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	0	0.0%
Asian or Asian British - Indian	2	1.2%
Asian or Asian British - Pakistani	0	0.0%
Asian or Asian British - Bangladeshi	0	0.0%
Asian or Asian British - Any other Asian Background	1	0.6%
Black or Black British - Caribbean	1	0.6%
Black or Black British - African	2	1.2%
Black or Black British - Any other Black background	2	1.2%
Other Ethnic Groups - Chinese	0	0.0%
Other Ethnic Groups - Any other ethnic group	1	0.6%
Not stated	14	8.5%
Total Ethnicity	165	
Missing* Ethnicity	20	10.8%

Table 6: Baseline clinical characteristics

	N=185	
WHO performance status		
0 - Fully active, able to carry on all pre-disease performance without restriction	128	69.2%
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	54	29.2%
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	3	1.6%
Total WHO performance status	**185**	
Missing* WHO performance status	0	0.0%
Number of metastases**		
0	52	28.1%
1	107	57.8%
2	22	11.9%
3	4	2.2%
Average number of metastases (SD)		0.9 (0.7)
Total number of metastases	**185**	
Missing* number of metastases	0	0.0%
Prior systemic therapy		
Yes	131	70.8%
No	54	29.2%
Total prior systemic therapy	**185**	
Missing* prior systemic therapy	0	0.0%

*Missing % is based on overall number of patients in the specific category.

**Renal and Brain categories for site of metastases were hidden in PROPEL database.

Non metastatic lesions are listed under the 0 category.

The baseline primary tumour diagnosis of patients undergoing pelvic re-irradiation is reported in Table 7.

Table 7: Primary tumour diagnosis

	n=185	
Primary Site - N (%)		
Breast cancer	1	0.5%
Prostate cancer	73	39.5%
Renal cancer	1	0.5%
Colorectal cancer	53	28.6%
Endometrial cancer	21	11.4%
Cervical cancer	14	7.6%
Melanoma	1	0.5%
Sarcoma	2	1.1%
Bladder cancer	1	0.5%
Anal cancer	12	6.5%
Ovarian cancer	1	0.5%
Cholangiocarcinoma	1	0.5%
Urothelial cancer	1	0.5%
Other	3	1.6%
Total primary site	185	

4.10.2 Procedural information – pelvic re-irradiation

The CtE scheme also collected information relevant to the SABR treatment. Table 8 lists the procedural information for patients undergoing pelvic re-irradiation. Approximately half of the patients (49.19%) were treated with Cyberknife. Most patients were treated with 5 fractions of radiotherapy receiving 30Gy of radiation (median). Cone beam CT (CBCT) image guidance was the most commonly used technique to assist treatment delivery.

Table 8: SABR procedural characteristics

	n=185	
SABR treatment platform – N (%)		
Elekta	48	25.95%
Varian	37	20%
Cyberknife	91	49.19%
Tomotherapy	9	4.86%
IGRT* technique – N (%)		
CBCT (soft tissue)	84	45.41%

	n=185	
CBCT (fiducial)	1	0.54%
kV planar (fiducial)	55	29.73%
kV planar (spine)	32	17.3%
MVCT	9	4.86%
Missing	4	2.16%
Number of fractions - N (%)		
3	10	5.41%
4	2	1.08%
5	166	89.7%
6	5	2.7%
15	2	1.08%
Radiotherapy dose Gy		
Median	30	NA
*IGRT = image-guided radiotherapy NA = not applicable		

4.10.3 Overall survival analysis - pelvic re-irradiation

Median follow-up time for re-irradiation pelvis patients was 1.06 years (IQR 0.52 to 1.68). It was not possible to calculate the median overall survival time because it was past the two-year follow-up cut-off (see methods). Overall survival estimates at one and two years were calculated (Table 9) along with a corresponding Kaplan-Meier plot for patients undergoing pelvic re-irradiation (Figure 2).

Table 9 Overall Survival Estimates for re-irradiation pelvis patients

Survival interval	Probability of survival	95% Confidence interval
One Year	92.0%	86.0 to 95.5%
Two Years	71.9%	60.5 to 80.5%

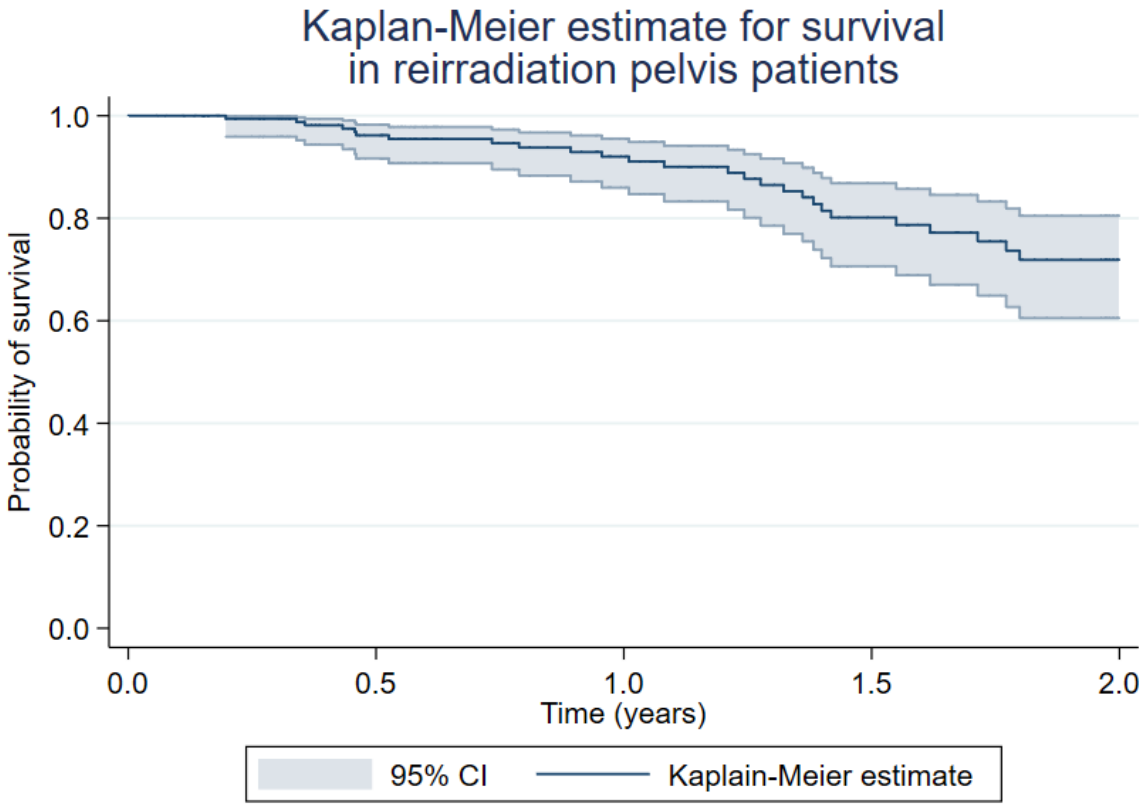


Figure 2: Kaplan-Meier estimate for overall survival in people undergoing pelvic re-irradiation.

4.10.4 Local control analysis – pelvic re-irradiation

Overall local control rates estimates at one and two years were calculated (Table 10) along with a corresponding Kaplan-Meier plot for re-irradiation pelvis patients (Figure 3). Median time to local control failure was 1.76 years.

Table 10: Overall local control rates estimates

Year of local control	Probability of local control	95% Confidence interval
One Year	75.8%	66.7 to 82.7%
Two Years	46.7%	34.8 to 57.7%

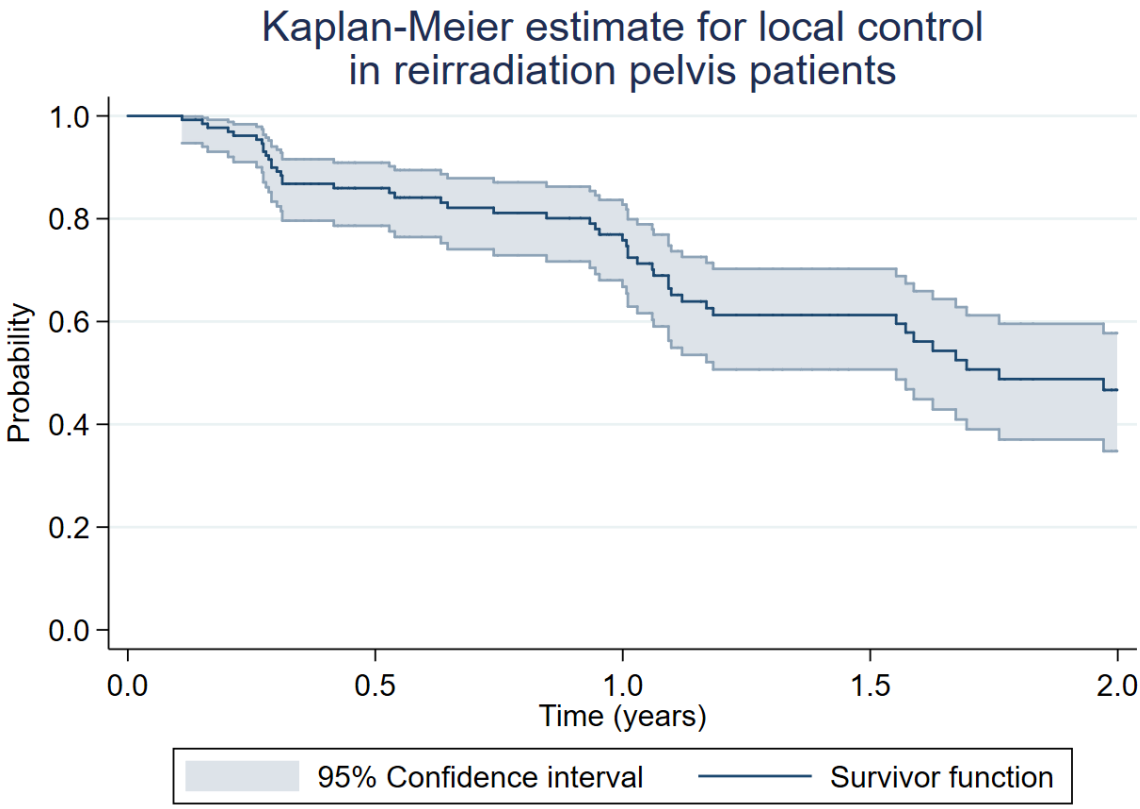


Figure 3: Kaplan-Meier estimate for local control rates in patients undergoing pelvic re-Irradiation

4.10.5 Adverse events – pelvic re-irradiation

Total number of adverse events recorded for all people undergoing pelvic re-irradiation is displayed in Table 11 and a summary of the percentages of patients with 1 or more adverse event reported are in Table 12.

Table 11: Frequency of adverse events

CTCAE grade	Tota number of events recorded for all Re-irradiation – Pelvis patients
Grade 1	518
Grade 2	118
Grade 3	10
Grade 4	0
Grade 5*	0
All grades	646

*Please see more information about the triangulation of grade 5 events in appendix F.

Table 12: Summary table for adverse events: percentage of patients with 1 or more event reported

CTCAE grade	Number of patients	Percentage patients with AE	95% Confidence Intervals
All grades (any AE)	130/185	70.0%	63 to 77.0%
Grade 3	7/185	3.8%	1.5 to 7.6%
Grade 4	0/185	0.0%	0.0 to 2.0%*

*one-sided, 97.5% confidence interval

Table 13 provides a further break-down of all adverse events by CTCAE grade for re-irradiation pelvis patients. Please note that empty grade fields reflect the CTCAE grading criterion, where there are not grading categories up to Grade 5.

Table 13: 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
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	
	1	0	0	0	0	1
Nausea	Grade 1 - Loss of appetite without alteration in eating habits	Grade 2 - Oral intake decreased without significant weight loss, dehydration or malnutrition	Grade 3 - Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	*	*	
	4	3	0			7
Vomiting	Grade 1 - 1 to 2 episodes (separated by 5 minutes) in 24 hrs	Grade 2 - 3 to 5 episodes (separated by 5 minutes) in 24 hrs	Grade 3 - >=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	
	1	0	0	0	0	1
Fatigue	Grade 1 - Relieved by rest	Grade 2 - Fatigue not relieved by	Grade 3 - Fatigue not relieved by rest, limiting self care ADL	*	*	

Adverse event type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
		rest; limiting instrumental ADL				
	188	30	5			223
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); limiting self care ADL; disability	Grade 4 - Life-threatening consequences; symptoms associated with neurovascular compromise	Grade 5 - Death	
	30	8	1	0	0	39
Myelitis	Grade 1 - Asymptomatic; mild signs (e.g., Babinskis reflex or Lhermittes sign)	Grade 2 - Moderate weakness or sensory loss; limiting instrumental ADL	Grade 3 - Severe weakness or sensory loss; limiting self care ADL	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	
	4	4	1	0	0	9
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; disabling	Grade 4 - Life-threatening consequences; urgent operative intervention indicated	Grade 5 - Death	

Adverse event type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	1	0	0	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	
	1	0	0	0	0	1
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	
	43	5	1	0	0	49
Proctitis	Grade 1 - Rectal discomfort, intervention not indicated	Grade 2 - Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Grade 3 - Severe symptoms; faecal urgency or stool incontinence; limiting self care ADL	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	
	22	2	1	0	0	25
Rectal Haemorrhage	Grade 1 - Mild; intervention not indicated	Grade 2 - Moderate symptoms; medical	Grade 3 - Transfusion, radiologic,	Grade 4 - Life-threatening	Grade 5 - Death	

Adverse event type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
		intervention or minor cauterization indicated	endoscopic, or elective operative intervention indicated	consequences; urgent intervention indicated		
	8	1	0	0	0	9
Haematuria	Grade 1 - Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Grade 2 - Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Grade 3 - Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Grade 4 - Life-threatening consequences; urgent radiologic or operative intervention indicated	Grade 5 - Death	
	9	2	0	0	0	11
Urinary frequency	Grade 1 - Present	Grade 2 - Limiting instrumental ADL; medical management indicated	*	*	*	
	85	6				91
Urinary incontinence	Grade 1 - Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Grade 2 - Spontaneous; pads indicated; limiting instrumental ADL	Grade 3 - Intervention indicated (e.g., clamp, collagen injections); operative	*	*	

Adverse event type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
			intervention indicated; limiting self care ADL			
	31	39	1			71
Urinary retention	Grade 1 - Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Grade 2 - Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Grade 3 - Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Grade 4 - Life-threatening consequences; organ failure; urgent operative intervention indicated	Grade 5 - Death	
	10	10	0	0	0	20
Urinary urgency	Grade 1 - Present	Grade 2 - Limiting instrumental ADL; medical management indicated	*	*	*	
	77	6				83
Bone pain	Grade 1 - Mild pain	Grade 2 - Moderate pain; limiting instrumental ADL	Grade 3 - Severe pain; limiting self care ADL	*	*	
	2	2	0			4
Fracture	Grade 1 - Asymptomatic; clinical or	Grade 2 - Symptomatic but non-displaced;	Grade 3 - Severe symptoms; displaced or open wound with	Grade 4 - Life-threatening	Grade 5 - Death	

Adverse event type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	diagnostic observations only; intervention not indicated	immobilization indicated	bone exposure; disabling; operative intervention indicated	consequences; urgent intervention indicated		
	1	0	0	0	0	1
Total adverse events	518	118	10	0	0	646

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

4.10.6 Patient experience – pelvic re-irradiation

The results of the patient experience question for people undergoing pelvis re-irradiation are in Table 14.

Table 14: Patient experience

	Number of patients (n=185)		
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	108	69%	61 to 76%
Likely	38	24%	18 to 32%
Neither likely or unlikely	4	2.6%	0.7 to 6.4%
Extremely unlikely	2	1.3%	0.2 to 4.6%
Don't know	4	2.6%	0.7 to 6.4%
Total	156		
Missing*	29	15.7%	
*Missing % is based on overall number of patients in the specific category.			

4.11 Spinal re-irradiation

4.11.1 Demographics – spinal re-irradiation

Baseline demographics and clinical characteristics of patients undergoing spinal re-irradiation are in Table 15 and Table 17.

Table 15: Cohort demographics

	n=18	
Age		
Age - N (%)	18	100%
Age – Median (years; IQR)	60	(48 to 67)
Sex		
Male - N (%)	11	61.10%
Female - N (%)	7	38.90%
Ethnicity - N (%)		

	n=18	
White - British	14	77.8%
White - Irish	0	0.0%
White - Any other white background	1	5.6%
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	0	0.0%
Asian or Asian British - Indian	0	0.0%
Asian or Asian British - Pakistani	0	0.0%
Asian or Asian British - Bangladeshi	0	0.0%
Asian or Asian British - Any other Asian Background	1	5.6%
Black or Black British - Caribbean	0	0.0%
Black or Black British - African	0	0.0%
Black or Black British - Any other Black background	0	0.0%
Other Ethnic Groups - Chinese	0	0.0%
Other Ethnic Groups - Any other ethnic group	0	0.0%
Not stated	2	11.1%
Total Ethnicity	18	

Table 16: Baseline clinical characteristics

	N=18	
WHO performance status		
0 - Fully active, able to carry on all pre-disease performance without restriction	8	44.4%
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	9	50%
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	1	5.6%
Total WHO performance status	**18**	
Missing* WHO performance status	0	0.0%
Number of metastases**		
0	4	22.2%
1	14	77.8%

	N=18	
2	0	0.0%
3	0	0.0%
Average number of metastases (SD)		0.8 (0.7)
Total number of metastases	**18**	
Missing* number of metastases	0	0.0%
Prior systemic therapy		
Yes	12	66.7%
No	6	33.3%
Total prior systemic therapy	**18**	
Missing* prior systemic therapy	0	0.0%
*Missing % is based on overall number of patients in the specific category. **Renal and Brain categories for site of metastases were hidden in PROPEL database. Non metastatic lesions are listed under the 0 category.		

The baseline primary tumour diagnosis of patients undergoing spinal re-irradiation is reported in Table 17.

Table 17: Primary tumour diagnosis

	Re-irradiation (spine) (n=18)	
Primary Site - N (%)		
Prostate cancer	1	5.6%
Renal cancer	3	16.7%
Colonic cancer	2	11.1%
Endometrial cancer	1	5.6%
Cervical cancer	2	11.1%
Sarcoma	3	16.7%
Germ cell tumour	1	5.6%
Ovarian cancer	1	5.6%
Other	4	22.2%
Total Primary Site	18	

4.11.2 Procedural information – spinal re-irradiation

The CtE scheme also collected information relevant to the SABR treatment. Table 8 lists the procedural information for patients undergoing pelvic re-irradiation. The majority of patients were treated with Cyberknife[10] and 5 fractions of radiotherapy receiving 30Gy of radiation (median). Planar kV images[11] using fiducial markers was the most commonly used image-guidance technique to assist treatment delivery.

Table 18: SABR procedural characteristics

	(n=18)	
SABR treatment platform – N (%)		
Elekta	1	5.56%
Varian	1	5.56%
Cyberknife	15	83.33%
Tomotherapy	1	5.56%
IGRT* technique – N (%)		
CBCT (soft tissue)	2	11.11%
CBCT (fiducial)	2	11.11%
kV planar (fiducial)	13	72.22%
kV planar (spine)	1	5.56%
MVCT	2	11.11%
Number of fractions - N (%)		
3	2	11.11%
5	15	83.33%
6	1	5.56%
Radiotherapy dose Gy		
Median	30	NA
*IGRT = image-guided radiotherapy NA = not applicable		

[10] The Cyberknife system is a medical technology that is used to deliver stereotactic radiotherapy.

[11] Planar kv image-guidance is a technique using xrays to guide the delivery of radiotherapy.

4.11.3 Overall survival analysis – spinal re-irradiation

Median follow-up time for people undergoing spinal re-irradiation was 1.11 years (IQR 0.60 to 1.94). It was not possible to calculate the median overall survival time because it was past the two-year follow-up cut-off (see methods). Overall survival estimates are given in a corresponding Kaplan-Meier plot for people undergoing spinal re-irradiation (Figure 4). Survival estimates were not calculable.

