Stereotactic Ablative Fractionated Radiotherapy versus Radiosurgery for Oligometastatic Neoplasia to the Lung: A Randomised Phase II Trial (SAFRON II)

Radiotherapy Planning, Delivery and Quality Assurance

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Protocol: These guidelines apply to the TROG 13.01 SAFRON II final protocol dated 16 January 2014 and all subsequent amendments

Revision Chronology:

V1 24 Dec 2014  New document
V2 18 Nov 2015  Inclusion of CyberKnife, clarification regarding the use of Flattening Filter Free modalities in combination with Inversely Planned Techniques, amendment to maximum allowed dose within the PTV, clarification of the prescription isodose equation, QA procedure update, QA data submission checklist added as an Appendix. Heart contour description amended to reflect protocol.

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TABLE OF CONTENTS

TABLE OF CONTENTS .................................................................................................................. 2
TRIAL SUMMARY ......................................................................................................................... 4

1  RADIOTherAPY SUMMARY .................................................................................................. 5

   1.1  TRIAL REGIMEN SUMMARY .......................................................................................... 5
           1.1.1  Single Fraction SABR ......................................................................................... 5
           1.1.2  Multi-fraction SABR .......................................................................................... 5

2  TROG PRE-TRIAL QUALITY ASSURANCE PROGRAM ...................................................... 5

   2.1  CREDENTIALING ACTIVITIES ....................................................................................... 5
           2.1.1  Phantom Dosimetry Audit .................................................................................. 6
           2.1.2  Facility Questionnaire ...................................................................................... 6
           2.1.3  Benchmarking ................................................................................................. 6
           2.1.4  Site Staff Training ............................................................................................ 7
   2.2  SUBMITTING DATA FOR QA ........................................................................................ 7

3  RADIOTherAPY TREATMENT SCHEDULE ....................................................................... 7

4  PLANNING SIMULATION ...................................................................................................... 8

   4.1  PATIENT POSITIONING ............................................................................................... 8
   4.2  IMMOBILISATION ......................................................................................................... 8
   4.3  CT SCAN ....................................................................................................................... 8
   4.4  MOTION MANAGEMENT ............................................................................................. 8
   4.5  SIMULATION PROCEDURE ........................................................................................ 8

5  STANDARDISED NAMING .................................................................................................... 10

6  TARGET VOLUME DEFINITIONS ......................................................................................... 10

   6.1  TARGET VOLUMES ....................................................................................................... 10
           6.1.1  Field Borders .................................................................................................... 11

7  ORGANS AT RISK (OAR) DEFINITIONS .......................................................................... 12

8  TREATMENT PLANNING AND DOSIMETRY ................................................................... 13

   8.1  PLANNING SYSTEM ..................................................................................................... 13
   8.2  DOSE PRESCRIPTION, FRACTIONATION AND DURATION ........................................ 13
           8.2.1  Stereotactic radiotherapy prescription ................................................................ 13
   8.3  TARGET VOLUME DOSE REPORTING .......................................................................... 13
           8.3.1  Conformity Indices ............................................................................................ 14
           8.3.2  Intermediate dose spillage ............................................................................... 14
   8.4  ORGAN AT RISK DOSE CONSTRAINTS .................................................................... 15
           8.4.1  Planning Previous Radiotherapy ....................................................................... 17
   8.5  TREATMENT TECHNIQUES .......................................................................................... 17
           8.5.1  Field Shaping .................................................................................................... 17
           8.5.2  Dose Rate ......................................................................................................... 17
           8.5.3  Number of Treatment Fields and Field Arrangements ....................................... 17
           8.5.4  Field Size and Shielding Margin ...................................................................... 17
   8.6  RESPIRATORY GATING ................................................................................................ 18

9  TREATMENT DELIVERY ...................................................................................................... 18

   9.1  TREATMENT DELIVERY EQUIPMENT ...................................................................... 18
10 TROG ON-TRIAL QUALITY ASSURANCE PROGRAM