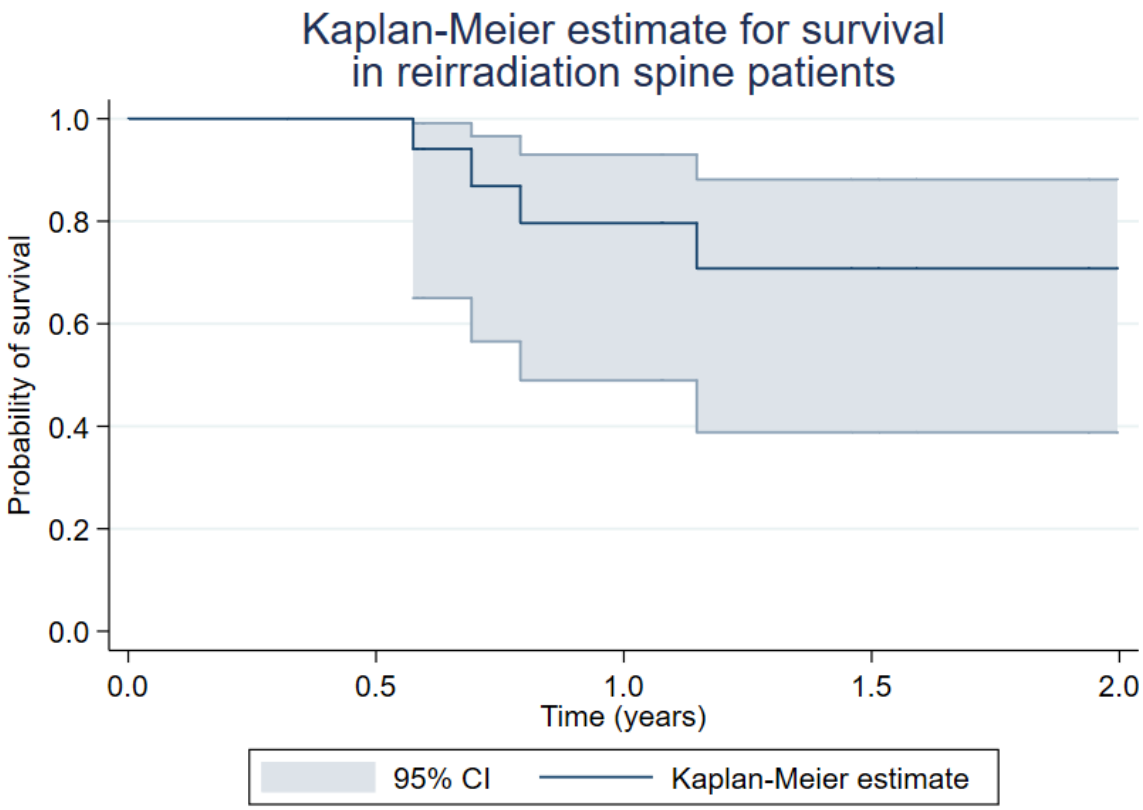


Figure 4 Kaplan-Meier estimate for overall survival

4.11.4 Local control analysis – spinal re-irradiation

Overall local control rates estimates at one and two years were calculated (see Table 19) along with a corresponding Kaplan-Meier plot for people undergoing spinal re-irradiation (Figure 5). Median time to local control failure was 1.08 years.

Table 19: Overall local control rates estimates

Year of local control	Probability of local control	95% Confidence Interval
One Year	53.9%	26.3 to 75.2%
Two year	37.0%	13.0 to 61.6%

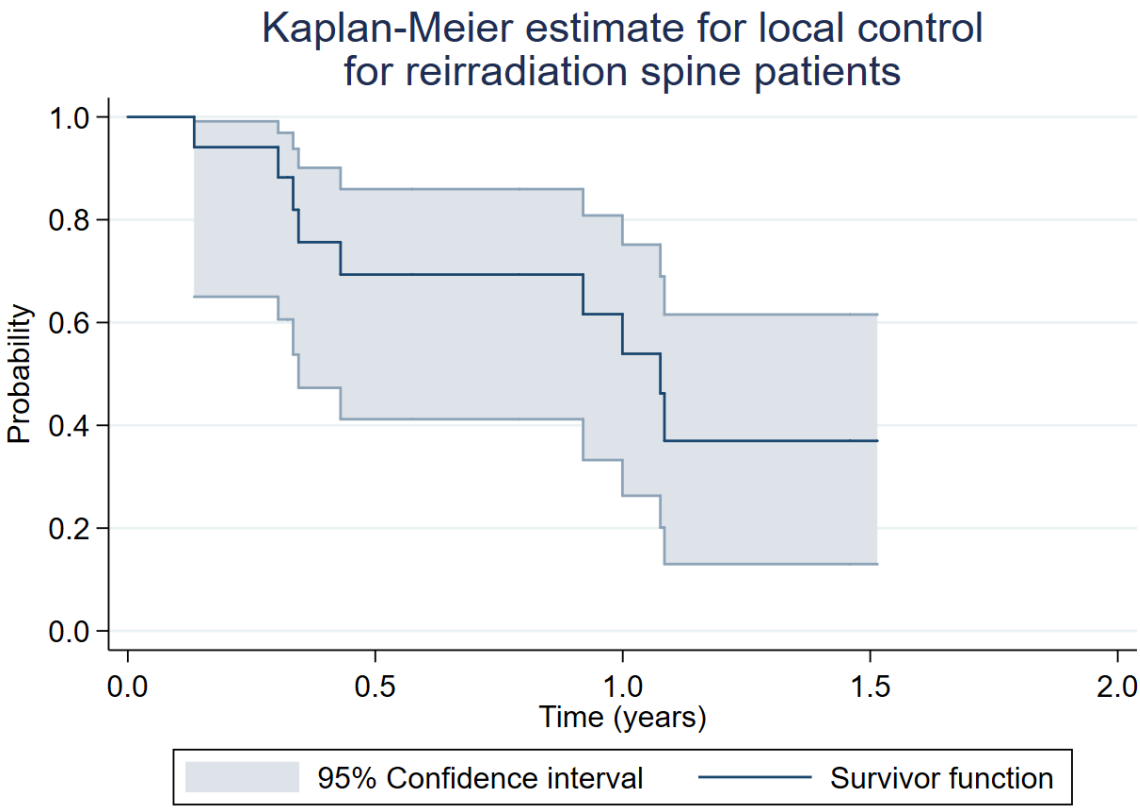


Figure 5 Kaplan-Meier estimate for local control rates in people undergoing spinal re-irradiation

4.11.5 Adverse Events – spinal re-irradiation

Total number of adverse events recorded for all people undergoing spinal re-irradiation is displayed in Table 20 and a summary of the percentages of patients with 1 or more adverse event reported are in Table 21.

Table 20: Frequency of adverse events

CTCAE grade	Re-irradiation - Spine
Grade 1	44
Grade 2	28
Grade 3	1
Grade 4	0
Grade 5*	0
All grades	73

*Please see more information about the triangulation of grade 5 events in appendix F.

Table 21: 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)	10/18	56.0%	31.0 to 78.0%
Grade 3	1/18	5.6%	0.1 to 27.0%
Grade 4	0/18	0.0%	0.0 to 18.5%*

*one-sided, 97.5% confidence interval

Table 22 provides a further break-down of all adverse events by CTCAE grade for people undergoing spinal re-irradiation. Please note that empty grade fields reflect the CTCAE grading criterion, where there are not grading categories up to Grade 5.

Table 22: 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
GI haemorrhage	Grade 1 - Mild, intervention not indicated	Grade 2 - Moderate symptoms; medical intervention or minor cauterization indicated	Grade 3 - Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	
	1	0	0	0	0	1
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	
	1	0	0	0	0	1
Nausea	Grade 1 - Loss of appetite without alteration in eating habits	Grade 2 - Oral intake decreased without significant weight loss, dehydration or malnutrition	Grade 3 - Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	*	*	
	2	7	0			9
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	*	*	
	21	11	1			33

Adverse event type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
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); limiting self care ADL	Grade 4 - Life-threatening consequences; symptoms associated with neurovascular compromise	Grade 5 - Death	
	5	6	0	0	0	11
Myelitis	Grade 1 - Asymptomatic; mild signs (e.g., Babinskis reflex or Lhermittes sign)	Grade 2 - Moderate weakness or sensory loss; limiting instrumental ADL	Grade 3 - Severe weakness or sensory loss; limiting self care ADL	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	
	3	1	0	0	0	4
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
Rectal Haemorrhage	Grade 1 - Mild; intervention not indicated	Grade 2 - Moderate symptoms; medical intervention or minor cauterization indicated	Grade 3 - Transfusion, radiologic, endoscopic, or elective operative intervention indicated; limiting self care ADL	Grade 4 - Life-threatening consequences; urgent intervention indicated	Grade 5 - Death	

Adverse event type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	1	0	0	0	0	1
Haematuria	Grade 1 - Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Grade 2 - Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Grade 3 - Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Grade 4 - Life-threatening consequences; urgent radiologic or operative intervention indicated	Grade 5 - Death	
	1	1	0	0	0	2
Urinary frequency	Grade 1 - Present	Grade 2 - Limiting instrumental ADL; medical management indicated	*	*	*	
	4	1				5
Urinary incontinence	Grade 1 - Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Grade 2 - Spontaneous; pads indicated; limiting instrumental ADL	Grade 3 - Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	*	*	
	0	1	0			1
Urinary urgency	Grade 1 - Present	Grade 2 - Limiting instrumental ADL; medical	*	*	*	

Adverse event type†	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
		management indicated				
	4	0				4
Total adverse events	44	28	1	0	0	73
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						

4.11.6 Patient Experience – spinal re-irradiation

The results of the patient experience question for people undergoing spinal re-irradiation are in Table 23.

Table 23: Patient experience

	Number of patients (n=18)		
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	10	71%	42 to 92%
Likely	4	29%	8.4 to 58%
Neither likely or unlikely	0	0%	0 to 23%
Extremely unlikely	0	0%	0 to 23%
Don't know	0	0%	0 to 23%
Total	14		
Missing*	4	22.2%	
*Missing % is based on overall number of patients in the specific category.			

4.12 Quality of life

The EuroQOL-5D-3L (EQ-5D-3L) questionnaire was used to collect QoL outcomes for people undergoing re-irradiation. 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. Given the low number of people undergoing spinal re-irradiation, both CtE cohorts are summarised together in this section.

Data on QoL were available for 169 (83%) patients at baseline (Table 24). According to the summary analysis, the majority of patients did not report issues at baseline and during follow-up. The highest proportion was observed for the self-care dimension with 90% of patients reporting no problems with self-care across all time points. It should be noted, however, that there was a small decrease in the proportion of patients reporting no issues over time, from 92% at baseline to 86% at the last follow up assessment (24 months). A smaller proportion of patients reporting no problems was observed for the dimensions capturing usual activities and anxiety/depression. For these two

aspects of quality of life, approximately 70% of patients declared no problems for the duration of follow-up. In the usual activities dimension, there was a small decrease from 74% to 67% in people reporting no problems. In the case of anxiety and depression the proportion of people reporting no problems remained unchanged between baseline and end of follow-up (67%).

For the pain/discomfort dimension, the proportion of patients without any problems was approximately 60% for most of the time points with a small decrease at the last follow-up (53%). Finally, on the question exploring the patient's overall state of health (0-100 scale) on average the performance oscillated around 75 for all time points with a small decrease noted at the last follow-up (70%).

Data completeness decreased over time with approximately 50% and 20% of the patients returning their questionnaires at 12 and 24 months, respectively. The analysis assumed that missing data have a random distribution and do not introduce bias.

Table 24: Summary statistics based on responses to the EQ-5D-3L from people undergoing re-irradiation 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	74	74	71	74	67	64	61
2-I have some problems in walking about	26	26	29	25	33	36	39
3-I am confirmed to bed	0	0	0	2	0	0	0
Total	169	166	142	125	85	53	36
Self Care (data in %)							
1-I have no problems with self-care	92	89	87	86	84	87	86
2-I have some problems washing or dressing myself	8	11	13	13	15	11	14
3-I am unable to wash or dress myself	0	0	0	1	1	2	0
Total	169	166	142	125	85	53	36
Usual activities (data in %)							
1-I have no problem with performing my usual activities	74	73	71	75	71	74	67
2-I have some problems performing my usual activities	25	26	27	23	27	26	31
3-I am unable to perform my usual activities	1	1	2	2	2	0	3
Total	169	166	142	125	85	53	36
Pain/discomfort (data in %)							
1-I have no pain or discomfort	61	64	63	61	65	64	53
2-I have moderate pain or discomfort	38	34	33	37	32	34	42
3-I have extreme pain or discomfort	1	2	4	2	4	2	6
Total	169	166	142	125	85	53	36
Anxiety depression (data in %)							
1-I am not anxious or depressed	67	72	67	70	73	75	67
2-I am moderately anxious or depressed	31	27	32	28	25	23	31

3-I am extremely anxious or depressed	2	1	1	2	2	2	3
Total	169	166	141	125	84	52	36
Your health today (range 0-100)							
Mean	76	78	76	76	74	74	70
Standard deviation	18	17	20	19	19	18	21
Total	166	163	136	114	77	49	32

4.13 Pain score

The numeric version of the VAS was used to collect pain control outcomes in people undergoing re-irradiation. The questionnaire, asks the respondent to select a number between 0-10 that best reflects the intensity of their pain. Given the low number of people undergoing spinal re-irradiation, both CtE cohorts are summarised together in this section.

Data on pain scores were available for 185 (91%) patients at baseline. According to the summary analysis, the majority of patients (70%) of patients did not report any pain at baseline. This proportion remained stable until 18 months of follow-up and decreased in the final follow-up (24 months) by approximately 15 points. 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 (9%). Table 25 and Table 26 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 over time with approximately 50% and 20% of the patients returning their questionnaires at 12 and 24 months, respectively. The analysis assumed that missing data have a random distribution and do not introduce bias.

Table 25: 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	1.25	1.23	1.41	1.45	1.32	1.37	1.80
Standard deviation	2.39	2.19	2.50	2.39	2.42	2.30	2.53
Total	185	181	153	137	94	57	40

Table 26: 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	72.43	68.51	70.59	68.61	72.34	70.18	57.50
1	3.78	4.42	1.96	1.46	1.06	0.00	0.00
2	3.24	6.63	3.27	3.65	3.19	5.26	12.50
3	3.24	3.31	3.92	4.38	4.26	1.75	10.00
4	2.16	3.87	3.27	4.38	5.32	5.26	0.00
5	6.49	8.29	6.54	8.03	4.26	8.77	7.50
6	2.16	1.10	3.92	3.65	3.19	7.02	5.00
7	3.24	0.55	1.96	3.65	2.13	0.00	2.50
8	1.62	2.76	3.27	2.19	3.19	1.75	5.00
9	1.08	0.00	1.31	0.00	1.06	0.00	0.00
10	0.54	0.55	0.00	0.00	0.00	0.00	0.00
N	185	181	153	137	94	57	40

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 pelvic exenteration for patients receiving re-irradiation in the pelvic region following recurrence of cervical or colorectal cancer. The comparator was chosen after discussion with clinicians at the commencement of the CtE study. Whilst data to populate the SABR arm of the model was taken from CtE cohort, many of the patients receiving SABR may not have been suitable candidates for exenteration. The implications of this are discussed in the limitations section.

5.2 Methods

5.2.1 Population & intervention

The base case for the analysis consisted of a hypothetical cohort of adult patients receiving re-irradiation in the pelvic region following recurrence of cervical or colorectal cancer. When entering the model, this patient group will receive an initial treatment of pelvic exenteration 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 progression[13] will receive palliative care.

5.2.2 Model structure

In order to compare the total cost and cost-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 in order to model patients' possible prognoses after treatments, which are expressed in several mutually exclusive health states. In this model, nine

[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).

mutually exclusive health states were included (Figure 7). Patients commence in either the 'progression free, no SAE' or the 'progression free and SAE' health state depending on whether they have a SAE following initial treatment, (defined as Clavien Dindo grade III-IV, including pelvic abscesses and enterocutaneous or enterovesical fistulae). The health state occupied by the patient depends on the patient's cancer progression status (no progression, local progression, or regional/ distant progression), number of treatments that the patient has received (initial treatment or retreatment). The cycle length is one month and the model adopted a 5-year horizon.

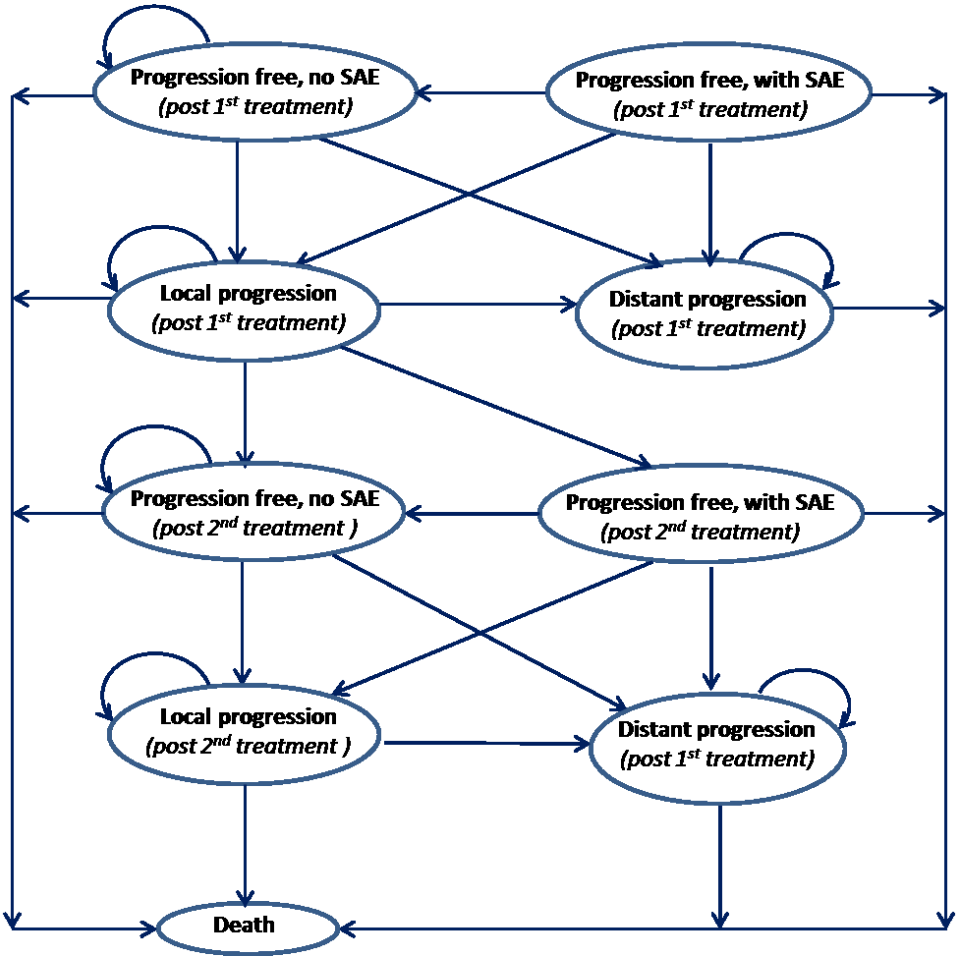


Figure 6: Markov model structure

5.2.3 Cost-effectiveness analysis

Each of the health states in Figure 6 is assigned a cost and effectiveness value that patients accrue while in that state. The costs reflect the treatment that the patient is currently receiving (e.g. pelvic exenteration 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 the quantity and quality of life. For each treatment, the overall costs and effectiveness are calculated on the basis of the total length of time patients spend in each health state over the time horizon. According to the National Institute for Health and Care Excellence (NICE) guideline manual (The National Institute for Health and Care Excellence 2017), costs and benefits incurred today are usually valued more highly than costs and benefits occurring in the future. Therefore, both costs and QALYs 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 has been undertaken to assess the quality and availability of evidence on costs, survival, and quality of life of patients undergoing pelvic exenteration. The databases searched were Medline (plus Epub Ahead of Print, In-Process & Other Non-Indexed Citations) and Embase; the search terms are included in Appendix B. These studies were supplemented by checking references and citations of relevant studies. After de-duplication, the initial database search retrieved 1104 studies. After initial screening and exclusion of non-relevant studies there were 578 relevant studies for patients undergoing pelvic exenteration. 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 5.2.5), and health-related quality of life (HRQoL) data (section 5.2.6). 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 bias arising from differences in patient populations across studies. This assumption was tested in structural sensitivity analysis, using data obtained from the SABR CtE scheme and the best available literature. It should be noted that all probability data reported in Table 27 and Table 28 are probability per cycle (per month), unless otherwise specified.

5.2.4.2 Cancer progression data

This section describes cancer progression data for patients receiving re-irradiation in the pelvic region after treatment (including initial treatment and retreatment), and recurrent patients without retreatment. In the base case analysis, it was assumed that both interventions of interest (pelvic exenteration 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 who received treatment, and recurrent patients without retreatment are presented in Table 27, and briefly described below.

Table 27: Cancer progression rates for patients after initial treatment or after retreatment

	Monthly transition rate
No progression to local progression	0.85% [a]
No progression to regional/distant progression	0.52% [a]
Local progression to regional/distant progression	3.53% [a]
a: Estimated from Milne et al.	

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 number of systematic reviews about the outcomes for patients receiving pelvic exenteration have been published (Mendez et al. 2017, Sasikumar et al. 2017, Platt et al. 2018, Barrera et al. 2019), however none of them reported the transitional probabilities of interest for the target population. Therefore, progression rates were obtained from a recent cohort study which reports outcomes for 100 patients undergoing pelvic exenteration in Australia (Milne et al. 2014). This study reports that cancer recurred in 36 patients: locally in 14, as a distant metastasis in 14, and both locally and with distant metastasis in 8. Based on the assumption that patients who had both local and distant recurrence developed local recurrence first, the cancer progression rates were calibrated and are presented in Table 27. It was assumed that the progression rate is the same for patients who are receiving initial and repeated treatment. In sensitivity analysis the short-term progression rate for patients receiving SABR was obtained from the CtE scheme (see below); the long-term progression rate was assumed the same as pelvic exenteration.