10.1 Pre-Treatment QA Technical Reviews

10.2 Post-Treatment QA Technical Reviews

10.3 Additional Guidelines to assist with QA Submissions

11 REFERENCES

12 APPENDIX A: CYBERKNIFE ROBOTIC STEREOTACTIC RADIATION THERAPY SYSTEM

12.1 Radiotherapy Summary

12.2 TROG Pre-Trial Quality Assurance Program

12.2.1 Phantom Dosimetry Audit

12.2.2 Facility Questionnaire

12.2.3 Benchmarking Exercise

12.2.4 Site Staff Training

12.2.5 Submitting Data For QA

12.3 Radiotherapy Treatment Schedule

12.4 Planning Simulation

12.4.1 Patient Positioning

12.4.2 Immobilisation

12.4.3 CT scan

12.4.4 Motion Management

12.4.5 Simulation Procedure

12.5 Standardised Naming

12.6 Target Volume Definitions

12.6.1 Target Volumes

12.6.2 Field Borders

12.7 Organs At Risk (OAR) Definitions

12.8 Treatment Planning and Dosimetry

12.8.1 Planning System

12.8.2 Dose Prescription, Fractionation and Duration

12.8.3 Target Volume Dose Reporting

12.8.4 Organ At Risk Dose Constraints

12.8.5 Treatment Techniques

12.8.6 Respiratory Gating

12.9 Treatment Delivery

12.10 On-Trial Quality Assurance Program

13 APPENDIX B: SOURCE DOCUMENTATION CHECKLISTS FOR QA TECHNICAL REVIEW
## TRIAL SUMMARY

<table>
<thead>
<tr>
<th>Primary sponsor</th>
<th>Trans-Tasman Radiation Oncology Group (TROG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborating groups</td>
<td>Australasian Lung Trials Group (ALTG)</td>
</tr>
</tbody>
</table>
| Trial Coordinator | Rebecca Montgomery  
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| Public title | A Randomised Phase II Study of Stereotactic Ablative Body Radiotherapy for Metastases to the Lung |
| Scientific title | A Randomised Phase II Trial of Stereotactic Ablative Fractionated Radiotherapy versus Radiosurgery for Oligometastatic Neoplasia to the lung (SAFRON II) |
| Countries of recruitment | Australia and New Zealand |
| Health condition(s) or problem(s) studied | Oligometastatic Cancer to the Lung (from any non-haematological malignancy) |
| Intervention(s) | **ARM 1** Single fraction SABR; 28Gy delivered in 1 fraction.  
**ARM 2** Multi-fraction SABR; 48Gy delivered in 4 fractions, delivered over 2 weeks, with each fraction on non-consecutive days |

### Key inclusion and exclusion criteria

#### Inclusion Criteria
- A maximum of three metastases to the lung from any non-haematological malignancy
- Tumour diameter ≤ 5cm
- Targets are located away from central structures (defined as 2cm beyond bifurcation of lobar bronchi and central airways). Targets in proximity to chest wall and mediastinum that meet these inclusion criteria are eligible.
- Primary and extrathoracic disease controlled with local therapy (e.g. surgery/definitive radiotherapy)

#### Exclusion Criteria
- Previous high-dose thoracic radiotherapy in the same area as the proposed stereotactic treatment (please see section 9.1.5.1 Constraints for Retreatment of Irradiated Lung).
- Cytotoxic chemotherapy within 3 weeks of commencement of treatment, or concurrently with treatment. Hormonal manipulation agents are not excluded (e.g. aromatase inhibitors, selective oestrogen receptor modulators, and gonadotrophin releasing hormone receptor modulators)
- Concurrent targeted agents (such as sunitinib, bevacizumab and tarceva) are not allowed. It is recommended that targeted agents be not be delivered within 7 days of delivery of treatment.
- Germ cell and small cell histologies

<table>
<thead>
<tr>
<th>Study type</th>
<th>Interventional</th>
</tr>
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<tbody>
<tr>
<td>Target sample size</td>
<td>84</td>
</tr>
<tr>
<td>Trial Hypotheses</td>
<td>The central hypothesis of this study is that single fraction SABR has an acceptable toxicity and efficacy profile, but is more cost-effective and immunogenic than multi-fraction SABR.</td>
</tr>
</tbody>
</table>
1 RADIOTHERAPY SUMMARY

1.1 Trial Regimen Summary

This trial compares single fraction SABR and multi-fraction SABR for the treatment of oligometastases to the lung.

1.1.1 Single Fraction SABR

Stereotactic radiotherapy to a Total Dose (TD) of 28Gy in a single fraction. The Total Dose is prescribed to the covering isodose, which is expected to be between 70-80% of the maximum dose. Ideally, a normalised Dmax within the PTV of 125% should be achieved (resulting in a covering isodose of 80%). Treatment planning will typically involve 3D conformal planning using between 8-12 beams, with a minimum of 1-2 non-coplanar beams. The use of fixed gantry IMRT, VMAT, TomoTherapy and CyberKnife techniques are permissible provided centres have successfully completed TROG credentialing activities. Please contact qa@trog.com.au for further information. All sites wishing to use CyberKnife must refer to Appendix A: CyberKnife Robotic Stereotactic Radiation Therapy System. The CyberKnife specific appendix has been created to accompany the main Radiotherapy Planning, Delivery and QA Guidelines document where differences in the process occur.

1.1.2 Multi-fraction SABR

Stereotactic radiotherapy to a total dose of 48Gy in 4 daily 12Gy fractions delivered twice a week over 2 weeks. Each fraction should be delivered on non-consecutive days. The total dose is prescribed to the covering isodose, expected to be the 70-80% isodose line. Ideally, a normalised Dmax within the PTV of 125% should be achieved (resulting in a covering isodose of 80%). Treatment planning will typically involve 3D conformal planning using between 8-12 beams, with a minimum of 1-2 non-coplanar beams. The use of fixed gantry IMRT, VMAT, TomoTherapy and CyberKnife techniques are permissible provided centres have successfully completed TROG credentialing activities. Please contact qa@trog.com.au for further information. All sites wishing to use CyberKnife must refer to Appendix A: CyberKnife Robotic Stereotactic Radiation Therapy System. The CyberKnife specific appendix has been created to accompany the main Radiotherapy Planning, Delivery and QA Guidelines document where differences in the process occur.

2 TROG PRE-TRIAL QUALITY ASSURANCE PROGRAM

2.1 Credentialing Activities

All participating centres must successfully complete pre-trial quality assurance procedures prior to enrolling patients to the study. This will consist of an initial credentialing phase involving the following activities:

1. Phantom Dosimetry Audit
2. Facility Questionnaire
3. Benchmarking
4. Site Staff Training

As part of the credentialing process, all sites wishing to use inversely planned techniques for this trial must seek explicit approval by TROG. This includes IMRT, VMAT, TomoTherapy, CyberKnife and Flattening Filter Free delivery methods. Please note that the use of FFF in conjunction with IMRT/VMAT is not permitted for this trial. All sites wishing to use CyberKnife must refer to Appendix A: CyberKnife Robotic Stereotactic Radiation Therapy System.

To complete the QA requirements you will need access to CQMS and the TROG website (password protected documents). Please email qa@trog.com.au to arrange access.

Timely feedback will be provided to participating centres regarding the outcome of credentialing activities; via the TROG QA office.

2.1.1 Phantom Dosimetry Audit

Each participating centre must have completed a TROG-approved dosimetry study. Successful completion of the TROG 09.02 CHISEL phantom study will be accepted for this trial. If inversely planned techniques are being used E.g. IMRT/VMAT, the centre must provide evidence of a TROG-approved IMRT/VMAT audit. Contact TROG QA, qa@trog.com.au for further information about the requirements for your site.

2.1.2 Facility Questionnaire

All sites must complete necessary facility questionnaires corresponding to the techniques intended for use on the trial. The questionnaires are designed to gauge the experience of a centre as well as equipment in use for inversely planned techniques and SABR. Previously completed facility questionnaires may be accepted if the information provided is considered sufficient for the purposes of this trial. Documentation outlining centre practice for IGRT and immobilisation will be requested. The facility questionnaire can be accessed on the TROG website (www.trog.com.au).

2.1.3 Benchmarking

Each study centre will be required to complete a benchmarking exercise. Centres that have completed the benchmarking exercise for the TROG 09.02 CHISEL trial must complete the dual-lesion benchmarking case. Centres that have not participated in the TROG 09.02 CHISEL trial must complete both the single and dual-lesion benchmarking cases. Planning CT datasets will be available via the TROG website (www.trog.com.au). Centres must develop a plan in accordance with the protocol specifications. Plans meeting the dose constraints must be submitted using CQMS to the TCOO for review.

The treatment planning and delivery technique intended to be used by the site for this trial must be replicated for the benchmarking cases. Sites must clearly indicate the planning and delivery techniques that will be used for the trial including the use of 3DCRT, Conformal Dynamic Arcs, VMAT, IMRT, TomoTherapy, CyberKnife and Flattening Filter Free (FFF) delivery methods. Where a centre proposes using multiple delivery methods, credentialing plans must be submitted for each proposed delivery method. Please note: FFF delivery methods are NOT permitted to be used with inversely planned techniques. Conformal Dynamic Arcs can be used in combination with FFF.

Sites must also demonstrate during this activity that they are able to provide appropriate
planning information and radiotherapy documentation to enable QA review of radiotherapy treatment.

2.1.4 Site Staff Training

A minimum of one radiation oncologist, two radiation therapists and one physicist of the treatment team at each site must have successfully completed the online learning tool (eLearning module) available on the TROG website (www.trog.com.au).