Cancer progression data – Data obtained from the CtE scheme

Of the 61 patients receiving re-irradiation in the pelvic region for colorectal cancer or cervical cancer included in the trial, 14 developed local recurrence, and 19 developed regional/distant recurrence. The exponential distribution appears to give the closest fit to the progression rate from no

progression to local recurrence (monthly transition rate = 2.44%), while the lognormal distribution appears to give the closest fit to the progression rate from no progression to regional/distant recurrence. 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 (see section 5.4.1).

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 28 and briefly described below.

Table 28: Monthly mortality rate for patients with different progression status

	Monthly mortality rate	**Source**
Operative mortality for patients receiving pelvic exenteration	1.60%	(Barrera et al. 2019)
Patients with no progression	0.15%	Calibrated based on published data [a]
Patients with local progression	0.87%	
Patients with regional/distant progression	3.70%	

Notes:

[a]: Calibrated based on: (1) the overall survival data for patients received pelvic exenteration reported in a systematic review (Barrera et al. 2019); (2) the five-year relative risk of mortality data between different colorectal cancer progression status reported by Office for National Statistics (Office for National Statistics 2016); (3) the cancer progression rates reported in Table 27.

Mortality data – Data obtained from published literature

The 30-day operative mortality for patients receiving pelvic exenteration was obtained from a recent meta-analysis including 56 studies with 3,067 patients who received pelvic exenteration for primary and recurrent rectal or gynaecological malignancies (Barrera et al. 2019). After the first 30 days, it was assumed that 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. None of the systematic reviews (Sasikumar et al. 2017, Platt et al. 2018, Barrera et al. 2019) reported survival outcomes by cancer progression status. Therefore, the mortality data for patients at different progression status were calibrated based on the following data:

(1) the overall survival data for patients receiving pelvic exenteration reported in the latest systematic review (5-year survival: 41.8%; Barrera et al. 2019);

(2) the five-year relative risk of mortality data between different colorectal cancer progression status reported by the Office for National Statistics in England (Office for National Statistics 2016);

(3) the cancer progression rates reported in Table 27.

In sensitivity analysis, the mortality risk over the first two years for patients receiving SABR were obtained from the CtE scheme (see below); mortality after two years was assumed to be the same as for pelvic exenteration due to lack of data.

Mortality data – Data obtained from the CtE scheme

Of the 61 patients receiving re-irradiation in the pelvic region included in the CtE scheme, 3 died during the trial period. The exponential distribution appears to give the closest fit to mortality data (monthly mortality rate = 0.53%). Due to the small sample size and short observation period, the mortality data obtained from the CtE scheme was not used in the base case analysis and was only tested in the structural sensitivity analysis (see section 5.4.1).

5.2.4.4 Probability of retreatment

This section describes the probabilities of receiving retreatment with the same treatment initially given for patients who develop local progression after initial treatment. Patients who develop recurrence after receiving pelvic exenteration are not eligible for another pelvic exenteration.

However, some of them will be eligible for resection of the recurrent cancer: this was estimated at 33.33% as reported by Mourton et al (2007). The probability of retreatment with SABR was obtained from published literature (Zerini et al. 2015).

Table 29 Probability of retreatment received different treatment

	Probability of retreatment	Source
For patients received pelvic exenteration	0%[1]	(Mourton et al. 2007)
For patients received SABR	50%	(Zerini et al. 2015)
Notes: [1] Although patients who develop recurrence after pelvic exenteration are not eligible for another pelvic exenteration, in the model it was assumed that 33.33% of them were eligible for resection of the recurrent cancer (Mourton et al. 2007).		

5.2.4.5 Severe adverse events (SAEs)

The probability of developing SAEs for patients receiving different treatments are reported in Table 29. The probability of developing SAEs for patients who received pelvic exenteration was obtained from recent systematic reviews (Platt et al. 2018, Barrera et al. 2019): 31.22% was used as the baseline value while a range 7.69% to 58.10% was tested in one-way sensitivity analysis. The probability of developing SAEs for patients receiving SABR was obtained from the CtE scheme (0/61, 0%). The probability of SAEs reported by a recent systematic review for SABR was tested in sensitivity analysis (6.34%) (Murray et al. 2017).

Table 30: Probability of developing SAEs for patients received different treatment

	Probability of SAEs	Source
Probability of developing SAEs for patients received pelvic exenteration	31.22%	Calculated from studies included in a recent systematic review (Platt et al. 2018)
After patients received SABR	0.00%	CtE scheme

5.2.5 Cost and resource data

This model takes the perspective of the NHS and Personal Social Services (PSS), as recommended by NICE (October 2014). The financial year is 2016. The cost components considered in the model include: initial treatment (pelvic exenteration or SABR), 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 31. 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 Hospital & Community Health Services Index (Curtis 2016). The resource use data for patients receiving pelvic exenteration were mainly obtained from published literature. The package price for SABR is £3,432 for 3 fractions, £4,856 for 5 fractions and £6,992 for 8 fractions (NHS England 2015). Data from the SABR CtE scheme, showed that of 61 patients receiving re-irradiation in the pelvic region, 5 patients had three fractions, 1 patient had four fractions, 54 had five fractions, and 1 patient had six fractions. Assuming that NHS England reimburses 4 and 6 fractions at the lower package price, the weighted cost per patient was calculated as £4,716.

Table 31: Unit cost and resource use data

Item	Unit cost	Resource use	Total cost
Total pelvic exenteration			
Total pelvic exenteration	£19,069.89 [a]	1	£19,069.89
Resection of recurrent cancer after receiving pelvic exenteration			
Surgical procedure	£6,272.87 [b]	1	£6,272.87
Additional bed days	£297.00 [c]	2.24 [d]	£665.28
		Total	£6,938.15
SABR			
SABR	£4,716 [e]	1	£4,716.00
Outpatient follow-up			
Outpatient follow-up	£346 [f]	Every 3 months prior to disease progression	£346
SAEs			

Treatment for SAEs	£4,809 [g]	N/A	£4,809
Retreatment			
Retreatment	Assume to be the same as initial treatment		
Palliative care			
Palliative care for patients with regional/distant progression	£546.43 per month [h]	N/A	£546.43 per month

a. NHS Reference Costs 2015–16 (Department of Health 2016), HRG code LB71Z: 'Total Pelvic Exenteration', including 15.76 elective inpatient bed days, 20 non-elective long stay bed days and outpatient procedure.

b. 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.

c. 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).

d. 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.

e. The package price for SABR is £3,432 for 3 fractions, £4,856 for 5 fractions and £6,992 for 8 fractions (NHS England 2015). The data of CtE scheme showed that of 61 patients receiving re-irradiation in the pelvic region, 5 patients had three fractions, 1 patient had four fractions, 54 had five fractions and 1 patient had six fractions. Assuming that NHS England reimbursees 4 and 6 fractions at the lower package price, the weighted cost per patient was calculated as £4,716.

f. NHS Reference Costs 2015-16 (Department of Health 2016), currency code LB71Z, service code 3023: outpatient procedure for total pelvic exenteration.

g. NHS Reference Costs 2015–16 (Department of Health 2016), currency code WH07A, WH07B, WH07C, WH07D: 'Infections or Other Complications of Procedures, with single or Multiple Interventions', weighted by number of activities.

h. End of life cost for people with colorectal cancer, uplifted from Round et al (2015).

5.2.6 Health-related quality of life (HRQoL)

The model required utility values for four health states: progression free without SAEs, progression free with SAEs, local progression, and regional/distant progression. A recently published systematic review reported utility values for patients with colorectal cancer (Jeong and Cairns 2016). Of the 57 studies included in this systematic review, three of them reported utility data by cancer progression stage. Of these three studies, the one conducted by Ness et al was considered to be most appropriate because this study used standard gamble method to directly elicit utility values from patients with colorectal cancer (Ramsey et al. 2000). The utility values reported by the other two studies were tested in one-way sensitivity analysis. A recently published systematic review examined the utility for patients undergoing pelvic exenteration (Harji et al. 2016). However, none of the studies included by this systematic review reports disutility caused by SAEs. Therefore, a UK study which reported the disutility of SAEs for patients who experienced major complications of any pelvic exenteration was used (Archer et al. 2018). The utility assessment tool used by the study was the 12-Item Short Form Health Survey (SF-12). The reported SF-12 score was mapped to EQ-5D values using the algorithm suggested by Sullivan et al (Sullivan and Ghushchyan 2006). All utility data used in the model are presented in Table 32.

The original intention to quantify the impact of adverse events on quality of life using the CtE data was not undertaken. This analysis had been specified conditional on the data being of sufficient quality. The analysis was judged inappropriate for the following reasons: there were concerns regarding the accuracy of the capture of the date of adverse events and whether this was sufficiently close to the date at which quality of life was measured; it was unclear how data measured using the EQ-5D-5L had been entered into the database by centres; and the number of patients suffering a severe adverse event was low.

Table 32: Health states and their utility weight used in the model

Health state in model	Utility weight	Range	Source
Progression free	0.84	0.74-0.84	CtE scheme, Ness et al (Ness et al. 1999), Ramsey et al (Ramsey et al. 2000) and Wong (Wong et al. 2013)
Local progression	0.74	0.74-0.84	As above
Regional/ distant progression	0.46	0.46-0.84	As above
Disutility of SAEs	0.08	0.0-0.10	Archer et al (Archer et al. 2018) and Sullivan et al (Sullivan and Ghushchyan 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 assumes same cancer progression rate and same mortality rate for all three interventions. 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 pelvic exenteration were calibrated from published literature (Table 27). The cancer progression rates for patients who received SABR were obtained from the CtE scheme: no progression to local progression (exponential distribution, monthly transition rate=2.44%); no progression to regional/distant recurrence: (rate varying over time modelled as lognormal distribution (μ=0.4322; σ=1.1934)).

(2) Assuming different mortality rates for patients receiving different interventions. The mortality rate for patients who received pelvic exenteration was obtained from the published literature (1.44% per month; Barrera 2019). The 2-year mortality rate for patients who received SABR was obtained from the CtE scheme (exponential distribution, monthly mortality rate=0.53%), while the 2-year onwards mortality rate for SABR was assumed to be the same as for patients who received pelvic exenteration.

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

The base case and structural sensitivity analysis results are presented in pelvic exenteration became the most cost-effective intervention (Table 33). In the base case analysis, it was assumed that: The cancer progression rates are the same for all patients, regardless of which intervention they received;

(1) Patients' 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.

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 with SABR or exenteration (patients who had recurrence after receiving pelvic exenteration are not eligible for another pelvic exenteration, however some of them are eligible for resection of recurrent cancer).

The results of base case analysis show that SABR dominates pelvic exenteration. This is likely to be because compared with pelvic exenteration, SABR is associated with a lower probability of SAEs (0% vs 31.22%), and higher probabilities of receiving re-treatment (50.00% vs 30.33%). In structural sensitivity analyses, when it was assumed that different interventions are associated with different cancer progression rates and/or different mortality rates, SABR remained the most cost-effective intervention except in one scenario (SA1 in Table 33). In this scenario pelvic exenteration became the most cost-effective intervention.

Table 33: 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	13,801	3.1973	-14,827	0.0935	Dominating	1	1
Pelvic exenteration	28,628	3.1038	–	–	Dominated	2	2
SA 1: Assuming different cancer progression rate for patients received different interventions [1] *(base case analysis assumes same progression rate for both interventions)*							
SABR	18,080	2.1590	–	–	–	2	2
Pelvic exenteration	28,628	3.1038	10,547	0.9448	11,164	1	1
SA 2: Assuming different morality rate for patients received different interventions, short-term mortality for SABR was obtained from CtE, while long-term mortality for SABR was assumed to be the same as pelvic exenteration [2] *(base case analysis assumes same mortality rate for both interventions)*							
SABR	14,087	2.8162	-13,425	0.4590	Dominating	1	1
Pelvic exenteration	27,511	2.3572	–	–	Dominated	2	2

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

Notes: [1]. The cancer progression rates for patients who received pelvic exenteration were calibrated from published literature (Table 1). The cancer progression rates for patients who received SABR were obtained from the CtE scheme: no progression to local progression: exponential distribution, monthly transition rate=2.44%; no progression to regional/distant recurrence: lognormal distribution (μ=0.4322; σ=1.1934)). [2]. The mortality rate for patients who received pelvic exenteration was obtained from published literature (1.44% per month) (Barrera et al. 2019). The 2-year mortality rate for patients who received SABR was obtained from the CtE scheme (exponential distribution, monthly mortality rate=0.53%), while the 2-year onwards mortality rate for SABR was assumed to be the same as patients who received pelvic exenteration.

5.4.2 One-way sensitivity analysis results

34 scenarios were tested using one-way sensitivity analysis (Appendix E). The results show that under the NICE £20,000 per QALY willingness-to-pay threshold, the base case conclusion (SABR being the most cost-effective intervention) is robust to all scenarios tested.

5.4.3 PSA results

The results of PSA (Figure 7) show that, for both lower and higher thresholds of NICE, the probability that SABR is cost-effective compared to pelvic exenteration is 99.94%.

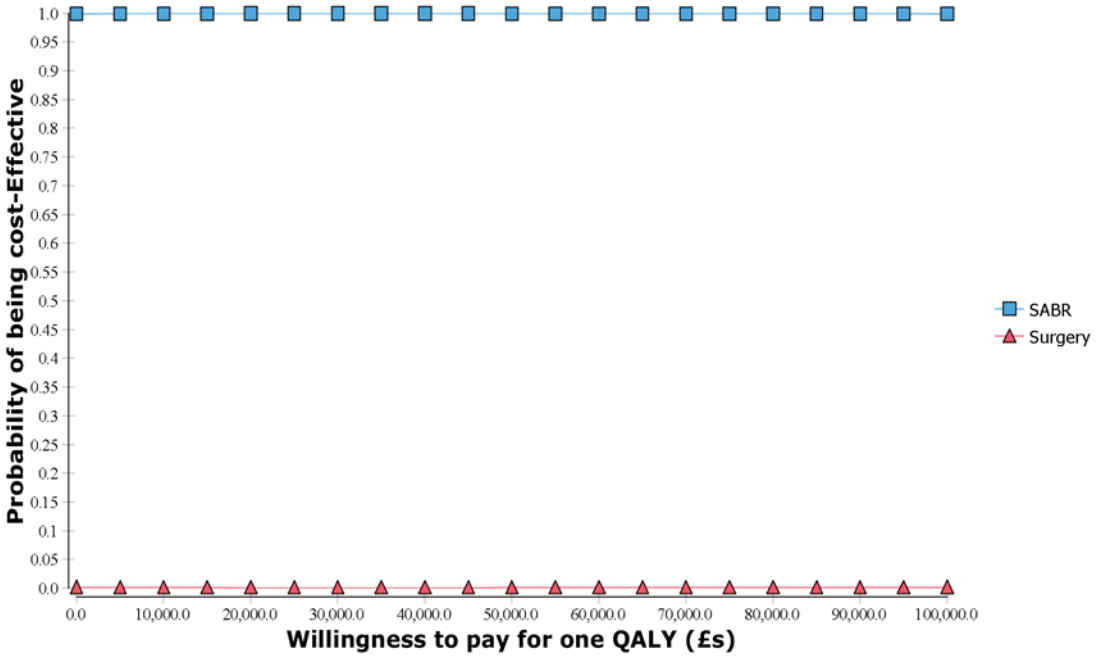


Figure 7 Cost-Effectiveness Acceptability Curve

5.5 Discussion and conclusions

5.5.1 Comparison with published studies

The literature search conducted for this study did not identify any published economic evaluations which compared pelvic exenteration with SABR for adult patients receiving re-irradiation in the pelvic region following recurrence of cervical or colorectal cancer. Therefore, it is not possible to directly compare our findings with published studies.

5.6 Strengths and limitations of the analysis

5.6.1 Strengths

There are three strengths of our study:

(1) To our knowledge, this is the first economic analysis which compare pelvic exenteration and SABR for patients receiving re-irradiation in the pelvic region following recurrence of cervical or colorectal cancer.

(2) The clinical data for pelvic exenteration were carefully selected from the best evidence sources identified from the literature review, while the clinical data for SABR were mainly 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 the CtE scheme and published studies which reported different utility for patients at 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.

5.6.2 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) Lack of clinical studies which directly compare SABR with pelvic exenteration. Therefore, we had to use naive indirect comparisons to capture the relative effects between interventions. This can potentially introduce significant selection bias.

(2) Lack of clinical evidence about cancer progression rates for patients who received alternative treatments. As a result, the progression rates used in the base case analysis were calibrated based on published data.

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

(4) Comparability of patients undergoing exenteration in the literature and patients in the CtE cohort. Most patients undergoing SABR in the CtE cohort would not have been eligible for exenteration surgery. It likely that outcomes for these patients after SABR will be worse than those of patients whose tumour is still amenable to surgical resection. While we cannot be certain, the likely bias introduced by the lack of comparability is in favour of exenteration.

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

5.7 Conclusion

This analysis found that for adult patients receiving re-irradiation in the pelvic region following recurrence of cervical or colorectal cancer, SABR results in more QALY gains and lower cost compared to pelvic exenteration, indicating SABR is the more cost-effective intervention. The finding needs to be interpreted carefully in the light of limitations in the available data on exenteration and the comparability of the cohort undergoing SABR with patients undergoing exenteration in the literature. If, as seems likely, it is reasonable to assume that outcomes in patients amenable to surgical exenteration would be improved, the analysis is likely to be conservative with respect to SABR and would support a role for SABR instead of exenteration for patients in which surgery is feasible.

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 re-irradiation of the spine and pelvis/para-aortic.

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 searches were carried out on 8th March 2019). The searches retrieved 1830 records (Appendix A: Prisma flow

chart). Following de-duplication in EndNote X7, 1254 records were assessed for relevance according to the criteria outlined in Table 34. The full details of the search strategy are included in Appendix B.

Table 34: PICO table

Population and Indication	Patients who have locally recurrent and previously irradiated pelvic, spinal or para-aortic tumours (primary or secondary). Patients may have had or be having standard care, which differs depending on primary tumour site. Systemic treatments may include chemotherapy, hormone treatment or molecular targeted treatments.
Intervention	Stereotactic ablative body radiotherapy (up to 5 fractions and a total dose of 30Gy).
Comparators	No local treatment. Palliative care. Local treatment of tumour recurrence which may be conventionally fractionated radiotherapy or surgical excision.
Outcomes	• Median overall survival • 1 year survival • Local control • Progression free survival‡ • Acute and late radiotherapy toxicity (including, but not limited to, fatigue, nausea, diarrhoea and bone fracture) • Quality of life • Pain control • Cost effectiveness
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 Any study with a patient population of <30 patients
‡Progression free survival (PFS) is the length of time during which the disease does not worsen, or the proportion of patients without worsening disease at a defined follow-up point after beginning treatment. 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.	

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 Study identification and selection

The 1254 abstracts identified after deduplication, were first assessed by title and abstract alone. Following the first sift, 40 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, 13 were found to 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 35, Table 36 and Table 37 list the methodological characteristics of all included studies.

6.2.2 Evidence summary tables

Table 35: Studies for re-irradiation of the spine

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Boyce-Fappiano et al. 2017 Retrospective case series Single centre US Recruitment period 2001-2013 162 patients with 237 spinal metastases from various primary cancers (21% lung*, 16% breast) Median age 64.3 years, 99 men (61%). Mean lesion size: Not reported	Initial treatment with EBRT EBRT median dose 30Gy/10fx. Median time to re-irradiation 10.2 months Median dose of 16Gy/1fx Median 4 month follow-up.	Pain improvement 81% Neurological response: 82% Radiographic response: 71% All adverse events: 6.8% Dysphagia or odynophagia = 1.9% Sensory changes, weakness, or radiculopathy = 3.1% Radionecrosis = 0.6% Vertebral compression fractures [VCF] = 9.3%	**Appraisal:** Non-comparative case series – no randomisation, blinding, concealment. Single centre experience therefore less generalisable results. Recruitment period was over a decade starting from early 2000s. The intervention and standard care may be less comparable with current standards. The study population and intervention are matched to the scope of the CtE scheme however, the authors do not report detailed eligibility criteria. The patient population is heterogeneous with regard to primary tumour site. Pain and neurologic response are subjective outcomes and retrospective analysis is not reliable. Short-term follow-up does not allow capturing long-term toxicity. It is unknown if the study was adequately powered to detect any of the clinical outcomes. **Quality of evidence score:** 4 **Applicability:** Low

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Chang et al. 2012 Retrospective cohort Single centre Korea Recruitment period 2002-2008 185 patients with spinal metastases from various primary cancers of which 54 underwent re-irradiation Mean age: 54.5 years Mean lesion size: 58.4 cm^3	Initial treatment with EBRT EBRT mean dose 39.2Gy Median time to re-irradiation 24.5-months (mean EQD2[14] 51.1Gy). Mean 17.3-month follow-up.	Overall survival [OS]: Re-irradiation 20.7 months (mean), 11 months (median), first line SABR 32.4 months (p=0.022). Progression free survival [PFS]: Re-irradiation 18.0 months, first line SABR 26.0 months (p=0.029). 2-yr pain/radiographic control rates: Re-irradiation 85.7%/78.6%, first line SABR 90.2%/90.2% (both non-significant) Adverse events: Overall 12 symptomatic vertebral compression fractures were seen	**Appraisal:** Non-comparative case series – no randomisation, blinding, concealment. Single centre experience therefore less generalisable results. Recruitment period was over a decade ago, starting from early 2000s. The intervention and standard care may be less comparable with current standards. The study population and intervention are matched to the scope of the CtE scheme however the authors do not report detailed eligibility criteria. The patient population is heterogeneous with regard to primary tumour site. The study treated lesions ranging from 1.3cm^3 to 265cm^3 resulting in a highly heterogeneous cohort potentially increasing the risk of toxicity (larger treatment area) and lowering efficacy for the largest lesions. The toxicity outcomes are poorly reported. It is unknown if the study was adequately powered to detect any of the clinical outcomes. CIs are not reported. **Quality of evidence score:** 5 **Applicability:** Low

[14] EQD2 (Equivalent Dose in Gy-2 fractions) has been reported here to make it easier to compare doses between studies which used different fractionation schedules. This is also sometimes known as Biological Equivalent Dose (BED) but EQD2 is used to avoid confusion with Biological Effective Dose, which is also abbreviated to BED in some literature.