2.2 Submitting Data for QA

Plans and additional source data are to be submitted to the TROG Central Office via CQMS. A checklist of the required source documentation will be provided by the TROG QA Office. Please refer to Appendix B. This checklist can also be accessed via the TROG website (www.trog.com.au). For additional support submitting data please see Section 10.3 Additional Guidelines to assist with QA Submissions.

3 RADIOThERAPY TREATMENT SCHEDULE

Radiotherapy should ideally commence within 4 weeks after participant randomisation. However, if radiotherapy is scheduled outside of the 4 week timeframe (up to eight weeks post randomisation) the patient may still be eligible. Please contact the Trial Coordinating Centre to determine eligibility.

In the case of multiple pulmonary metastases, each tumour should be treated individually, using separate plans. Tumour specific inclusion criteria should apply to all intended targets. In the instance of 2 tumours in close proximity, then a single isocentre and single target volume may be considered when the sum of the cumulative largest diameter of the tumours and the intervening normal lung between is $\leq 5$cm. In these cases, both tumours may be considered a single target and treated simultaneously.

Fractions of SABR should be delivered on non-consecutive days. In the instance of multiple pulmonary lesions, the treatment delivery schedule is different for single fraction and multi-fraction treatments. When participants are randomised to 28Gy in one single fraction treatment, then each metastasis should be treated at separate sessions on non-consecutive days. When patients are randomised to 48Gy in four-fraction treatments, then each metastasis can be treated concurrently with each fraction delivered on non-consecutive days.

It is advised that systemic chemotherapy (after protocol treatment has been completed) should be delivered in consultation with the treating radiation oncologist in the absence of disease progression.
4 PLANNING SIMULATION

4.1 Patient positioning

Patients will be positioned supine with at least one hand above their head, and a bolster under their knees. Longitudinal and latitudinal laser systems will be used to align patient reference marks or tattoos. Standard reference tattoos are expected to be:

- 10cm inferior to palpable Sternal Notch/Midline (Treatment Reference Point)
- Lateral marks at ¼ Antero/Posterior width (where appropriate)
- 20-25cm inferior to palpable Sternal Notch/Midline or equivalent thereof.

4.2 Immobilisation

A half body vacuum immobilisation device would be considered a minimum requirement for immobilisation. Abdominal compression is not routinely recommended.

4.3 CT Scan

All participants must undergo a planning CT scan with a maximum 3mm slice spacing. This should be a respiratory gated 4D CT scan. In order to allow placement of non-coplanar beams through valid body contours, it should extend as a minimum from above the chin to a sufficient inferior volume to include the whole lung, as much of the liver as possible and appropriate body contours. The size of the tumour and its relationship to the chest wall and proximal bronchial tree will be confirmed. For definitions of 4DCT scan and Maximum Intensity Projection (MIP) please see Appendix 5 of the SAFRON II protocol.

4.4 Motion Management

All participants must be informed of the importance of breathing, in a shallow and regular fashion, as well as not moving prior to and during their scan. Each patient’s breathing trace will be assessed by a suitably trained nuclear medicine technologist and/or radiation therapist. If the breathing trace is deemed to be irregular, the amplitude of the patient’s respiratory cycle seems abnormally large, or conversely not large enough to obtain a signal, participants will be given simple breathing instructions.

Imaging used for treatment planning in both treatment arms must explicitly consider tumour motion due to breathing. Centres are encouraged to use the Internal Target Volume (ITV) concept developed by the International Commission on Radiation Units and Measurements1. An ITV is developed by combining all positions the target may be in during the breathing cycle. Therefore, the use of 4D CT series of three dimensional CT datasets for different phases of the breathing cycle is mandatory, with the creation of MIP images required if available (or otherwise all of the breathing cycles must be transferred to the planning system). An MIP image shows the combined contour of a high density structure such as a tumour in all phases of the breathing cycle2. An ‘average’ image set derived from 4D CT would provide a suitable basis for dose calculation and a reference image set for verification prior to treatment.

An exception may be possible where implanted fiducial markers are used. In this case, stereoscopic kV imaging in conjunction with fluoroscopy may be used to generate an ITV margin for the MIP in combination with a 3DCT. If a centre is planning to use this approach, please contact qa@trog.com.au or principal investigator for further clarification. Fluoroscopy alone is not considered sufficient to determine three dimensional tumour motion.
Gated radiotherapy delivery may be considered on a centre by centre basis. If gated radiotherapy is planned, a 4D CT is mandatory. The insertion of radio-opaque fiducial markers into the target volume should be considered.