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Choi et al. 2010 Retrospective case series study Single-centre US Recruitment period 2002-2008 42 patients with 51 spinal metastases from various primary cancers (31% breast, 21% non-small cell lung cancer [NSCLC]) KPS= 93% ≥70 Median age: 57 years; men = 40% Median lesion size: 10.29cm^3 (range 0.2-128.60cm^3)	Initial treatment with EBRT EBRT median dose 40Gy/10fx. Median time to re-irradiation 19 months SABR median dose of 20Gy/1-5fx Median 7 month follow-up.	LC: 6-months: 87%; 12-months 73%. Interval between EBRT and SABR ≤12 months significantly predicted local failure (multivariate analysis p<0.0006). OS: 6-months: 81%; 12-months: 68%. Median OS: 27 months. Adverse events: 1 patient developed myelopathy and died of progressive systemic disease 53 months after SABR.	**Appraisal:** Non-comparative case series – no randomisation, blinding, concealment. Single centre experience therefore less generalisable results. Recruitment period was over a decade ago, starting from early 2000s. The intervention and standard care may be less comparable with current standards. The study population and intervention are matched to the scope of the CtE scheme however, the authors do not report detailed eligibility criteria. The patient population is heterogeneous with regard to primary tumour site. The study treated lesions ranging from 0.2cm^3 to 128.6cm^3 resulting in a highly heterogeneous cohort potentially increasing the risk of toxicity (larger treatment area) and lowering efficacy for the largest lesions. The toxicity outcomes are poorly reported. Short term follow-up does not allow capturing long-term toxicity. It is unknown if the study was adequately powered to detect any of the clinical outcomes. CIs are not reported. **Quality of evidence score:** 5 **Applicability:** Low

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Garg et al. 2011 Prospective case series study Single-centre US Recruitment period 2003-2009 59 patients with 63 spinal metastases from various cancers (31% renal cell carcinoma [RCC], 13% lung) KPS: 93% ≥70 Median age: 60 years; men = 59% Median lesion size: 51.2cm^3 (range 3.5-266cm^3)	Initial treatment with EBRT EBRT median dose 30Gy/10fx. Time to re-irradiation > 3 months SABR median dose of 27Gy/3fx Median 17.6 month follow-up.	Local control [LC]: 76% Median OS: 22.5 months. Actuarial 1-yr survival 76%. Initial EBRT dose of ≥35Gy had significantly higher median survival time (33 vs. 21 months, p=0.01). Actuarial freedom from neurologic deterioration was 92% at 1-yr and 81% at 3-yrs. Adverse events: 2 cases of grade 3 neurotoxicity.	**Appraisal:** Non-comparative case series – no randomisation, blinding, concealment. Single centre experience therefore less generalisable results. Recruitment period was over a decade ago, starting from early 2000s. The intervention and standard care may be less comparable with current standards. The study population and intervention are matched to the scope of the CtE scheme and the authors report detailed eligibility criteria. The patient population is heterogeneous with regard to primary tumour site. The study treated lesions ranging from 3.5cm^3 to 266cm^3 resulting in a highly heterogeneous cohort potentially increasing the risk of toxicity(larger treatment area) and lowering efficacy for the largest lesions. It is unknown if the study was adequately powered to detect any of the clinical outcomes. CIs are not reported. **Quality of evidence score:** 5 **Applicability:** Moderate
Hashmi et al. 2016 Retrospective case series study Multi-centre International (Canada, US, Germany, Switzerland)	Initial treatment with EBRT EBRT median dose 30Gy/10fx. Median time to re-irradiation 13.5 months SABR median dose of 18Gy/1fx	Median OS: 11.8 months. Actuarial 6- and 12-month OS rates 64% and 48%, respectively. Median time to local failure 8.3 months Adverse events: dysphagia 11.3%, dermatitis 3%, increased pain 12.4%, vertebral compression fractures 4.5%.	**Appraisal:** Non-comparative case series – no randomisation, blinding, concealment. Multi-centre international experience analysing a large cohort of patients means that the results are generalisable. The study population and intervention are matched to the scope of the CtE scheme, however, the authors do not report detailed eligibility criteria. The patient population is heterogeneous with regard to primary tumour site. In addition, almost 50% of the patients underwent additional surgical treatment.

Study Design and Population Characteristics	**Methodology**	**Results**	**Critical Appraisal Summary**
Recruitment period unknown 215 patients with 247 spinal metastases from various cancers (29.1% breast, 16.6% NSCLC) KPS: not reported Median age: 62 years; men = 49% Median lesion size: not reported	Median 8.1 month follow-up.		Short term follow-up. The study did not report the size of the treated lesions. It is unknown if the study was adequately powered to detect any of the clinical outcomes. CIs are not reported. **Quality of evidence score:** 5 **Applicability:** Moderate

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Mahadevan et al. 2011 Retrospective case series Single-centre US Recruitment period 2005-2008 60 patients with 81 spinal metastases from various cancers (29% RCC, 20% melanoma) KPS: not reported Median age: 56 years; men = 60% Mean lesion size: 84cm^3 (range 46-174cm^3)	Initial treatment with EBRT EBRT median dose 30Gy/10fx Median time to re-irradiation 20 months SABR median dose of 24Gy/3fx Median 12 month follow-up.	Median OS: 11 months LC: 9 months (most patients were lost to follow-up or died due to progressive systemic disease – at final follow-up 93% had improved or stable disease). Of 34 patients with pain at baseline 64.7% reported improvement at 1-month follow-up. Adverse events: Acute: -grade 1 fatigue = 40% -grade 2 nausea = 20% Four patients had persistent or worsening neurological symptoms; 3 of these patients had persistent radicular pain, and 1patient developed new onset of lower-extremity weakness. All 4 patients had worsening radiological progression directly corresponding to their symptoms.	**Appraisal:** Non-comparative case series – no randomisation, blinding, concealment. Single centre experience therefore less generalisable results. Recruitment period was over a decade ago, starting from the mid-2000s. The intervention and standard care may be less comparable with current standards. The study population and intervention are matched to the scope of the CtE scheme however, the authors do not report detailed eligibility criteria. The patient population is heterogeneous with regard to primary tumour site. Most patients were lost to follow-up or died due to progressive systemic disease. Long-term follow-up, however, due to the unavailability of restaging imaging at progression following SABR, it is unknown if disease progression resulted from treatment failure or from disease progression outside the treated area. It is unknown if the study was adequately powered to detect any of the clinical outcomes. CIs are not reported. **Quality of evidence score:** 4 **Applicability:** Low

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Nikolajek et al. 2011 Retrospective case series Single-centre Germany Recruitment period 2005-2009 54 patients with 70 spinal primary tumours (24.1%) and spinal metastases (75.9%) from various cancers (18.5% RCC, 13% breast) Median KPS: 80 Median age: 56 years; men = 59% Mean lesion size: 17.6 cm^3	Initial treatment with EBRT EBRT median dose 42.8Gy/10fx Median time to re-irradiation 15 months SABR median dose of 18Gy Median 14.5 month follow-up.	Local control: Actuarial rates at 6-, 12- and 18-months: 93%, 88% and 85%. Larger tumour volume was significantly associated with local failure (p=0.001). Median OS: 16.2 months. Pain: Of 32 patients who suffered pain the median VAS score improved from 6 to 4 (p=0.0056) Adverse events: No grade 3 or higher toxicity observed	**Appraisal:** Non-comparative case series – no randomisation, blinding, concealment. Single centre experience therefore less generalisable results. Recruitment period was over a decade ago, starting from the mid-2000s. The intervention and standard care may be less comparable with current standards. The authors do not report detailed eligibility criteria. The study included some patients with primary tumours which is outside the scope of the CtE scheme. VAS score was used to measure pain outcomes. It is unknown if the study was adequately powered to detect any of the clinical outcomes. CIs are not reported. **Quality of evidence score:** 4 **Applicability:** Low

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Ogawa et al. 2018 Retrospective case series Single-centre Japan Recruitment period 2013-2017 66 patients with spinal metastases from various primary cancers (20% rectal, 17% lung) ECOG-PS: ≥1 77% Median age: 65 years; men = 69% Mean lesion size: not reported	Initial treatment with EBRT EBRT median dose 30Gy Median time to re-irradiation 21 months SABR median dose of 24Gy/2fx Median 10 month follow-up.	<u>Pain control:</u> 52% achieved complete pain response and 86% achieved partial or complete response.[15] Numerical pain rating scale improved significantly over baseline value of 5.7 at all follow-ups (1-3 months, 2.1 ($p<0.0001$), 4-6 months, 2.2 ($p<0.0001$), 7-9 months, 2.3 ($p=0.0005$) and 10-12 months, 1.6 ($p=0.0002$)). Median pain control duration was 13 months and 1-year pain control rate was 55%.	**Appraisal:** Non-comparative case series – no randomisation, blinding, concealment. Single centre experience therefore less generalisable results. This is a contemporary cohort with recruitment period starting from 2013, therefore, more comparable with current standards. The authors do report detailed eligibility criteria. NPRS score was used to measure pain outcomes It is unknown if the study was adequately powered to detect any of the clinical outcomes. CIs are not reported. **Quality of evidence score:** 5 **Applicability:** Low

[15] Complete reponse = score of 0 at treated site, no increase in analgesic requirements (oral morphine equivalent dose); partial response = score reduction of ≥2 with no increase in analgesic requirements, or analgesic reduction of ≥25% with no pain response.

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Sahgal et al. 2009 Retrospective case series Single-centre US Recruitment period 2003-2006 39 patients with 60 spinal metastases from various cancers All patients had an ECOG performance status ≤2, and a KPS ≥70. Median age: 59 years; men = not reported Median lesion size:21cm^3	25 patients (37 lesions) had initial treatment with EBRT EBRT median dose 36Gy/14fx Median time to re-irradiation 11 months SABR median dose of 24Gy/3fx Median 8.5 month follow-up (entire cohort).	Median OS time: 21 months 2-year OS: 45% (1-year OS not reported)(no significant differences between irradiated and re-irradiated groups). Local control: 1-year = 85% 2-year = 69% (no significant differences between irradiated and re-irradiated groups, for either 1- or 2-year LC). <u>Toxicity:</u> -grade 1-2 = 4.5% -grade 3+ = 0% (authors do not distinguish between acute and late toxicity)	**Appraisal:** Non-comparative case series – no randomisation, blinding, concealment. Single centre experience therefore less generalisable results. Recruitment period was over a decade ago, starting from early 2000s. The intervention and standard care may be less comparable with current standards. The authors do not report detailed eligibility criteria. The study included 14 patients (23 lesions) that had no previous radiotherapy which is outside the scope of the CtE scheme. NPRS score was used to measure pain outcomes It is unknown if the study was adequately powered to detect any of the clinical outcomes. CIs are not reported. **Quality of evidence score:** 3 **Applicability:** Low

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
CtE cohort (unpublished) Prospective registry Multicentre UK Recruitment period 2015-2018 18 patients with spinal metastases from various primary cancers (16.7% renal cancer, 16.7% sarcoma) PS: 0-1 94.4% Median age: 60 years; men = 61.1% Median lesion size: not reported	Initial treatment with EBRT: not reported EBRT median dose: not reported Median time to re-irradiation: not reported SABR median dose: 30Gy in 5 fx. Median 13.3 months follow-up, IQR: 7.2- 23.8 months.	Median overall survival >24 months Actuarial OS: -1-year = 80% -2-year = 70% Local control: -1-year = 54% (95%CI 26.3-75.2%) -2-year = 37% (95%CI 13-61.6%) Toxicity: -grade 3: 5.6% (95%CI 0.1-27%) -grade 4: 0% -grade 5: 0%	**Appraisal:** Non-comparative cohort – no randomisation, blinding, concealment. Multicentre experience in a UK NHS setting increases the external validity of the results. This is a contemporary cohort with recruitment period starting from 2015, therefore, more comparable with current standards. 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 met. LC was assessed qualitatively without using objective lesion size-based measurements. This limits the generalizability of the results and introduces potential detection bias. It is unknown if the study was adequately powered to detect any of the clinical outcomes. CIs are reported for most outcomes It was not possible to ascertain if patients received further treatment after SABR as patients were often treated at other centres during the follow-up period. 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 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 the multicentre setting but also potentially increasing safety. **Quality of evidence score: 7** **Applicability: High**

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
* The cancer types with the highest % representation in the sample Quality of evidence score: 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 included in the report. CtE – Commissioning through Evaluation CIs – Confidence intervals EBRT – External beam radiotherapy ECOG-PS – Eastern Cooperative Oncology Group Performance Status – describes disability status of patient as one of five categories, '0' being fully active and '5' being dead. fx – Fractions Gy – Grays KPS – Karnofsky Performance Status – describes the ability of patient to tolerate chemotherapy as a percentage score, 0% being dead and 100% being no evidence of disease/symptoms. LC – Local control NPRS – Numerical Pain Rating Scale – patients rate their own level of pain as a score out of 10; also known as the Visual Analogue Score (VAS) NSCLC – Non-small cell lung cancer OS – Overall survival PFS – Progression free survival PS – Performance status RCC – Renal cell carcinoma SABR/SBRT – Stereotactic ablative radiation therapy/Stereotactic body radiation therapy VCF – Vertebral compression fracture 95%CI – 95% confidence interval			

Table 36: Studies for re-irradiation of the pelvis

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Loi et al. 2018 Retrospective case series Single-centre Italy Recruitment period 2012-2016 50 patients with recurrent prostate cancer Median PSA at relapse 2.6nmol/L KPS: not reported Median age: 76 years; men = 100% Median lesion size: 15.5cm^3	Initial treatment with EBRT EBRT median dose 74Gy Median time to re-irradiation 76 months SABR median dose of 30Gy/5fx Median 21.3 month follow-up.	Toxicity: **Acute (0 to 3 months post-SABR):** -Gastrointestinal: grade 1= 8% -Gastrointestinal: grade 2= 0% -Gastrointestinal: grade 3+= 0% -Genitourinary: grade 1= 18% -Genitourinary: grade 2= 2% -Genitourinary: grade 3= 2% -Genitourinary: grade 4-5= 0% **Late (>3 months post-SABR):** -Gastrointestinal: grade 1= 2% -Gastrointestinal: grade 2= 4% -Gastrointestinal: grade 2+= 0% -Genitourinary: grade 1= 18% -Genitourinary: grade 2= 6% -Genitourinary: grade 3= 2% -Genitourinary: grade 4-5= 0%	**Appraisal:** Non-comparative case series – no randomisation, blinding, concealment. Single centre experience therefore less generalisable results. This is a contemporary cohort with recruitment period starting from 2012, therefore more comparable with current standards. The study population and intervention are well matched to the scope of the CtE scheme. With the exception of toxicity other clinical outcomes outside the scope of the review. Follow-up is long enough to capture long-term toxicity, however this was not consistent between patients (range 6.1-49.2 months). It is unknown if the study was adequately powered to detect any of the clinical outcomes. CIs are not reported. **Quality of evidence score:** 4 **Applicability:** Low

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Miszczyk et al. 2018 Retrospective case series Single-centre Poland Recruitment period 2012-2017 38 patients with recurrent prostate cancer Median PSA at relapse 3.26nmol/L 55.3% of patients on androgen deprivation therapy [ADT] during study period. KPS: not reported Median age: 71.6 years; men = 100% Median lesion size: not reported	Initial treatment with EBRT (1 patient was treated with BT and 3 with EBRT and BT boost) EBRT median dose 76Gy Median time to re-irradiation 100 months SABR median dose of 36.25Gy Median 14.4 month follow-up.	Toxicity: **Acute (0 to 3 months post-SABR):** -Gastrointestinal: grade 1= 7.4% -Gastrointestinal: grade 2= 4.8% -Gastrointestinal: grade 3+= 0% -Genitourinary: grade 1= 31.8% -Genitourinary: grade 2= 13% -Genitourinary: grade 3= 4.8% -Genitourinary: grade 4-5= 0% **Late (>3 months post-SABR):** -Gastrointestinal: grade 1= 11.1% -Gastrointestinal: grade 2+= 0% -Genitourinary: grade 1= 22% -Genitourinary: grade 2= 16.7% -Genitourinary: grade 3= 12.5% -Genitourinary: grade 4-5= 0%	**Appraisal:** Non-comparative case series – no randomisation, blinding, concealment. Single centre experience therefore less generalisable results. This is a contemporary cohort with recruitment period starting from 2012, therefore, more comparable with current standards. The study population and intervention are well matched to the CtE scope. With the exception of toxicity other clinical outcomes are outside the scope of the review. Follow-up is long enough to capture long-term toxicity, however this was not consistent between patients (range 1.6-46.4 months). It is unknown if the study was adequately powered to detect any of the clinical outcomes. CIs are not reported. **Quality of evidence score:** 3 **Applicability:** Low

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
CtE cohort (unpublished) Prospective registry Multicentre UK Recruitment period 2015-2018 185 patients undergoing pelvic re-irradiation for various primary cancers (39.5% prostate, 28.6% colorectal) PS: 0-1 98.4% Median age: 68 years; men = 61.1% Median lesion size: not reported	Initial treatment with EBRT: not reported EBRT median dose: not reported Median time to re-irradiation: not reported SABR median dose: 30Gy in 5 fx. Median 12.7 months follow-up (IQR 0.52-1.68 months).	Median overall survival >24 months Actuarial OS: -1-year = 92.0% (95%CI 86.0-95.5%) -2-year = 71.9% (95%CI 60.5-80.5%) Local control: -1-year = 75.8% (95%CI 66.7-82.7%) -2-year = 46.7% (95%CI 34.8-57.7%) Toxicity: -grade 3: 3.8% (95%CI 1.5-7.6%) -grade 4: 0% -grade 5:0%	**Appraisal:** Non-comparative cohort – no randomisation, blinding, concealment. Multicentre experience in a UK NHS setting increases the external validity of the results. This is a contemporary cohort with recruitment period starting from 2015, therefore, more comparable with current standards. Prospectively recruited and analysed the largest contemporary cohort of patients undergoing pelvic re-irradiation. 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 met. LC was assessed qualitatively without using objective lesion size-based measurements. This limits the generalisability of the results and introduces potential detection bias. It is unknown if the study was adequately powered to detect any of the clinical outcomes. CIs are reported for most outcomes It was not possible to ascertain if patients received further treatment after SABR as patients were often treated at other centres during the follow-up period. 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 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 ia nationally assured training system for SABR treatment, ensuring not only consistency of the intervention across the multicentre setting but also potentially increasing safety. **Quality of evidence score: 7** **Applicability: High**

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
* The cancer types with the highest % representation in the sample BT - Brachytherapy CtE – Commissioning through Evaluation CIs – Confidence intervals EBRT – External beam radiotherapy ECOG-PS – Eastern Cooperative Oncology Group Performance Status – describes disability status of patient as one of five categories, '0' being fully active and '5' being dead. fx – Fractions Gy – Grays IQR – Interquartile range KPS – Karnofsky Performance Status – describes the ability of patient to tolerate chemotherapy as a percentage score, 0% being dead and 100% being no evidence of disease/symptoms. LC – Local control NSCLC – Non-small cell lung cancer OS – Overall survival PFS – Progression free survival PS: Performance status RCC – Renal cell carcinoma SABR/SBRT – Stereotactic ablative radiation therapy/Stereotactic body radiation therapy VCF – Vertebral compression fracture 95%CI – 95% confidence interval			

Table 37: Systematic reviews

Study Design and Population Characteristics	Methodology	Results	Critical Appraisal Summary
Murray et al. 2017 Systematic review of retrospective case series Recruitment period 2002-2014 205 patients (from 17 primary studies) comprising of: -prostate cancer (82 patients) -cervical or endometrial cancer (50 patients) - rectal cancer (50 patients) Some studies included both re-irradiated and irradiated patients KPS: not reported Median age: not reported Median lesion size: 20.8-37.6 cm^3	Initial treatment with EBRT EBRT median dose: 45-50.4Gy in non-prostate, 80Gy in prostate cases Median time to re-irradiation 22 months (based on reported means SABR median dose of 30Gy/4.5fx Median follow-up ranged from 12-31 months.	Local control: At 1-yr: 51.4-100% (success was associated with dose >60Gy) Overall survival: Median overall survival: -11.5-14 months with mixed primary tumour sites (2 studies) -26-40 months for colorectal patients (2 studies) -28 months for gynaecological patients (1 study) -1-yr overall survival: -46-52% with mixed primary tumour sites (2 studies) -77-90% for colorectal patients (2 studies) -60% for gynaecological patients (1 study) Pain control: 50-100% improvement was seen in 4 studies. **Acute (0 to 3 months post-SABR):** -grade 3+= 4.4% (reported in 7 out of 10 studies) **Late (>3 months post-SABR):**	**Appraisal:** Systematic review of retrospective case series, with no pooled analysis of the results. The search methods are described briefly but they appear to be adequate for a systematic review of this kind. The search strategy is not reported. Individual study data is reported extensively in supplementary files. **Quality of evidence score:** 6 **Applicability:** Moderate

		-grade 3+= 1.9% (reported in 8 out of 10 studies)	
Myrehaug et al. 2017 Systematic review of retrospective case series Recruitment period 2002-2014 405 patients (from 9 previously published studies) with spinal metastases KPS: not reported Median age: 76 years; men = 100% Median lesion size: 15.5cm^3	Initial treatment with EBRT or SABR Initial median dose ranged from 24-40 (up to 14fx) SABR median dose ranged from 20-30Gy in single or multiple (2-5) fx Median follow-up ranged from 6.8-17.6 months	Local control: EBRT-> SABR: at 1-yr: 66-90% (as reported in 7 studies). Progression was most common with epidural metastases. SABR->SABR: at 1-yr 81% (1 study). Median overall survival: cEBRT->SBRT: median ranged from 10-22.5 months (7 studies). SBRT->SBRT: 6.8 months (1 study) Pain: 65-81% (crude analysis of 5 studies) Toxicity: VCF = 12% Myelopathy: 1.2%	**Appraisal:** Systematic review of retrospective case series, with no pooled analysis of the results. The search methods are described and the search strategy is reported; the methods are adequate for this kind of review. All included studies were GRADE scored as Low or Very Low quality (3 were prospective case series, 1 was described as a phase I/II study, and 5 were retrospective case series). There is no supplementary data provided on the individual studies and the patient population is poorly reported. There is some overlap between the primary studies in spinal re-irradiation included in Myrehaug et al. 2017 and the evidence review conducted as part of the CtE scheme. **Quality of evidence score:** 6 **Applicability:** Moderate

* The cancer types with the highest % representation in the sample

CtE – Commissioning through Evaluation

CIs – Confidence intervals

EBRT – External beam radiotherapy

fx – Fractions

Gy – Grays

IQR – Interquartile range

KPS – Karnofsky Performance Status – describes the ability of patient to tolerate chemotherapy as a percentage score, 0% being dead and 100% being no evidence of disease/symptoms.

LC – Local control

NSCLC – Non-small cell lung cancer

OS – Overall survival

PFS – Progression free survival

RCC – Renal cell carcinoma

SABR/SBRT – Stereotactic ablative radiation therapy/Stereotactic body radiation therapy

VCF – Vertebral compression fracture

95%CI – 95% confidence interval

6.2.3 Studies outcomes tables

Table 38, Table 40, Table 43, Table 46, Table 48, Table 43, Table 44, Table 45, Table 46 below report the survival, local control, progression free survival, toxicity, and quality of life results from the included studies.

Table 38: Survival, spinal re-irradiation

Study	EBRT dose (EQD2[16])	Median interval in months	SBRT dose (EQD2)	Median overall survival in months	Survival at 6-months	Survival at 12-months	Survival probability at 2-years
Chang et al (2012)	39.2Gy	24.5	51.1Gy	11	-[17]	-	-
Choi et al (2010)	40Gy	19	15Gy	27	81%	68%	-
Garg et al (2011)	30Gy (EQD2 not reported)	>3	27Gy/3fx (EQD2 not reported)	22.5	-	76%	-

[16] EQD2 = Equivalent dose in 2-Grays. This is sometimes also referred to as Biologically Equivalent Dose (BED).

[17] A dash indicates the outcome was not reported.

Study	EBRT dose (EQD2[16])	Median interval in months	SBRT dose (EQD2)	Median overall survival in months	Survival at 6-months	Survival at 12-months	Survival probability at 2-years
Hashmi et al (2016)	32.2Gy	13.5	36.0Gy	11.8	64%	48%	-
Mahadevan et al (2011)	30Gy/10fx (EQD2 not reported)	20	5-6Gy/5fx or 8Gy/3fx (EQD2 not reported)	11	-	-	-
Nikolajek et al (2011)	42.8Gy	15	18Gy	16.2	-	-	-
Sahgal et al (2009)	47Gy	11	31Gy	21	-	-	45%
Myrehaug et al (2017) - systematic review	24-40Gy (up to 14fx) (EQD2 not reported)	-	20-30Gy (single or 2-5fx) (EQD2 not reported)	10-22.5	-	-	-

Table 39 Survival, pelvic re-irradiation

Study	EBRT dose (EQD2)	Median interval in months	SBRT dose (EQD2)	Median overall survival in months	Survival at 12-months
Murray et al (2017) – systematic review	45-50.4Gy (non-prostate) 80Gy (prostate)	22	41.7-58Gy	11.5-14 (mixed primaries) 26-40 (colorectal) 28 (gynaecological)	46-52% (mixed primaries) 77-90% (colorectal) 60% (gynaecological)

Table 40: Local control, spinal re-irradiation

Study	EBRT dose (EQD2)	Median interval in months	SBRT dose (EQD2)	Radiographic response	Neurological response	Local actuarial control 6-months	Local actuarial control 12-months	Local actuarial control 18-months	Median time to local failure in months
Boyce-Fappiano et al (2017)	32.5Gy	10.2	34.67Gy	71%	82%	-	-	-	-
Chang et al (2012)	39.2Gy	24.5	51.1Gy	78.6%	-	-	-	-	-
Choi et al (2010)	40Gy	19	15Gy	-	-	87%	73%	-	-
Garg et al (2011)	30Gy (EQD2 not reported)	>3	27Gy/3fx (EQD2 not reported)	-	92%	-	76%	-	-
Hashmi et al (2016)	32.2Gy	13.5	36.0Gy	-	-	-	-	-	8.3
Mahadevan et al (2011)	30Gy/10fx (EQD2 not reported)	20	5-6Gy/5fx or 8Gy/3fx (EQD2 not reported)	-	-	-	93%	-	-
Nikolajek et al (2011)	42.8Gy	15	18Gy	-	-	93%	88%	85%	-
Myrehaug et al (2017) -	24-40Gy (up to	-	20-30Gy (single or	-	-	-	66-90%	-	-

systematic review	14fx) (EQD2 not reported)		2-5fx) (EQD2 not reported)						

Table 41: Local control, prostate re-irradiation

Study	EBRT dose (EQD2)	Median interval in months	SBRT dose (EQD2)	Biochemical response 2-months	Biochemical response 6-months	PSA decline 2-months	PSA decline 6-months	Local control
Loi et al (2018)	74Gy	76	30Gy/5fx (EQD2 not reported)	86%	82%	55.6%	77.1%	-
Miszczyk et al (2018)	76Gy	101	36.25Gy	-	-	-	-	86.8%

Table 42: Local control, pelvic re-irradiation

Study	EBRT dose (EQD2)	Median interval in months	SBRT dose (EQD2)	Local control rate at 1-yr	Radiographic response
Murray et al (2017) – systematic review	45-50.4Gy (non-prostate) 80Gy (prostate)	22	41.7-58Gy	51.4-100%	35-83%

Table 43: Toxicity, spinal re-irradiation

Study	EBRT dose (EQD2)	Median interval in months	SBRT dose (EQD2)	Vertebral compression fractures (%)	Symptomatic myelopathy	Lower extremity weakness/ radiculopathy	Grade 1-2 neurotoxicity - number of patients affected and percentage of entire cohort in brackets	Grade 1-2 gastrointestinal toxicity	Grade 3 neurotoxicity[18]
Boyce-Fappiano et al (2017)	32.5Gy	10.2	34.67Gy	22 (9.3%)	0.6%	-	5 (3.1%)	-	-
Chang et al (2012)	39.2Gy	24.5	51.1Gy	12 (22%)	-	-	-	-	-
Choi et al (2010)	40Gy	19	15Gy	-	2%	-	-	-	-
Garg et al (2011)	30Gy (EQD2 not reported)	>3	27Gy/3fx (EQD2 not reported)	-	-	-	11 (18.6%)	12 (20.3%)	2 (3.4%)
Hashmi et al (2016)	32.2Gy	13.5	36.0Gy	11 (4.5%)	-	-	-	-	-

[18] Please note that grade 3 gastrointestinal toxicity was not reported in any study.

Mahadevan et al (2011)	30Gy/10fx (EQD2 not reported)	20	5-6Gy/5fx or 8Gy/3fx (EQD2 not reported)	-	-	-	0	12 (20%)	0
Ogawa et al (2018)	30Gy	21	23.4Gy	5 (7.5%)	1 (1.5%)	-	-	-	-
Sahgal et al (2009)	47Gy	11	31Gy	-	0	0	-	3 (7.7%)	-
Myrehaug et al (2017) - systematic review	24-40Gy (up to 14fx) (EQD2 not reported)	-	20-30Gy (single or 2-5fx) (EQD2 not reported)	22 (12%)	8 (1.2%)	-	-	-	0

Table 44: Toxicity, pelvic re-irradiation

Study	EBRT dose (EQD2)	Median interval in months	SBRT dose (EQD2)	Grade 3-4 events
Murray et al (2017) – systematic review	45-50.4Gy (non-prostate) 80Gy (prostate)	22	41.7-58Gy	15 (7.3%)

Table 45: Toxicity, prostate re-irradiation

Study	EBRT dose (EQD2)	Median interval in months	SBRT dose (EQD2)	Grade 1-2 complications at 3-months	Grade 1-2 complications at final follow-up	Grade 3 complications at final follow-up
Loi et al (2018)	74Gy	76	30Gy/5fx (EQD2 not reported)	20% urinary 8% rectal	24% urinary 6% rectal	2% urinary 0% rectal
Miszczyk et al (2018)	76Gy	101	36.25Gy	7.4% gastro 25.9% genitourinary	4.8% gastro 5.3-9.1% genitourinary	0% gastro 3.7% genitourinary

Table 46: Quality of life (pain), spinal re-irradiation

Study	EBRT dose (EQD2)	Median interval in months	SBRT dose (EQD2)	Pain response rate	Pain control rate	Improvement in pain at 1-month (patients)	Median VAS/NPRS improvement over baseline	Pain free at 1-yr (patients)	Median pain failure free in months
Boyce-Fappiano et al (2017)	32.5Gy	10.2	34.67Gy	81%	-	-	-	-	-
Chang et al (2012)	39.2Gy	24.5	51.1Gy	-	85.7% (at 2-yrs)	-	-	-	-
Hashmi et al (2016)	32.2Gy	13.5	36.0Gy	-	87.6%	-	-	-	-
Mahadevan et al (2011)	30Gy/10fx (EQD2 not reported)	20	5-6Gy/5fx or 8Gy/3fx (EQD2 not reported)	-	-	64.7%	-	-	-

Study	EBRT dose (EQD2)	Median interval in months	SBRT dose (EQD2)	Pain response rate	Pain control rate	Improvement in pain at 1-month (patients)	Median VAS/NPRS improvement over baseline	Pain free at 1-yr (patients)	Median pain failure free in months
Nikolajek et al (2011)	42.8Gy	15	18Gy	-	-	-	Baseline **6** to **4** (p=0.0056)	-	-
Ogawa et al (2018)	30Gy	21	23.4Gy	86%	-	-	Baseline **5.7** to (1-3 months, **2.1** (p<0.0001), 4-6 months, **2.2** (p<0.0001), 7-9 months, **2.3** (p=0.0005) and 10-12 months, **1.6** (p=0.0002)	55%	13
Myrehaug et al (2017) - systematic review	24-40Gy (up to 14fx) (EQD2 not reported)	-	20-30Gy (single or 2-5fx) (EQD2 not reported)	-	65-81% (crude)	-	-	-	-

Table 47 Quality of life (pain), pelvic re-irradiation

Study	EBRT dose (EQD2)	Median interval in months	SBRT dose (EQD2)	Pain response rate
Murray et al (2017) – systematic review	45-50.4Gy (non-prostate) 80Gy (prostate)	22	41.7-58Gy	50-100%

Table 48: Progression free survival, spinal re-irradiation

Study	EBRT dose (EQD2)	Median interval in months	SBRT dose (EQD2)	PFS in months	Progression free survival probability 1-yr	Progression free survival probability 2-yr
Chang et al (2012)	39.2Gy	24.5	51.1Gy	18.0 (mean)	-	-
Garg et al (2011)	30Gy (EQD2 not reported)	>3	27Gy/3fx (EQD2 not reported)	-	-	-
Mahadevan et al (2011)	30Gy/10fx (EQD2 not reported)	20	5-6Gy/5fx or 8Gy/3fx (EQD2 not reported)	9 (median)	-	-
Sahgal et al (2009)	47Gy	11	31Gy	-	85%	69%

Table 49: Progression free survival, prostate re-irradiation

Study	EBRT dose (EQD2)	Median interval in months	SBRT dose (EQD2)	Biochemical relapse free survival at 1-year
Loi et al (2018)	74Gy	76	30Gy/5fx (EQD2 not reported)	80%

6.2.4 Clinical effectiveness of SABR in patients undergoing spinal or pelvic re-irradiation

6.2.4.1.1 Median overall survival

The majority of studies reported median overall survival in terms of duration from initiation of SABR, although Choi et al (2010), Garg et al (2011), Hashmi et al (2016) and Murray et al (2017) also reported actuarial OS at 1-year follow-up.

The lowest median OS in spinal metastases studies was reported by Chang et al. (2012) and Mahadevan et al. (2011) with a median overall survival of 11 months for re-irradiated patients. In the Chang et al. study the SABR dose was the highest of any study (median EQD2 51.1Gy), though it is unclear what influence this has on OS. The longest median OS was reported by Choi et al (2010) with their cohort achieving median overall survival of 27 months (median EQD2 15Gy). The authors did not discuss reasons for the longer OS but it is notable that the majority of patients were aged <65 years and 93% had a Karnofsky performance status of ≥70. Myrehaug et al (2017), in a systematic review of 9 previous studies, reported median overall survival ranging from 10-22.5 months (in 7 studies). The study did not attempt any pooled analyses. In some of the studies, subgroup analysis was used to explore the impact of certain parameters on survival. For example in Garg et al (2011) who reported a median overall survival of 22.5 months, patients receiving an initial dose of ≥35Gy had a significantly higher median survival time compared to patients receiving <35Gy (33 vs. 21 months, Kaplan-Meier estimate p=0.01). Nikolajek et al (2011) reported a median overall survival of 16.2 months (median EQD2 18Gy). Sahgal et al (2009) reported a median overall survival of 21 months (median EQD2 31Gy). Figure 1 shows the median OS survival rates reported for spinal re-irradiation.

For patients undergoing pelvic re-irradiation, a systematic review of 17 previous studies reported median OS rates ranging from 11.5-14 months for patients with different cancer histology (2 studies), 26-40 months for patients with colorectal cancer (2 studies) and 28 months patients with for gynaecological cancer (1 study) Murray et al (2017).

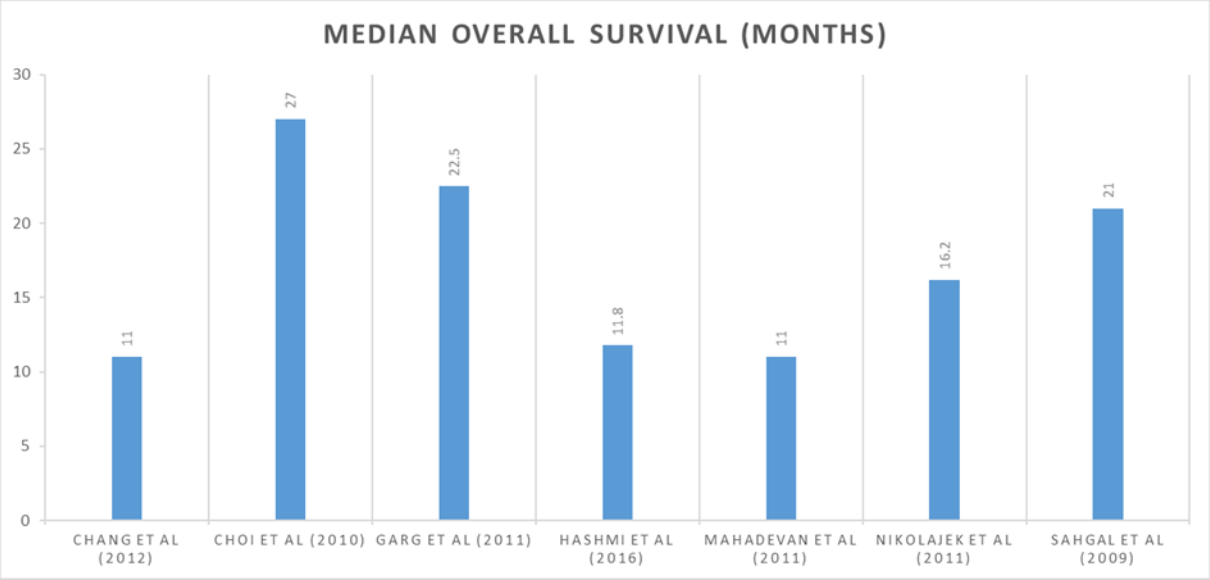


Figure 8: Median overall survival in months for patients treated for spinal metastases with SABR. The studies are arranged in alphabetical order.

6.2.4.1.2 Actuarial overall survival

The results for actuarial OS were more consistent for spinal tumours. At 1-year follow-up, Garg et al (2011), Choi et al (2010) and Hashmi et al (2016) reported OS of 76%, 68% and 48%, respectively.

The systematic review by Murray et al. (2017) also reported differing 1-year OS rates depending on the primary tumour histology at 46-52% (patients with different cancer histology), 77-90% (colorectal cancer), and 60% (gynaecological cancer). The study did not attempt any pooled analyses. A recent analysis of 100 cases of exenteration[19] for advanced primary and recurrent pelvic colorectal cancer reported a 1-year OS at 76% and 50% at 2-years (for cases that the whole tumour was removed within clear margins), which provides indirect evidence that SABR re-irradiation potentially achieves the same degree of overall survival for this patient cohort (Milne et al. 2014).

6.2.4.1.3 Local control

Ten of the included studies reported local control (LC) rates. With the exception of Garg et al. (2011) which was prospective, the rest were retrospective case series. Two of the included studies (Murray

[19] Pelvic exenteration is a major operation that involves removing all of the organs in the pelvic area and can include the cervix, uterus (womb), vagina, ovaries, bladder, and the lower end of the large bowel (rectum).

et al. 2017, Myrehaug et al. 2017) were systematic reviews, mainly including evidence from small retrospective case series (of between 3 and 31 patients in Murray et al, and between 37 and 180 patients in Myrehaug et al).

In studies focusing on spinal metastases there were a variety of different measures used with the two main being radiographic and neurological response rates. Boyce-Fappiano et al (2017) reported a local control (radiographic response) rate of 71% (29% progressed), with a median EQD2 of 34.67Gy at a median follow-up of 4 months. Chang et al (2012) reported a radiographic control rate of 78.6% at 2-year follow-up (mean EQD2 51.1Gy). Choi et al (2010) reported an actuarial local control rate of 73% at 1-year, measured by follow-up MRI (median EQD2 15Gy). Garg et al (2011) reported that 76% of patients were free from local progression at 1-year. The authors also reported actuarial freedom from neurologic deterioration of 92% at 1-year and 81% at 3-years. Hashmi et al (2016) reported a median time until local failure of 8.3 months (median EQD2 36Gy). The authors found that treatment given in a single fraction was a positive predictive factor for LC (compared to multiple-fractionation, Kaplan-Meier curve p=0.002). Nikolajek et al (2011) reported actuarial rates of local control of 93% at 6-months, 88% at 12-months, and 85% at 18-months (median dose 18Gy). Larger tumour volume (median 49.9 cc) was significantly associated with local failure (p=0.001). Myrehaug et al (2017), in a systematic review of 9 previous studies, reported 1-year local control of between 66% and 90% in 6 studies focusing on re-irradiation SBRT following initial conventional external beam radiation therapy, and 81% in 1 study on re-irradiation SABR following initial SBRT. The study did not attempt any pooled analyses.