4.5 Simulation Procedure

Prior to undertaking the simulation procedure, the participant will be provided education regarding the importance of regular breathing.

Participants will be positioned supine with the arms elevated above the head to permit beam access to the thoracic region. Where maintaining this position proves difficult for the patient and stability is perceived to be compromised due to patient discomfort, consideration may be given to placing the contralateral arm by the side for patient comfort. Thoracic bony landmarks will be palpated by the Radiation Therapist to assist in aligning the patient midline. Once the participant position has been established, the immobilisation device will be created to stabilise the participant in the final treatment position.

Once participant positioning is finalised, reference skin markings as outlined in 3.1 will be established, and documented into the patient record consistent with department protocols. Preparation of equipment for acquisition of a 4DCT scan (e.g. placement of bellows) will be performed according to department and equipment protocol. The CT couch will be positioned and zeroed on the relevant treatment reference point in readiness for scanning. Orthogonal tomograms will be acquired and utilised to determine the upper and lower extends of the 4DCT scan, consistent with scanning volume indicated in section 3.3. Prior to acquisition of the 4DCT, the participant respiratory trace will observed by an experienced radiation therapist for a period of at least one minute to verify that the participant is breathing in a regular manner with relatively consistent respiratory rate and amplitude. Where an irregular breathing trace is observed prior to 4DCT acquisition, participant education regarding the need for regular breathing should be reaffirmed. Participants exhibiting a persistent irregular breathing trace should be consulted to identify and resolve any issues related to discomfort which are perceived to impact on the patients breathing. The number of breaths per minute will be recorded and utilised in the selection of an appropriate pitch for the 4DCT in consultation with manufacturer guidelines.

Post- acquisition of the 4DCT, the planning Radiation Therapist will assess the respiratory trace for regularity. Any irregularities identified should be discussed with the relevant clinician and medical physicist.

Following completion of the simulation procedure, reconstruction of 3D data sets as outlined in 3.4 will be performed and transferred to the treatment planning system.
5 STANDARDISED NAMING

The increasing adoption of standardised contouring names has been encouraged both internationally [10] and in Australasia by RANZCR. TROG QA has adopted the international recommendations, and applied them to currently recruiting TROG trials. The use of standardised names has led to increased efficiency in QA plan reviews, and has been welcomed by participating centres and reviewers.

All structures in the radiotherapy treatment plan must adhere to the following standardised names in Table 1.

Table 1: Structure Standardised Names:

<table>
<thead>
<tr>
<th>Structure Name</th>
<th>Standardised Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal Target Volume</td>
<td>ITV1, ITV2, ITV3</td>
</tr>
<tr>
<td>Planning Target Volume</td>
<td>PTV1, PTV2, PTV3</td>
</tr>
<tr>
<td>Normal Lungs</td>
<td>BilatLung-ITV</td>
</tr>
<tr>
<td>Heart</td>
<td>Heart</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Oesophagus</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>SpinalCord</td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>BrachialPlexus</td>
</tr>
<tr>
<td>Skin (5mm subcutis)</td>
<td>Skin</td>
</tr>
<tr>
<td>Chest wall*</td>
<td>ChestWall</td>
</tr>
<tr>
<td>Great Vessels</td>
<td>GreatVessel</td>
</tr>
<tr>
<td>Liver</td>
<td>Liver</td>
</tr>
</tbody>
</table>

6 TARGET VOLUME DEFINITIONS

6.1 Target Volumes

Target Volumes must be defined as per ICRU 50, 62 and 83, with clear definitions, individual contouring and specific labeling. These include:

- Internal Target Volume (ITV) – The ITV will be used to take into account the total tumour excursion through respiration. It is a Boolean combination of all locations that would be occupied by the tumour at any phase of the breathing cycle. ITV delineation will require 4DCT simulation.
- Planning Target Volume (PTV) – ITV to PTV margins must take into consideration set-up uncertainties. An ITV to PTV isotropic expansion of 5mm is required.

The use of smaller margins than outlined above are prohibited unless justified to the principal investigator.
In the instance of two tumours in close proximity, then a single isocentre and single target volume may be considered when the sum of the cumulative largest diameter of the tumours and the intervening normal lung is ≤ 5cm. In these cases, both tumours may be considered a single target and treated simultaneously. The ICRU reference point should be in the centre of the PTV volume which incorporates both targets.