For pelvic tumours (prostate, gynaecologic, rectal), Murray et al (2017), in a systematic review of 17 previous studies, reported rates of 1-year local control between 51.4% and 100% (which was significantly associated with EQD2 >60Gy, p=0.04). The study did not attempt any pooled analyses.

The studies often provided further information for local control. For example, Sahgal et al (2009) noted that in 6 of the 17 local failures, they had to give a lower dose to respect spinal cord constraints. Boyce-Fappiano et al (2017) suggested that their LC rate of 71% could be improved with higher doses, and noted the low rate of toxicity in their patients. Murray et al (2017) also concluded that LC rates are promising given the low levels of toxicity (see section 6.2.5).

LC may be related to dose delivered and the size of the lesion being treated (Aubusaris et al 2012), but the substantial heterogeneity among these studies on both counts means that it is difficult to draw any firm conclusions about this outcome. Furthermore, Murray et al (2017) note that the evidence does not provide certainty on how or even if systemic treatments should be combined with SABR re-irradiation.

6.2.4.1.4 Progression free survival

Spinal metastases studies reported either the duration of time without progression or the proportion of patients without progression at a defined follow-up point. Chang et al (2012) reported a mean of 18.0 months for re-irradiated patients (mean dose 51.1Gy), which compared to 26 months for patients treated with EBRT alone (p=0.029). Mahadevan et al (2011) reported both a median 9 month local progression free survival and that 93% of patients had improved or stable disease at final follow-up (median 12-months), although most patients had been lost to follow-up or died. Sahgal et al (2009) reported progression free survival rates of 85% at 1-year and 69% at 2-years (median EQD2 31Gy).

For prostate cancer Loi et al (2018) reported 80% of patients had biochemical relapse free survival at 1-year (SABR dose of 30Gy/5fx – EQD2 not reported); failure (i.e. relapse) was significantly associated with tumour grading of ≥3a (high risk) and ongoing androgen deprivation therapy [ADT] (p=0.014 and p=0.025, respectively). In studies focusing on prostate cancer, Loi et al (2018) reported biochemical response alongside median prostate specific androgen [PSA] decline (86% and 55.6% decline at 2-months; 82% and 77.1% decline at 6-months). Miszczyk et al (2018) reported 86.8% biochemical failure, which was significantly associated with the time taken to PSA nadir following EBRT (hazard ratio 1.03, p=0.005), and neoadjuvant ADT before EBRT (HR 4.82, p=0.0218).

6.2.4.1.5 Quality of life – Pain

Studies reporting pain outcomes tended to report the number or proportion of patients experiencing pain or response rates to treatment. In the four studies that reported this outcome, the crude rate ranged from 81% to 87.6%, which was remarkably consistent across the studies (see Figure 9). Some studies used specific tools, such as Visual Analogue Score (VAS) or Numerical Pain Rating Scale (NPRS). For spinal metastases studies Boyce-Fappiano et al (2017) reported pain response in 81% of patients (5% were stable and 14% progressed), with a median EQD2 of 34.67Gy.

Chang et al (2012) reported pain control rates at 2-year follow-up of 85.7% (mean dose 51.1Gy). Hashmi et al (2016) reported increased pain in 12.4% of patients (median EQD2 36Gy). Mahadevan et al (2011) reported that, in patients suffering from pain at baseline, at 1-month follow-up 64.7% of them reported improvement in pain, 20.6% had stable pain levels and in 14.7% pain levels got worse (35 lesions 5-6Gy/5fx; 46 lesions 8Gy/3fx). Myrehaug et al (2017), in a systematic review of 9 previous studies, reported pain control of 65-81% in 5 of the studies (4 with subjective pain reporting, and 1 using validated Brief Pain Inventory). Nikolajek et al (2011) reported on 32 patients who suffered pain at baseline, in whom the median VAS improved from 6 to 4 (p=0.0056), with a median dose of 18Gy. Ogawa et al (2018) reported 52% of patients achieved complete pain response and 86% achieved partial or complete response[20]. NPRS also improved significantly (5.7 at baseline) at all follow-up points (1-3 months, 2.1 (p<0.0001), 4-6 months, 2.2 (p<0.0001), 7-9 months, 2.3 (p=0.0005) and 10-12 months, 1.6 (p=0.0002)). Median pain control duration was 13 months and the 1-year pain control rate was 55%. There were no significant correlations between pain results and primary tumour site, age, sex, performance status, initial radiation dose, or history of decompression surgery (mean EQD2 23.4Gy). Boyce-Fappiano et al (2017) commented on the importance of pain control to quality of life in patients with spinal metastases and noted their pain response result (81%) was comparable with a large previous case series reporting on first line SBRT (86% in Gertzen et al, 2007).

[20] Complete reponse = score of 0 at treated site, no increase in analgesic requirements (oral morphine equivalent dose); partial response = score reduction of ≥2 with no increase in analgesic requirements, or analgesic reduction of ≥25% with no pain response.

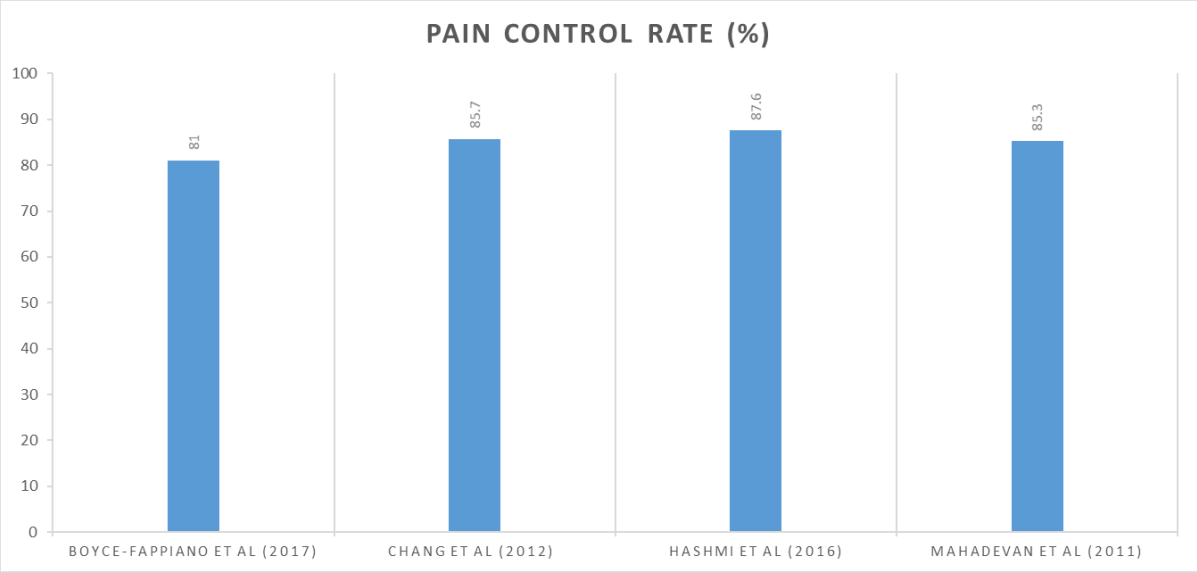


Figure 9: Pain control rate in spinal metastases studies

Four studies (analysing 205 patients) included in the systematic review by Murray et al. (2017) reported pain control rate ranging between 50-100%.

The two studies on prostate cancer did not report pain outcomes.

6.2.5 Safety of SABR in patients undergoing spinal or pelvic re-irradiation

A few of the studies reported safety and toxicity related outcomes as outlined in Table 43, Table 44 and Table 45. The main side effect reported by spinal metastases studies was the incidence of vertebral compression fractures (VCFs). This adverse event has been observed both as an acute and late adverse effect and can result in pain and subsequent surgical interventions (Faruqi et al. 2017). The incidence of VCF in the included studies ranged from 4.5% to 22%. Hashmi et al (2016) reported the lowest rate of VCFs in 4.5% of patients (median EQD2 36Gy). As the authors note, almost half of their patients had undergone surgery prior to SABR, resulting in a cohort consisting mainly of patients at low risk of VCF, as those at high risk of VCF were likely to have undergone surgical stabilization prior to SABR re-irradiation. Common risk factors for VCF include the presence of osteolytic changes that make the vertebrae weaker to compressive stress, and the shrinkage of metastatic soft-tissue after SABR that could lead to vertebral collapse because the soft-tissue mass itself provides resistance to the compressive stress in the involved vertebra (Yoo et al. 2017). On the contrary, in Chang et al (2012), which reported the highest VCF rate (22%, mean dose 51.1Gy), almost half of their patients had lesions involving an epidural mass with large volume disease. The

authors also do not report whether any of their patients had undergone stabilisation surgery prior to SABR. As previously mentioned, the Chang et al. study also had the highest SABR dose (EQD2 51.1Gy). The combination of high SABR dose, lack of stabilisation surgery and presence of large volume disease, will have resulted in a population with higher risk for VCFs. Other studies reported intermediate rates of VCFs with Ogawa et al (2018) reporting VCFs in 5 patients (7.5%) and radiation induced myelopathy in 1 patient (mean EQD2 23.4Gy), and Boyce-Fappiano et al (2017) reported 77 VCFs (32.5% of lesions) although only 22 (9.3% of all lesions) were considered attributable to radiation (median EQD2 34.67Gy).

Myrehaug et al (2017), in a systematic review of 9 previous studies, reported a 12% VCF rate with1.2% of patients developing symptomatic myelopathy. No other grade 3-4 events were reported (doses ranged from 20-30Gy in single or multiple (2-5) fractions). Choi et al (2010) also reported 1 patient who developed myelopathy. The patient had previously received 40 Gy to the spinal cord 81 months before receiving SABR. Garg et al (2011) reported 2 cases (3.3% of all patients) of severe (grade 3) neurotoxicity, while 18.6% of patients reported mild (grade 1-2) neurotoxicity and 20.3% had mild gastrointestinal toxicity (dose: 27Gy/3fx). Mahadevan et al (2011) reported that 40% of patients suffered grade 1 fatigue and 20% suffered grade 2 nausea at 1-month follow-up, while 30% had radiculopathy or lower limb weakness (35 lesions 5-6Gy/5fx; 46 lesions 8Gy/3fx). Saghal et al (2009) reported 3 patients had grade 1 or 2 events (nausea) and no patients suffered radiation-induced myelopathy or radiculopathy at ≥6-month follow-up (EQD2 31Gy).

A recent systematic review of studies using SABR in non-previously irradiated spinal metastases reported that VCF rates ranged from 5.7% to 39% (Faruqi et al. 2017). The reported range is similar to the VCF rate range identified in the re-irradiation studies included in this review (4.5%-22%). As a result it is reasonable to assume that there is indirect evidence that SABR re-irradiation does not increase the rate of VCF in this patient cohort.

Another serious side effect of spinal irradiation is myelopathy. Radiation myelopathy is a late toxicity side-effect resulting from radiation-induced injury to the spinal cord and is frequently associated with upper or lower extremity weakness, paraesthesia, and urinary retention. In severe cases this can lead to paraplegia and even death (Marcus and Million 1990). With the adoption of strict guidelines for radiation tolerance thresholds of the spinal cord, the incidence of radiation myelopathy in non-previously irradiated spinal lesions is considered very low (Sahgal et al. 2013). Even in historical studies conducted before 2000, the incidence of radiation-induced myelopathy

was very low (0.18%) (Marcus and Million 1990). The systematic review by Myrehaug et al (2017), reported that 1.2% of the patients developed symptomatic myelopathy. No other grade 3-4 events were reported (doses ranged from 20-30Gy in single or multiple (2-5) fractions). One more study by Choi et al (2010) also reported 1 patient who developed myelopathy.

In prostate cancer studies, Loi et al (2018) reported 8% rectal and 20% urinary acute grade 1-2 complications during the 3 months following SBRT. At subsequent follow-up (median 21.3 months) there were 6% rectal and 24% urinary complications (grade 1-2). One patient experienced grade 3 urinary and rectal complications (patient dose: 30Gy/5fx). Miszczyk et al (2018) reported that 4.8% of patients suffered acute grade 2 gastrointestinal reactions, while 5.3%-9.1% suffered acute grade 2 genitourinary reactions and 3.7% suffered acute grade 3 genitourinary reactions (EQD2 36.25Gy).

For mixed pelvic tumours (prostate, gynaecologic, rectal) Murray et al (2017), in a systematic review of 17 previous studies including 205 patients, reported that overall 9 patients (4.4%) suffered grade 3 events and 6 (2.9%) suffered grade 4 events. Ten of the included studies reported no grade 3+ toxicities. The authors noted the 'surprising' low levels of toxicity and how the 'worst case' crude rate of 8.3% grade 3+ toxicities compares favourably with rates of 20-36% reported for hyperfractionated regimens (Guren et al, 2014).

Most studies used the CTCAE criteria for adverse events, but due to study heterogeneity, it is impossible to draw any conclusions about the safety profile of SABR relative to standard care. In addition, most studies did not have a long enough follow-up to adequately capture late toxicity, increasing the risk of detection bias. Finally, a few studies did not report acute and late toxicity separately minimising the ability to estimate its overall impact on patients.

6.2.6 Subgroup analyses

In general, the studies did not report subgroup analyses, although Hashmi et al (2016) reported a median time until local failure of 8.3 months in the entire cohort but 8.2 months in the single-fraction sub-group and 11.3 months in the multiple fraction subgroup, which was not statistically significant. Nikolajek et al (2011) also reported that larger tumour volume was significantly associated with local failure (p=0.001) after SABR re-irradiation. Moreover, the median time interval from first EBRT to SABR tended to be shorter in this subgroup (p = 0.165).

The literature was divided between spine (10 studies), prostate (2 studies) and pelvic (1 study with a mix of prostate, cervical, endometrial and rectal cancers). A notable difference between these

studies was the large difference in the interval between initial EBRT and SABR: in spinal metastases studies the interval ranged from 3-24.5 months, compared with 76-101 months in prostate studies, and a median of 22 months for pelvic studies (Murray et al, 2017).

6.3 Conclusions

Thirteen studies provide evidence relevant to the scope of the CtE scheme. All included evidence is for an adult population. There is low quality evidence, mainly from retrospective single centre case series, that re-irradiation of spinal and pelvic cancer metastases can achieve local control and can be delivered without severe toxicity. The evidence from these studies have reported a 1-year local control between 51.4-100% and 66-90% for pelvis and spinal re-irradiation, respectively. They also report median overall survival ranging from 11.5-40 months and 10-22.5 months for pelvis and spinal re-irradiation, respectively. Pain control rates are reported between 50-100% and 65-81% for pelvis and spinal re-irradiation, respectively. The results reported have a high degree of variability and there is absence of comparative data and thorough long-term follow-up.

There is no evidence on how treatment with SABR affects quality of life in patients undergoing spinal or pelvic re-irradiation. Given the relatively high toxicity resulting from re-treatment of cancer recurrence, quality of life should be investigated further in future studies.

7 Discussion

7.1 Summary of findings from primary data collection (CtE registry)

Between 2015 and 2018, the CtE scheme collected outcomes from 203 (185 undergoing pelvic and 18 spinal re-irradiation) patients recruited from 8 centres nationally. From these 149 patients had their data also linked to the Hospital Episode Statistics (HES) and Office for National Statistics (ONS) registries. The median age of patients was 68 and 60 years, respectively, and most (61.1%) were men. The cohort undergoing pelvic re-irradiation was mainly comprised of patients with prostate (39.5%) and colorectal cancer (28.6%). The cohort undergoing spinal re-irradiation was mainly comprised of patients with sarcoma (16.7%) and renal cancer (16.7%). Approximately half of the patients (49.19%) undergoing pelvic re-irradiation were treated with Cyberknife. Cone beam CT (CBCT) image guidance was the most commonly used technique to assist treatment delivery in this patient cohort. The majority of patients undergoing spinal re-irradiation, were treated with Cyberknife and planar kV images using fiducial markers was the most commonly used image-

guidance technique to assist treatment delivery. For both cohorts, most patients were treated with 5 fractions of radiotherapy receiving 30Gy of radiation (median).

The analysis of people treated under the CtE scheme reported median overall survival (OS) >24 months for both cohorts. The 1-year OS was 92.0% (95%CI 86.0-95.5%) for people undergoing pelvic re-irradiation. For people undergoing spinal re-irradiation it wasn't possible to estimate 1-year OS due to the small number of events (a minimum of 6 deaths was required to provide estimates). The examination of the Kaplan-Meier curves for people undergoing spinal re-irradiation, indicates an 80% 1-year OS with large 95%CIs. Both results were higher than the OS targets proposed at the beginning of the CtE scheme (1-year target = 60% for both cohorts). In addition, the CtE analysis reported a 2-year OS estimate for pelvic re-irradiation at 71.9% (95%CI 60.5-80.5%). The examination of the Kaplan-Meier curves for people undergoing spinal re-irradiation, indicates a 70% 2-year OS with large 95%CIs. The literature does not provide an estimate of 2-year OS for pelvic re-irradiation, therefore, the CtE is the only evidence available.

The CtE data analysis also reported local control (LC) rates at 1-year of 54% (95%CI 26.3-75.2%) and 75.8% (95%CI 66.7-82.7%) for people undergoing spinal and pelvic re-irradiation, respectively. Both results were higher than the local control targets proposed at the beginning of the CtE scheme (1-year target = 50% for both cohorts), however, the 95%CIs for the spinal re-irradiation include the LC targets proposed at the beginning of the CtE scheme. This is probably attributable to the small patient cohort recruited for this indication (n=18 patients).

The CtE data analysis reported grade 3 toxicity of 3.8% (95%CI: 1.5 to 7.6%) for people undergoing pelvic re-irradiation which is lower than the proposed target of 20%. No grade 4 or 5 toxicity was reported which is lower than the target set of 5%. For people undergoing spinal re-irradiation, the CtE analysis reported grade 3 adverse event rate of 5.6% (95%CI: 0.1-27%) which is within the proposed target set of 20%. No grade 4-5 toxicity was reported which is lower than the target set of 5%.

Data on Quality of life (QoL) were available for 169 (83%) patients at baseline. Due to the low number of people undergoing spinal re-irradiation, both CtE cohorts were analysed together. According to the summary analysis, the majority of patients did not report issues at baseline and during follow-up. Data completeness decreased over time with approximately 50% and 20% of the patients returning their questionnaires at 12 and 24 months, respectively.

Data on pain scores were available for 185 (91%) patients at baseline. Due to the low number of people undergoing spinal re-irradiation, both CtE cohorts were analysed together. According to the summary analysis, the majority of patients (70%) of patients did not report any pain at baseline. This proportion remained stable until 18 months of follow-up and decreased in the final follow-up time point (24 months) by approximately 15 points. 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 (9%). Data completeness decreased over time with approximately 50% and 20% of the patients returning their questionnaires at 12 and 24 months, respectively. 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, often missing data are 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.

7.2 Results in the context of other studies

A literature review was performed to retrieve published evidence for patients undergoing spinal and pelvic re-irradiation. All available evidence was non-comparative and all but one study were retrospective case series. The available evidence included 2 systematic reviews of mainly retrospective case series (1 spinal metastases (Myrehaug et al (2017) and 1 pelvic tumours (Murray et al, 2017)). One prospective non-comparative cohort study (spinal metastases (Garg et al, 2011)), and 10 retrospective non-comparative case series studies (8 spinal metastases (Boyce-Fappiano et al (2017), Chang et al (2012), Choi et al (2010), Hashmi et al (2016), Mahadevan et al (2011), Nikolajek et al (2011), Ogawa et al (2018), Sahgal et al (2009), 2 prostate cancer (Loi et al (2018), Miszczyk et al (2018)).

The strongest evidence came from the two systematic reviews, although neither study reported pooled analyses or patient level data. Murray et al (2017) included 205 patients undergoing pelvic re-irradiation (from 17 previously published studies, mostly in prostate cancer). The included primary studies reported small patient cohorts (maximum of 31 patients). Myrehaug et al. (2017) included 405 patients undergoing spinal re-irradiation (from 9 previously published studies). As mentioned earlier contrary to published literature that mainly reported outcomes of patients with spinal re-irradiation, the CtE recruited a small number of spinal re-irradiation cases. The difference

was mainly attributed to the focus of the CtE scheme being to recruit patients with good prognosis, contrary to the literature that often treated patients with palliative intent.

The small cohort size of the CtE scheme for spinal re-irradiation and the resulting large 95%CIs of the OS analysis do not allow conclusions to be drawn about the OS of patients undergoing spinal re-irradiation. To this end, the literature reports 1-year OS rates of 46-90%. However, the absence of clear inclusion criteria, low quality reporting and the inclusion of cases with high heterogeneity (for example mixed cohorts of patients treated with radical and palliative intent, and patients with poor and good prognosis) does not allow a meaningful comparison between CtE data and published literature.

For patients undergoing re-irradiation for pelvic tumours, in a systematic review of 17 previous studies, Murray et al (2017) reported 1-year OS rates ranging between 46% and 90%. The study did not attempt any pooled analyses. The CtE data analysis reported higher 1-year OS for patients undergoing pelvic re-irradiation at 92.0% (95%CI 86.0-95.5%). It should be noted that 39.5% of the patients included in the CtE had prostate cancer and this is a cohort of patients considered to have a relatively good prognosis in terms of OS rates. This may have resulted in the higher 1-year OS for the CtE cohort. The only study from the literature that reported OS in prostate re-irradiation patients (Loi et al. (2018) reported 98% OS at a median follow-up of 21.3 months. The possible impact of primary tumour histology is also supported by the findings of the systematic review by Murray et al. (2017) that reported 1- year OS of 46-52% in a mixed primary tumour series, 77–90% for colorectal patients, and 60% for gynaecological patients. In addition, contrary to most studies that included patients treated more than a decade ago, the CtE included a contemporary cohort that could have potentially benefited from recent advances to systemic chemotherapy and supportive care that may in turn have influenced OS outcomes. The literature does not provide an estimate of 2-year OS for pelvic re-irradiation, therefore, the CtE is the only evidence available.

A recent analysis of 100 cases of exenteration for advanced primary and recurrent pelvic colorectal cancer reported a 1-year OS at 76% and 50% at 2-years in patients with the whole tumour removed within clear margins, and provided indirect evidence that SABR re-irradiation potentially achieves the same degree of OS for this patient cohort (Milne, 2014).

The CtE analysis estimated a >24 months median OS for both pelvic and spinal re-irradiation. The literature reports median OS ranges from 11.5-40 months and 10-22.5 months for pelvic and spinal re-irradiation, respectively. Similar to actuarial OS the absence of clear inclusion criteria, low quality

reporting and the inclusion of cases with high heterogeneity prevent a meaningful comparison between CtE analysis and published literature.

The literature evidence reported a 1-year LC between 51.4-100% and 66-90% for pelvic and spinal re-irradiation, respectively. The results are comparable with the CtE analysis, however, for pelvic re-irradiation the CtE outcomes are at the lower end of the range (54%) with the lower 95%CI estimate reaching 26%. It should be noted, however, that the CtE did not use RECIST criteria to assess response to treatment, therefore, it is not easy to compare the LC rates with the results from the literature.

Finally, the studies included report good safety outcomes with SABR, with crude rates of vertebral compression fractures ranging from 4.5%-22% and a rate for symptomatic radiation-induced myelopathy of 1.2%. Both these results are comparable with studies using SABR in non-previously irradiated spinal metastases, therefore, they provide low quality evidence that SABR re-irradiation does not lead to severe toxicity. The findings of the literature are in accordance with the CtE analysis that reported absence of grade 4-5 toxicity for both cohorts. The CtE also showed absence of VCF-related grade 3 or higher toxicity.

There is absence of quality of life outcomes, and of outcomes in children in the published literature.

7.3 Strengths and limitations

7.3.1 Strengths of available evidence

The CtE registry had several strengths. Firstly, the scheme prospectively recruited and analysed the largest contemporary cohort of patients undergoing pelvic re-irradiation. These patients were all recruited and treated 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 but also technical feasibility aspects of the treatment were met. All centres taking part in the scheme had to undergo a nationally 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, patient data recorded 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. Finally, the CtE registry reported clinical outcomes missing from the literature such as OS at 2-years and quality of life.

7.3.2 Limitations of available evidence

Both the published evidence and the CtE registry data are non-comparative, therefore, no robust conclusions can be reached about the efficacy and safety of SABR against any of the comparators. In addition, the low reporting quality of the published literature, the high degree of variability (study design and reporting) among studies, and the absence of long-term follow-up means that comparison of the CtE results with the published data is limited. All comparisons between the CtE outcomes and published data should be considered low quality and subject to considerable uncertainty.

Other limitations with the registry include the following:

- The CtE only had a maximum of two years follow-up. As a result, the long-term safety of and efficacy of SABR cannot be evaluated. In addition, not all patients completed 2 years of follow-up, increasing the possibility of detection bias (for example the ability to adequately capture late adverse events) for these patients.
- There is a lot of uncertainty about the QoL conclusions and the results should be interpreted with caution because of the low data completeness for this outcome during follow-up.
- The small size of the spinal re-irradiation cohort and the high heterogeneity in patient prognosis between the CtE and the literature, increases the uncertainty around any conclusions drawn for this cohort.
- The CtE included patients with multiple cancer types, however, often outcomes such as OS are influenced by the tumour's primary histology. Histology specific differences in tumour biology (such as the relatively good prognosis of patients with prostate cancer) that affect the effectiveness of SABR cannot be excluded based on the CtE results and cannot be investigated further due to the small size of the overall cohort.
- It was not possible to ascertain if patients received further treatment after SABR as patients were often treated at other centres during the follow-up period.
- 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 analysis. For OS this limitation is mitigated by the use of HES and ONS databases for data triangulation (see strengths section 7.3.1).

- For LC the CtE 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 between acute and late toxicity.

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. 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 reports covers the feedback provided for all three of the CtE cohorts.

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 implementation within the centre

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.

Multidisciplinary team (MDT)

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.

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.

Radiotherapy Trial Quality Assurance (RTTQA) approval/input:

All centres felt that the RTTQA[21] 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.

[21] The RTTQA group is a national UK group providing radiotherapy quality assurance programmes for all trials that include a radiotherapy component as part of the NIHR CRN portfolio. The group is multi-disciplinary consisting of radiographers, clinical scientists, clinicians, IT and admin staff working across different NHS sites.

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.

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 centre. 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

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. 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”.

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 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.

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.

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.

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.

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

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 volume assessment).
- 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 the criteria were interpreted and applied to patients. Some centres mentioned that when deciding who was eligible for re-irradiation, strict adherence meant scrutinising the DICOM treatment data and including patients where there was a clear overlap between the previous irradiation and the current treatment area. A less rigorous process may not include reviewing the images after a relapse within the same anatomical boundaries. In the case of overlap, the centre would treat as re-irradiation. In the absence of overlap, the disease would be treated as oligometastatic.

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.

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.

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.

Pathway standardisation

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

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. Re-irradiation was considered more of a grey area for meeting dose constraints. 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. Centres recommended that standard constraints should be regularly reviewed in the future as more evidence becomes available.

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 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.

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 8.2.2 and 8.2.3).
- **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 anatomical sites where the where there are fewer patients and it may not be possible to have enough clinicians available locally to peer review.
- **Dose constraints:** Centres noted that future commissioning of SABR will need to provide clear guidelines of how to meet the dose constraints.
- **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 undergoing pelvic and spinal re-irradiation. The following table (Table 50) contains KiTEC's response to the evaluation questions (based on Version 6.3, updated 22 December 2015)

Table 50: 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:** • **Re-irradiation pelvis:** OS rate of 60% at 1 year for SABR (figure derived from the findings of an SR including different radiotherapy techniques which reported a 2-year OS rate ranging from 56 to 78.8% and clinical expertise). • **Re-irradiation spine:** OS rates of 60% at 1-year for SABR (figure derived from findings reported	• **Re-irradiation pelvis:** The CtE data analysis reported OS result for patients undergoing pelvic re-irradiation of 92.0% (95%CI: 86.0 to 95.5%) at 1-year and 71.9% (95%CI: 60.5 to 80.5%) at 2-years post treatment. The 1 year OS is higher than the proposed actuarial survival estimates set at the beginning of the CtE scheme (1-year target = 60%). The result of the CtE scheme on the effect of SABR in OS of patients undergoing pelvic re-irradiation, is partially supported by low quality published evidence, mainly from retrospective single centre case series. • **Re-irradiation spine:** It was not possible to calculate OS rates for spinal re-irradiation as only 18 patients were included in the analysis and there were too few outcomes to calculate a Kaplan-Meier estimate. To this end, the literature reports 1-year OS rates

	in literature of between 60% and 70% at 1 year and clinical expertise).	estimates of 46-90%. However, the absence of clear inclusion criteria, low quality reporting, and the inclusion of cases with high heterogeneity (for example mixed cohorts of patients treated with radical and palliative intent and patients with bad and good prognosis) does not allow a meaningful comparison between CtE data and published literature.
Does treatment with SABR for the clinical indications covered within the CtE scheme increase local control?	**Proposed target:** • **Re-irradiation pelvis:** LC rate of 50% at 1 year for SABR. • **Re-irradiation spine:** LC rate of 50% at 1 year for SABR.	• **Re-irradiation Pelvis:** The CtE data analysis reported LC rates for patients undergoing pelvic re-irradiation of 75.8% (95%CI: 66.7-82.7%) at 1-year which is higher than the target set (50%). The literature evidence reported a 1-year LC between 51.4-100% for pelvic re-irradiation. The results are comparable with the CtE analysis. It should be noted, however, that the CtE did not use RECIST criteria to assess response to treatment, therefore, it is not easy to compare the LC rates with the results from the literature. • **Re-irradiation Spine:** The CtE data analysis reported LC rates for patients undergoing spinal re-irradiation of 53.9% (95%CI: 26.3 to 75.2%) at 1-year and 37.0% (95%CI: 13.0 to 61.6%) at 2- years. The result for 1-year, is higher than the local control target set at the beginning of the CtE scheme, however, the 95%CIs for the

		spinal re-irradiation include the LC targets set at the beginning of the CtE scheme. This is probably attributable to the small patient cohort recruited for this indication (n=18 patients). The literature evidence reported a 1-year LC between 66-90% for spinal re-irradiation. The results are comparable with the CtE analysis. It should be noted, however, that the CtE did not use RECIST criteria to assess response to treatment, therefore, it is not easy to compare the LC rates with the results from the literature.
What Adverse Events occur as a result of SABR in the CtE cohort of patients?	**Proposed target:** • **Re-irradiation pelvis:** a target outcome of grade 3 toxicity of 20% and grade 4-5 toxicity of 5% was set for people undergoing pelvic re-irradiation. • **Re-irradiation spine**: a target outcome of grade 3 toxicity of 20% and grade 4-5 toxicity of 5% was set for people undergoing spinal re-irradiation.	• **Re-irradiation Pelvis:** The results of the CtE analysis report a grade 3 adverse event rate of 3.8% (95%CI: 1.5 to 7.6%) which is lower than the target set of 20%. No grade 4-5 adverse events are reported which is lower than the target set of 5%. The findings are supported from the literature that reports low rates of grade 3 toxicity and absence of grade 5 events. • **Re-irradiation Spine**: The results of the CtE analysis report a grade 3 adverse event rate of 5.6% (95%CI: 0.1-27%) which is lower than the target set of 20%. No grade 4-5 adverse events are reported which is lower than the target set of 5%. The findings are supported from the literature that reports low rates of grade 3 toxicity and absence of grade 5 events.

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	• **Re-irradiation Pelvis:** Amongst the re-irradiation pelvis patients, 69% (95%CI: 61 to 75%) would be extremely likely to recommend the SABR service to friends and family if they needed similar care or treatment. • **Re-irradiation Spine**: Amongst the people undergoing spinal re-irradiation, 71% (95%CI: 42 to 92%) would be extremely likely to recommend the SABR service to friends and family if they needed similar care or treatment.
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 CtE data analysis found that for adult patients receiving re-irradiation in the pelvic region following recurrence of cervical or colorectal cancer, SABR results in more QALY gains and lower cost compared to pelvic exenteration, therefore SABR is the more cost-effective intervention.

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.		
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.	The re-irradiation cohort has been analysed based on treatment location (spinal and pelvic). Given the low number of patients recruited no further subgroup analysis is possible.

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 should be considered alongside the evaluative findings of the CtE scheme?	NA	There is low quality data from a number of retrospective case series that SABR re-irradiation leads to local control without severe toxicity.

10 Conclusions

The available evidence from the literature and the CtE data supports the use of SABR in adult patients undergoing pelvic re-irradiation. There is evidence that the treatment provides good local control without severe toxicity for pelvic re-irradiation. The small cohort size of the CtE scheme for spinal re-irradiation and the resulting large 95%CIs of the LC and OS analysis do not allow robust conclusions to be drawn for this patient cohort. Because of the heterogeneity in treatment doses and schedules used, the optimal dose and fractionation of SABR, and the optimal number of lesions treatable with acceptable risk, remain unknown from the current evidence. According to the summary analysis, the majority of patients did not report issues with QoL or pain at baseline and during follow-up. There is, however, a lot of uncertainty about the QoL and pain conclusions and the results should be interpreted with caution because of the low data completeness during follow-up.

The cost-effectiveness analysis found that for adult patients receiving re-irradiation in the pelvic region following recurrence of cervical or colorectal cancer, SABR results in more QALY gains and lower cost compared to pelvic exenteration, indicating SABR is the more cost-effective intervention. The finding needs to be interpreted carefully in the light of limitations in the available data on exenteration and the comparability of the cohort undergoing SABR with patients undergoing exenteration in the literature. If, as seems likely, it is reasonable to assume that outcomes in patients amenable to surgical exenteration would be improved, the analysis is likely to be conservative with respect to SABR and would support a role for SABR instead of exenteration for patients in which surgery is feasible.

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

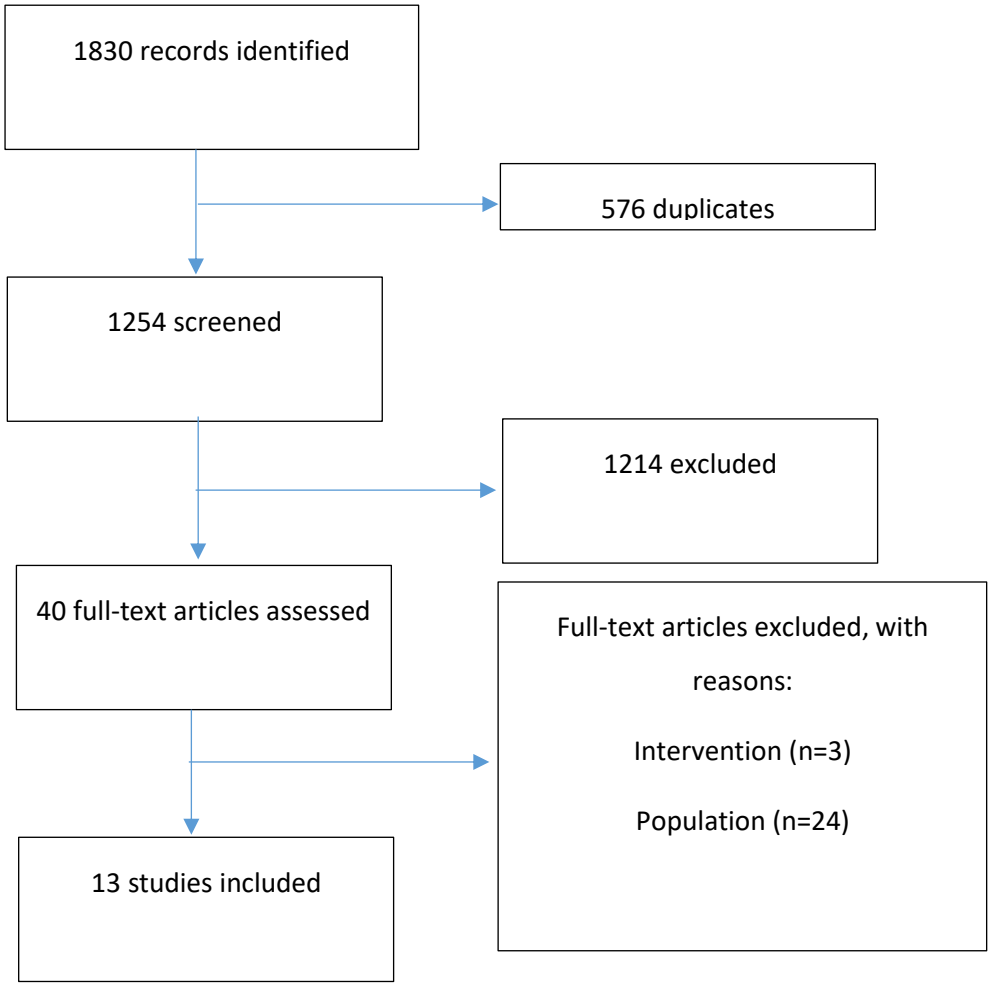


Figure 1: PRISMA table for SABR re-irradiation literature

12 Appendix B: Search strategies

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

Total number of references: 1830

Total following de-duplication: 1254

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 07, 2019
- 8th March 2019

1	(salvage treat* or salvage therap* or radiorecurrent or re-irradiat* or reirradiat* or repeat irradiat* or second irradiat* or secondary irradiat*).tw.	9628
2	Salvage Therapy/	13228
3	Re-Irradiation/	201
4	or/1-3	19473
5	(SABR or SBRT or stereotactic ablati* or stereotactic body radio* or stereotactic radio*).tw.	11342
6	(arc therap* or vmat).tw.	2815
7	radiosurg*.tw.	11519
8	exp Radiosurgery/	13787
9	or/5-8	22504
10	4 and 9	875

11	limit 10 to yr="2009 -Current"	723
12	(editorial or letter or case report or comment or news or conference abstract or Conference Paper or Conference Review).pt.	1880897
13	11 not 12	704

- Embase 1974 to 2019 Week 09
- 8th March 2019

1	(salvage treat* or salvage therap* or radiorecurrent or re-irradiat* or reirradiat* or repeat irradiat* or second irradiat* or secondary irradiat*).tw.	16869
2	Salvage Therapy/	20351
3	Re-Irradiation/	860
4	or/1-3	29131
5	(SABR or SBRT or stereotactic ablati* or stereotactic body radio* or stereotactic radio*).tw.	20863
6	(arc therap* or vmat).tw.	7217
7	radiosurg*.tw.	17079
8	exp Radiosurgery/	61567
9	or/5-8	72601
10	4 and 9	1981

11	limit 10 to yr="2009 -Current"	1790
12	(editorial or letter or case report or comment or news or conference abstract or Conference Paper or Conference Review).pt.	5688078
13	11 not 12	1071

- Cochrane (CDSR and CENTRAL)
- 8th March 2019

ID	Search	Hits
#1	(salvage treat* or radiorecurrent or re-irradiat* or reirradiat*):ti,ab,kw	2420
#2	[mh "Salvage Therapy"]	545
#3	[mh " Re-Irradiation"]	0
#4	(Murray et al. -#3)	2462
#5	(SABR or SBRT or stereotactic ablati* or stereotactic body radio* or stereotactic radio*):ti,ab,kw	975
#6	radiosurg*:ti,ab,kw	617
#7	[mh Radiosurgery]	196
#8	(arc therap* or vmat):ti,ab,kw	570
#9	{OR #5-#8}	1714
#10	#4 and #9 with Cochrane Library publication date from Jan 2009 to present	55

12.2 Search strategies for Cost-effectiveness

- Embase 1974 to 2019 Week 16
- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to Apr 19, 2019
- Search date: 22nd April 2019

1	prostate.tw.	417535

2	gyn?ecologic$.tw.	130090
3	(rectum or rectal or cervix).mp. or ovarian.tw.	918954
4	pelvic.tw.	254940
5	pelvis.tw.	94199
6	1 or 2 or 3 or 4 or 5	1611772
7	(salvage treatment or radiorecurrent or re-irradiation or reirradiation or exenteration).tw.	19860
8	SABR.tw.	2103
9	SBRT.tw.	11398
10	7 or 8 or 9	32661
11	Survival Analysis/ or Survival/	444548
12	(survival or progression-free survival or PFS or progression free survival or local control).tw.	2144929
13	(quality of life or QoL or EQ-5D or EQ5D or utilit$).tw.	1074069
14	(cost$ or economic$).tw.	1687582
15	(pain control or pain management or toxicity or patient experience).tw.	913531
16	11 or 12 or 13 or 14 or 15	5437132
17	6 and 10 and 16	4360

18	limit 17 to english language	4081
19	limit 18 to yr="2016 -Current"	1455
20	remove duplicates from 19	1104

13 Appendix 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** **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	Assymptomatic 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	Assymptomatic 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
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss,	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-

Toxicity A: cervical spine, thorax, lung, mediastinum					
		dehydration or malnutrition			
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 diagnostic observations only;	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g.,	Death

Toxicity A: cervical spine, thorax, lung, mediastinum					
	intervention not indicated			tracheotomy or intubation)	

13.5Site-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	Assymptomatic 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
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

Toxicity B: Upper lumbar spine, liver, adrenal, kidney, para-aortic region					
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	>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 diagnostic observations only;	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic,	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death

Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall					
	intervention not indicated		radiologic or operative intervention indicated; limiting self care ADL		
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 ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self	Life-threatening consequences; symptoms associated with neurovascular compromise	Death

Toxicity C: Lower lumbar spine, sacrum, pelvic bones, pelvic nodes/sidewall					
			care ADL; disability		
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