6.1.1 Field Borders

The margin between the planning target volume and the field edge is expected to be 0-2mm in the axial direction. To achieve 99% coverage of the target volume, it may be necessary to accept a larger than 0-2mm margin from the target volume to the MLC defined field edge, particularly in the craniocaudal axis. Negative PTV/field edge margins are allowable to improve conformality of the prescription isodose to the PTV.
## 7 ORGANS AT RISK (OAR) DEFINITIONS

Organs at risk must be contoured and labelled as in Table 2.

**Table 2: Organs at risk (OAR) definitions and standardised names**

<table>
<thead>
<tr>
<th>Organ at risk</th>
<th>Standardised name</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both normal lungs</td>
<td>BilatLung-ITV</td>
<td>Auto-contouring shall be used for lung outlining. This will be based on the “average” 4DCT. While separate outlines can be created for “Left Lung” and “Right Lung”, the constraints apply to the whole normal lung tissue. The lung volume is to be outlined as the whole lung excluding the ITV.</td>
</tr>
<tr>
<td>Heart</td>
<td>Heart</td>
<td>The heart will be contoured along with the pericardial sac. Superiorly, the whole heart starts just inferior to the left pulmonary artery. For simplification, a round structure to include the great vessels as well can be contoured.</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Oesophagus</td>
<td>The oesophagus should be contoured from the crico-oesophageal junction to its full length down to the gastro-oesophageal junction.</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>SpinalCord</td>
<td>As represented by bony spinal canal, extending at least 10mm above and below the PTV volume</td>
</tr>
<tr>
<td>Liver</td>
<td>Liver</td>
<td>Where the liver is encompassed by the CT, the liver should be contoured.</td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>BrachialPlexus</td>
<td>This is difficult to identify on CT, but a volume which extends from the C5-T1 intervertebral foramina, passes between the anterior and middle scalene muscles, then includes the subclavian and axillary arteries to the lateral border of pectoralis minor will incorporate the components of the plexus. Refer to the guidelines published by Hall et al for more detail.</td>
</tr>
<tr>
<td>Skin</td>
<td>Skin</td>
<td>To reduce radiation fibrosis, the subcutis, or the volume between the external contour and a contour 5mm deep to this will be labeled ‘skin’. This contour must be created circumferentially around the patient contour, and extend cranio-caudally to incorporate the entry and exit of all coplanar and non-coplanar beams through skin.</td>
</tr>
<tr>
<td>Chest wall</td>
<td>ChestWall</td>
<td>The chest wall will be outlined as a structure between the parietal pleura and encompassing the intercostal muscles and ribs. It will extend as far medially as, but not include, the vertebral body. Chest wall will be contoured on all slices from 5cm superior to 5cm inferior to the PTV so as to include all regions on chest wall traversed by any non-coplanar beams.</td>
</tr>
</tbody>
</table>
8 TREATMENT PLANNING AND DOSIMETRY

8.1 Planning System

A 3D computerised planning system capable of incorporating 4DCT datasets (or derived image sets such as MIP and AVE) and utilizing a type B 3D dose calculation algorithm e.g. convolution/superposition to account for variations in lateral scatter due to heterogeneities. All patients must undergo CT planning. All CT plans are to be calculated on a recommended dose matrix grid spacing of 2.5mm x 2.5mm x 2.5mm with a maximum of no more than 3mm x 3mm x 3mm. The dose calculation grid must cover all PTVs, PRVs and OARs.

8.2 Dose Prescription, Fractionation and Duration

For both treatment arms, if multiple treatment sessions are required then each fraction should be delivered on non-consecutive days, (e.g. a patient may be treated on a Monday afternoon and again on a Wednesday morning, but not on the intervening Tuesday).

8.2.1 Stereotactic radiotherapy prescription

Single-fraction SABR: - PTV - A total dose of 28Gy delivered in a single fraction will be prescribed to the isodose line covering the PTV. The optimal dose maximum within the PTV should be 125%, equivalent to a normalised covering isodose of 80%.

Multi-fraction SABR: - PTV - A total dose of 48Gy in 4 daily 12Gy fractions delivered twice a week over 2 weeks will be prescribed to the covering isodose line. The optimal dose maximum within the PTV should be 125%, equivalent to a normalised covering isodose of 80%.

For each PTV the following criteria must be adhered to:

- The maximum dose will be contained within the ITV.
- The dose outside the PTV will be minimised.
- D99% - The near-minimum dose, defined as the dose to 99 % of the PTV, shall be ≥100 % of the prescribed dose (i.e. either 28 Gy or 48 Gy).
- Plan normalisation should ideally provide a PTV max of 125% - 143%. Max doses below 125% are not acceptable. Maximum doses >143% constitute a minor violation.

Treatment will be delivered using conformal, fixed gantry IMRT or arc based treatments such as dynamic conformal arc or VMAT techniques. CyberKnife is also permitted. Please refer to Appendix A. The use of fixed gantry IMRT, VMAT, TomoTherapy and CyberKnife techniques requires each centre to have successfully completed relevant TROG credentialing activities. Please contact qa@trog.com.au for further information.

8.3 Target Volume Dose Reporting

The dose to the target shall be reported as the prescription dose that covers 99% of the PTV. This should be either 28Gy or 48Gy.

The mean, minimum and maximum dose in the PTV shall be calculated and reported as per ICRU 50, 62 and 83. The minimum dose received by the PTV is defined as the minimum isodose value encompassing 100% of the PTV. The maximum dose within the PTV should be 125%.
Dose is to be prescribed to satisfy the dose prescription criteria of 3.8.1 and the dose heterogeneity criteria. A dose volume histogram (DVH) is required for all normal tissue (as listed in table 2), as well as for the ITV and PTV.

The following must be reported:

PTV reporting
1) $D_{2\%}$ Near maximum dose.
2) $D_{99\%}$ Near minimum dose.
3) $D_{50\%}$ Median Dose.
4) Mean dose.
5) Conformity Index: The quotient of the Treated Volume and the volume of the PTV (ICRU 62). The following conformity indices will be reported:
   - $Cl_{100\%}$: The volume enclosed by the prescription isodose/Volume of the PTV
   - $Cl_{50\%}$: The volume enclosed by an isodose line constituting 50% of the prescribed dose/Volume of the PTV.
   
   E.g. For 28Gy prescription, the $Cl_{50\%}$ will be calculated as volume of 14Gy isodose / Volume of the PTV.

6) Prescription isodose calculated using:

$$\text{Prescription isodose} = \frac{\text{Absolute prescribed dose (i.e. 28Gy or 48Gy) \times 100\%}}{D_{2\%}}$$

### 8.3.1 Conformity Indices

Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose to the volume of the PTV, which is termed the $Cl_{100\%}$, is ideally < 1.2 (see table 3). These criteria are not expected to be met when treating very small tumours (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension) in which the required minimum field sizes often results in the inability to meet a conformality ratio of 1.2.

<table>
<thead>
<tr>
<th>PTV Volume (cm³)</th>
<th>Ratio of Prescription Isodose Volume to the PTV Volume, $Cl_{100%}$</th>
<th>Ratio of 50% Prescription Isodose Volume to the PTV Volume, $Cl_{50%}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Variation</td>
<td>Minor</td>
</tr>
<tr>
<td>0-10</td>
<td>&lt;1.2</td>
<td>&lt;1.5</td>
</tr>
<tr>
<td>11-40</td>
<td>&lt;1.2</td>
<td>&lt;1.5</td>
</tr>
<tr>
<td>&gt;40</td>
<td>&lt;1.2</td>
<td>&lt;1.5</td>
</tr>
</tbody>
</table>

### 8.3.2 Intermediate dose spillage

The falloff gradient beyond the PTV extending into normal tissue structures must be rapid in all directions. The ratio of the volume of 50% of the prescription dose isodose to the volume of
the PTV varies as a function of PTV size. The table below gives the goal value of CI50% for any given PTV volume.

In cases where a PTV is located in close proximity to a critical structure, it may be preferable to weight treatment beams to dilate the isodose pattern in a particular plane to maximize sparing of an adjacent OAR. This may have a detrimental effect on the CI50% value. In such cases, sparing of the OAR to maintain dose within tolerance should take priority over an optimal CI50% value.

8.4 Organ At Risk Dose Constraints

Imaging dose must be taken into account when considering dose constraints. Where two targets are to be treated on protocol, normal tissue dose constraints should apply cumulatively, so that summed doses do not exceed constraints outlined below.

Dose constraints listed in Table 3, unless stated otherwise, are applicable to clinically meaningful volumes. In the context of this protocol, a maximum dose refers to the representative volume of a voxel, or 0.03cc. Any dose exceeding the dose constraints will be scored as protocol deviation: minor deviation when 0-5% higher than dose constraint; major deviation when >5% higher than dose constraint. The exception to this rule is the chest wall constraint. The goal of any plan will be to optimise target treatment parameters per this protocol, being mindful of rib dosing (as low as reasonable achievable [ALARA]). However, in no way should the chest wall constraint result in compromise of target coverage. The chest wall limits listed above may be exceeded for an otherwise excellent plan. This will not be considered a violation.
**Table 3: Normal tissue dose-volume constraints based on ongoing multi-institutional randomised trials RTOG-0618\(^7\) and RTOG-0915\(^8\), and previously described dose constraints Lee et al\(^9\) and RTOG 0236\(^10\).**