13.7EQ-5D-3L

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 ❑

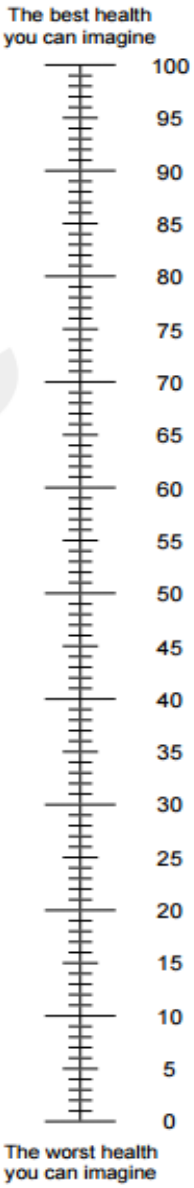
Anxiety / Depression

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

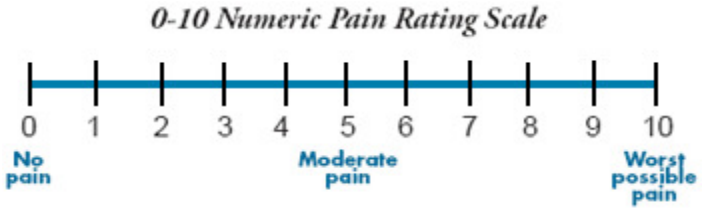
2

- 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 = ☐



13.8Visual analogues pain score (Brief Pain Inventory)



STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

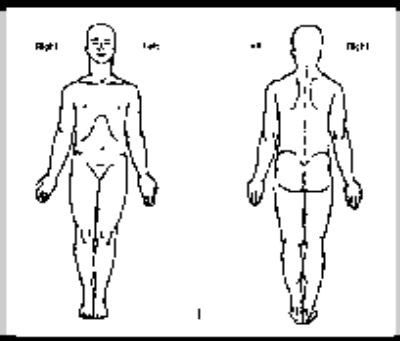
Name: _____ _____ _____

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 Definition, 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			Standard NHS ethnicity options

			6-Mixed-White and Asian 7-Mixed-Any other mixed background 8-Asian or Asian British-Indian 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 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)** 6-Tamoxifen	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
			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 24-Cis/Vinorelbine			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			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 39-carbo/5FU			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			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 **Kidney(CAB_PS=5)**			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			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)** 67-megase			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			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 83-Nivolumab			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			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)** 96-Gem/Cis			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			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 through treatment	numeric	1-yes 2-no	Required if CAB_CST(Current systemic therapy) is 1 (yes)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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		√	
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 9-gastrointestinal stromal tumour (GIST) 10-endometrial cancer	Required if CAB_PR (Previous radiotherapy) is 1 (yes)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			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] 27-other			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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 13 (sarcoma) or 12		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
				(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)		
CAB_WHO_PST	WHO performance status	numeric	0-Fully active, able to carry on all pre-disease performance without restriction		√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			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			√	
CAB_COMPDTE_1	Completion date of first	date			√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
	SABR treatment					
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) 3-kV planar (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) Required if CAB_TRT (Treatment option) is 3 (Cyberknife)	√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			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 4 (Tomotherapy)		
CAB_IDF_SBRT_1	Intended dose fractionation for first SBRT treatment	text			√	
CAB_PDOSE_1	Prescribed dose for first	numeric			√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
	SABR treatment					
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)
CAB_TRTDTE_2	Start date of second SABR treatment	text				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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) 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_2	Intended dose fractionation for second	text				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
	SBRT treatment					
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					
CAB_BED_2	Biological effective dose (100Gy as cutoff) for	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
	second SABR treatment					
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 3-Cyberknife 4-Tomotherapy			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
CAB_IGRT_TECH_3	IGRT technique for third SABR treatment	numeric	1-CBCT (soft tissue)	Required if CAB_TRT (Treatment option) is 1 (Elekta) or 2 (Varian)		
			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)		

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
			7-MVCT	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				
CAB_RSENSI_3	Radiosensitivity (a/b) for third SABR treatment					

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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)

Clinical Assessments – Follow-Up

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 6-LDH 7-PSA	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)			
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	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
						baseline form.	
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	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_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)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_LP_TRTDTE_3	Start date of third treatment at baseline	date				Cannot be modified. This is read 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.	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
CAF_LP_STATUS_3	Is the third treated area 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 clarify- or repeat the same image sequence in 3 months) 3-no (in field progression)	Required if CAF_ITR(Imaging to report) is 1 (yes)			
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)	Required if CAF_ITR(Imaging to report) is 1 (yes)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			2-no				
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	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
			2-no				
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	Required if CAF_ST_1 (site of 1st metastases) is 1 (lung)			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			2-Bilateral				
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	Required if CAF_FUTH_SABR(Details of further SABR treatment) is 2			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
			7-liver 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			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC	Comment_UHB
				of further SABR treatment) is 3			
			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	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
			6-Lower limbs				
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) 2-CBCT (fiducial) 3-kV planar (fiducial) 4-kV planar (spine) 5-kV planar (cranial) 6-kV planar (lung)	Required if CAF_TRT_3 (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAF_TRT_3 (Treatment option) is 1 (Elekta) or 2 (Varian) Required if CAF_TRT_3 (Treatment option) is 3 (Cyberknife) Required if CAF_TRT_3 (Treatment option) is 3 (Cyberknife) Required if CAF_TRT_3 (Treatment option) is 3 (Cyberknife) 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'			

KiTEC

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)		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_TS_3	Toxicity site 3	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_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		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
CTCAE_UGIU	Upper GI Ulcer	numeric	Grade (1-6)	Required if CTCAE_TD (Toxicity date) is completed and CTCAE_TS (Toxicity site)=1		
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		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
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		
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		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
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		
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		

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
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		
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

Item	Question	Type	Options	Validation	Mandatory	Comment_Kitec
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
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

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;	Moderate back pain;	Severe back pain;	Life-threatening	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
			nonprescription analgesics	prescription analgesics	hospitalization or intervention	consequences; symptoms		
			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

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
1	PNEU	**Pneumonitis**	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death	No Toxicities
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		

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
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 for >2 weeks	>20 *ULN	Death	No Toxicities
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	Symptoms (e.g., rectal	Severe symptoms; faecal	Life-threatening	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
			not indicated	discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	urgency or stool incontinence; limiting self care ADL	consequences; urgent intervention indicated		
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;	Symptomatic; urinary catheter or bladder irrigation indicated;	Gross haematuria; transfusion, IV medications or	Life-threatening consequences; urgent	Death	No Toxicities

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
			intervention not indicated	limiting instrumental ADL	hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	radiologic or operative intervention indicated		
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

CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
					indicated; limiting self care ADL			
3	URET	**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	No Toxicities
3	UURG	**Urinary urgency**	Present	Limiting instrumental ADL; medical management indicated	-	-	-	No Toxicities

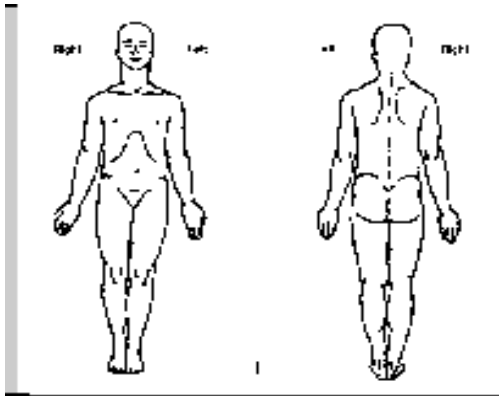
CTCAE_TS	CTCAE_????	CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 6
	BPAI	**Bone pain**	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	No Toxicities
	FRAC	**Fracture**	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; disabling; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	No Toxicities

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)

Patient Experience

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			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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			
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
LOWER ABDOMEN						
RPD_LA_TDOS_1	Total dose of radiotherapy administered	numeric				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				
RPD_LA_LB_D20_1	Large bowel: Dose to 20cc	numeric				
RPD_LA_BL_D15_1	Bladder: D15cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
LOWER LIMBS						
RPD_LL_TDOS_1	Total dose of radiotherapy administered	numeric				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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			

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_SITE_LABM_2	Lower Abdomen treated for second SABR treatment	numeric	-1-yes 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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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						
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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		√	

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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			
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_THO_SK_D10_3	Skin: D10cc	numeric				
RPD_THO_ST_DM05_3	Stomach: DMax (0.5cc)	numeric				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				
RPD_UA_PISO_3	Prescription isodose	numeric				
RPD_UA_SC_D01_3	Spinal Canal : DMax (0.1cc)	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LA_TDOS_FRAC_3	Total dose of radiotherapy administered: Number of fractions	numeric				
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				
RPD_LA_BL_D05_3	Bladder: DMax (0.5cc)	numeric				
RPD_LA_FHL_D10_3	Femoral heads - Left: D10cc	numeric				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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						
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
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				

Item	Question	Type	Options	Validation	Mandatory	Comment_KITEC
RPD_LL_TDOS_DAYS_3	Total dose of radiotherapy administered: Number of days	numeric				
RPD_LL_PISO_3	Prescription isodose	numeric				
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
Progression rate for treated patients (monthly)					
No progression to local progression	0.85%	Not reported	0.50-3%	Beta (α=0.85, β=99.15)	Calculated from Milne et al (Milne et al. 2014)
No progression to regional/distant progression	0.52%	Not reported	0.1-2%	Beta (α=0.52, β=99.48)	As above
Local progression to regional/distant progression	3.53%	Not reported	1-5%	Beta (α=0.49, β=13.51)	As above
Mortality rate (monthly)					
Operative mortality for patients receiving pelvic exenteration	1.60%	Not reported	0-5%	Beta (α=49, β=3,018)	(Barrera et al. 2019)
Patients with no progression	0.15%	Not reported	0.1-1%	Beta (α=1.52, β=1014.48)	Calibrated from cancer progression rate and published literature (Office for National Statistics 2016, Platt et al. 2018)
Patients with local progression	0.87%	Not reported	0.1-1%	Beta (α=1.24, β=141.00)	As above

Interventions	Base-line value	Standard error	Range	Distribution	Source
Patients with regional/distant progression	3.70%	Not reported	2-10%	Beta (α=5.26, β=136.98)	As above
Probability of retreatment (monthly)					
Probability of receiving resection of recurrent cancer after pelvic exenteration	30.33%	Not reported	20-50%	Beta (α=7, β=14)	(Mourton et al. 2007)
Probability of retreatment for patients receiving SABR	50.00%	Not reported	30-70%	Beta (α=2, β=2)	(Zerini et al. 2015)
SAEs (monthly)					
Probability of SAEs after pelvic exenteration	31.22%	Not reported	7.69-56.52%	Beta (α=305.02, β=671.98)	(Platt et al. 2018)
Probability of SAEs after SABR	0.00%	Not reported	0-6.34%	Beta (α=0, β=61)	CtE scheme and (Murray et al. 2017)
Cost of interventions					
Cost of pelvic exenteration	£19,069.89	Assumed 30% of mean value	£15,000-£25,000	Gamma	NHS reference cost 2015-16 (Department of Health 2016)
Cost of resection of recurrent cancer after pelvic exenteration	£6,938.15	Assumed 30% of mean value	£5,000-£8,000	Gamma	As above
Cost for SABR	£4,716	Assumed 30% of mean value	£3,000-£6,000	Gamma	(NHS England 2015)
Cost of retreatment with SABR	As above	As above	As above	As above	As above
Cost of treating SAEs					

Interventions	Base-line value	Standard error	Range	Distribution	Source
Cost of treating SAEs	£4,809	Assumed 30% of mean value	£1,000-£8,000	Gamma	Uplifted from Loveman et al (Loveman et al. 2014)
Other cost data					
Outpatient follow-up	£346	Assumed 30% of mean value	Assumed fixed	Gamma	(Department of Health 2016)
Palliative care (per month)	£546	As above	Assumed fixed	Gamma	Uplifted from Tappenden et al (Tappenden et al. 2007)
Utility					
Progression free without SAEs	0.84	0.0001	0.74-0.84	Beta	CtE scheme and other published data (Ness et al. 1999, Ramsey et al. 2000, Wong et al. 2013)
Local progression	0.74	Assumed 30% of mean value	0.74-0.84	Beta	As above
Regional/distant progression	0.46	Not reported	0.46-0.84	Beta	As above
Disutility of SAEs	**0.08**	**Not reported**	**0-0.2**	**Beta**	**(Sullivan and Ghushchyan 2006, Archer et al. 2018)**

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	13,801	3.1973	-14,827	0.0935	Dominating	1	1
Pelvic exenteration	28,628	3.1038	–	–	Dominated	2	2
Set transitional rate from no progression to local progression to 0.50% *(base case value: 0.85%)*							
SABR	13,343	3.2583	-14,774	0.0804	Dominating	1	1
Pelvic exenteration	28,117	3.1779	–	–	Dominated	2	2
Set transitional rate from no progression to local progression to 3% *(base case value: 0.85%)*							
SABR	15,797	2.8611	-14,905	0.1215	Dominating	1	1
Pelvic exenteration	30,702	2.7395	–	–	Dominated	2	2
Set transitional rate from no progression to regional/distant progression to 0.1% *(base case value: 0.52%)*							
SABR	12,644	3.4422	-14,903	0.1063	Dominating	1	1
Pelvic exenteration	27,546	3.3359	–	–	Dominated	2	2
Set transitional rate from no progression to regional/distant progression to 2% *(base case value: 0.52%)*							
SABR	16,505	2.5609	-14,658	0.0621	Dominating	1	1
Pelvic exenteration	31,163	2.4987	–	–	Dominated	2	2
Set transitional rate from local progression to regional/distant progression to 1% *(base case value: 3.53%)*							
SABR	13,419	3.2393	-14,685	0.0779	Dominating	1	1
Pelvic exenteration	28,104	3.1614	–	–	Dominated	2	2
Set transitional rate from local progression to regional/distant progression to 5% *(base case value: 3.53%)*							
SABR	13,930	3.1818	-14,875	0.0993	Dominating	1	1
Pelvic exenteration	28,806	3.0825	–	–	Dominated	2	2
Set operative mortality rate for patients receiving pelvic exenteration to 0% *(base case value: 1.6%)*							
SABR	13,801	3.1973	-15,293	0.0430	Dominating	1	1
Pelvic exenteration	29,093	3.1543	–	–	Dominated	2	2
Set operative mortality rate for patients receiving pelvic exenteration to 5% *(base case value: 1.6%)*							
SABR	13,801	3.1973	-13,838	0.2007	Dominating	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)
Pelvic exenteration	27,638	2.9966	–	–	Dominated	2	2
Set mortality rate for patients with no progression to 0.10% *(base case value: 0.15%)*							
SABR	13,907	3.2378	-14,825	0.0955	Dominating	1	1
Pelvic exenteration	28,732	3.1423	–	–	Dominated	2	2
Set mortality rate for patients with no progression to 1% *(base case value: 0.15%)*							
SABR	12,231	2.6064	-14,856	0.0658	Dominating	1	1
Pelvic exenteration	27,087	2.5406	–	–	Dominated	2	2
Set mortality rate for patients with local progression to 0.50% *(base case value: 0.87%)*							
SABR	13,866	3.2095	-14,843	0.0907	Dominating	1	1
Pelvic exenteration	28,709	3.1188	–	–	Dominated	2	2
Set mortality rate for patients with local progression to 1% *(base case value: 0.87%)*							
SABR	13,779	3.1932	-14,822	0.0944	Dominating	1	1
Pelvic exenteration	28,600	3.0988	–	–	Dominated	2	2
Set mortality rate for patients with regional/distant progression to 2% *(base case value: 3.70%)*							
SABR	14,757	3.2528	-14,866	0.0912	Dominating	1	1
Pelvic exenteration	29,624	3.1615	–	–	Dominated	2	2
Set mortality rate for patients with regional/distant progression to 10% *(base case value: 3.70%)*							
SABR	12,176	3.1032	-14,756	0.0976	Dominating	1	1
Pelvic exenteration	26,933	3.0056	–	–	Dominated	2	2
Set probability of receiving resection for recurrent patients after pelvic exenteration to 20% *(base case value: 30.33%)*							
SABR	13,801	3.1973	-14,632	0.1150	Dominating	1	1
Pelvic exenteration	28,432	3.0823	–	–	Dominated	2	2
Set probability of receiving resection for recurrent patients after pelvic exenteration to 50% *(base case value: 30.33%)*							
SABR	13,801	3.1973	-15,199	0.0525	Dominating	1	1
Pelvic exenteration	28,999	3.1448	–	–	Dominated	2	2
Set probability of receiving retreatment for patients who developed local recurrence after initial treatment of SABR to 30% *(base case value: 50%)*							
SABR	13,643	3.1548	-14,985	0.0510	Dominating	1	1
Pelvic exenteration	28,628	3.1038	–	–	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)
Set probability of receiving retreatment for patients who developed local recurrence after initial treatment of SABR to 70% *(base case value: 50%)*							
SABR	13,958	3.2398	-14,669	0.1360	Dominating	1	1
Pelvic exenteration	28,628	3.1038	–	–	Dominated	2	2
Set probability of developed SAEs after pelvic exenteration to 7.69% *(base case value: 31.22%)*							
SABR	13,801	3.1973	-14,169	0.0926	Dominating	1	1
Pelvic exenteration	27,970	3.1047	–	–	Dominated	2	2
Set probability of developed SAEs after pelvic exenteration to 58.10% *(base case value: 31.22%)*							
SABR	13,801	3.1973	-15,535	0.0945	Dominating	1	1
Pelvic exenteration	29,335	3.1028	–	–	Dominated	2	2
Set probability of developed SAEs after SABR to 6.34% *(base case value: 0%)*							
SABR	13,801	3.1973	-14,827	0.0935	Dominating	1	1
Pelvic exenteration	28,628	3.1038	–	–	Dominated	2	2
Set cost of pelvic exenteration to £15,000 *(base case value: £19,069.89)*							
SABR	13,801	3.1973	-10,822	0.0935	Dominating	1	1
Pelvic exenteration	24,623	3.1038	–	–	Dominated	2	2
Set cost of pelvic exenteration to £25,000 *(base case value: £19,069.89)*							
SABR	13,801	3.1973	-20,662	0.0935	Dominating	1	1
Pelvic exenteration	34,463	3.1038	–	–	Dominated	2	2
Set cost of resection for recurrent patients after receiving pelvic exenteration to £5,000 *(base case value: £6,938.15)*							
SABR	13,801	3.1973	-14,650	0.0935	Dominating	1	1
Pelvic exenteration	28,450	3.1038	–	–	Dominated	2	2
Set cost of resection for recurrent patients after receiving pelvic exenteration to £8,000 *(base case value: £6,938.15)*							
SABR	13,801	3.1973	-14,924	0.0935	Dominating	1	1
Pelvic exenteration	28,725	3.1038	–	–	Dominated	2	2
Set cost of SABR to £3,000 *(base case value: £4,716)*							
SABR	11,822	3.1973	-16,806	0.0935	Dominating	1	1
Pelvic exenteration	28,628	3.1038	–	–	Dominated	2	2
Set cost of SABR to £6,000 *(base case value: £4,716)*							

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	15,281	3.1973	-13,346	0.0935	Dominating	1	1
Pelvic exenteration	28,628	3.1038	–	–	Dominated	2	2
Set cost of treating SAEs to £1,000 *(base case value: £4,809)*							
SABR	13,801	3.1973	-14,136	0.0935	Dominating	1	1
Pelvic exenteration	27,936	3.1038	–	–	Dominated	2	2
Set cost of treating SAEs to £8,000 *(base case value: £4,809)*							
SABR	13,801	3.1973	-15,406	0.0935	Dominating	1	1
Pelvic exenteration	29,207	3.1038	–	–	Dominated	2	2
Set utility for 'progression free without SAEs' = 0.74 *(base case value: 0.84)*							
SABR	13,801	2.8620	-14,827	0.0762	Dominating	1	1
Pelvic exenteration	28,628	2.7858	–	–	Dominated	2	2
Set utility for 'Local progression' = 0.84 *(base case value: 0.74)*							
SABR	13,801	3.2223	-14,827	0.0875	Dominating	1	1
Pelvic exenteration	28,628	3.1348	–	–	Dominated	2	2
Set utility for 'Regional/ distant progression' = 0.84 *(base case value: 0.46)*							
SABR	13,801	3.3589	-14,827	0.0863	Dominating	1	1
Pelvic exenteration	28,628	3.2726	–	–	Dominated	2	2
Set disutility for SAEs = 0 *(base case value: 0.08)*							
SABR	13,801	3.1973	-14,827	0.0923	Dominating	1	1
Pelvic exenteration	28,628	3.1050	–	–	Dominated	2	2
Set disutility for SAEs = 0.2 *(base case value: 0.08)*							
SABR	13,801	3.1973	-14,827	0.0953	Dominating	1	1
Pelvic exenteration	28,628	3.1020	–	–	Dominated	2	2

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

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) 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.

17 Appendix G: Data working group membership

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