**Definitions:** \(V_x\) describes the volume that receives \(x\)Gy, e.g. \(V_5 < 60\%\) represents that the volume of specified OAR receiving 5 Gy shall be less than 60%.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Standardised name</th>
<th>Parameter</th>
<th>Constraint</th>
<th>Investigational Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Lungs</td>
<td>BilatLung-ITV</td>
<td>V5</td>
<td>66%</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 1000cc</td>
<td>7.4Gy</td>
<td>12.4Gy, (max 3.1Gy per fraction)</td>
</tr>
<tr>
<td>Heart</td>
<td>Heart</td>
<td>Maximum dose 0.03cc</td>
<td>22Gy</td>
<td>34 Gy, (max 8.5 Gy per fraction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 15cc</td>
<td>16Gy</td>
<td>28 Gy, (max 7 Gy per fraction)</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>Oesophagus</td>
<td>Maximum dose 0.03cc</td>
<td>15.4Gy</td>
<td>30Gy, (max 7.5Gy per fraction)</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>SpinalCord</td>
<td>Maximum dose 0.03cc</td>
<td>12Gy</td>
<td>20.8Gy, (max 5.2Gy per fraction)</td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>BrachialPlexus</td>
<td>Maximum dose 0.03cc</td>
<td>15Gy</td>
<td>24Gy, (max 6Gy per fraction)</td>
</tr>
<tr>
<td>Skin (5mm subcutis)</td>
<td>Skin</td>
<td>Maximum dose 0.03cc</td>
<td>26Gy</td>
<td>36 Gy, (max 9 Gy per fraction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 10cc</td>
<td>23Gy</td>
<td>33.2 Gy, (max 8.3 Gy per fraction)</td>
</tr>
<tr>
<td>Chest wall*</td>
<td>ChestWall</td>
<td>&lt; 70 cc</td>
<td>**26Gy to full thickness</td>
<td>30Gy</td>
</tr>
<tr>
<td>Great Vessels</td>
<td>GreatVessel</td>
<td>Maximum Dose 0.03cc</td>
<td>30Gy</td>
<td>49 Gy, (max 12.25 Gy per fraction)</td>
</tr>
<tr>
<td>Liver</td>
<td>Liver</td>
<td>V20, V30</td>
<td>No constraint, but dose / volume parameters to be documented</td>
<td>No constraint, but dose / volume parameters to be documented</td>
</tr>
</tbody>
</table>

* Chest wall dose limit may be exceeded if rib structure lies close to or in contact with the PTV
** 26Gy isodose line should not cross full thickness of the chest wall structure.
8.4.1 Planning Previous Radiotherapy

No overlap with areas of lung previously receiving high-dose radiotherapy is permissible. Previous high dose radiotherapy is defined as a biological equivalent dose (BED) $11>40Gy$ using an $\alpha/\beta$ ratio of 10. If a patient has received previous high dose radiotherapy, it is the treating radiation oncologist’s responsibility to review and approve the proposed treatment plan, ensuring that there is no overlap with previous high-dose regions.

This rule applies to retreatment of participants on protocol for subsequent pulmonary metastases. Dose constraints for organs at risk are the same as outlined in section 3.7 above.

8.5 Treatment techniques

Treatment must be delivered using a conformal or intensity modulated technique including IMRT, VMAT, TomoTherapy and CyberKnife.

8.5.1 Field Shaping

Treatment must be delivered conformally using a multileaf collimator. The use of fields with jaw settings of less than 3.0 x 3.0 cm is discouraged to maintain accuracy of dose modelling. Shielding using multileaf collimation within field sizes smaller than this should be verified wherever possible by using dose measurements within a phantom.

8.5.2 Dose Rate

High dose rate modes are allowed (e.g. flattening filter free delivery) in combination with conformal techniques only. FFF is NOT permitted to be used in combination with Inversely Planned Techniques. Please contact qa@trog.com.au for further information.

8.5.3 Number of Treatment Fields and Field Arrangements

For each treatment arm, radiation beams are expected to be of megavoltage quality and of 6MV energy. A nominal photon energy between 4MV and 10MV is acceptable. The use of field dimensions below 3cm is discouraged. For 3D conformal treatments, treatment must be delivered with at least eight (8) non-opposing conformal megavoltage photon beams. It is anticipated that a typical range of beam numbers would be 8 to 12. Conformal arcs are allowed with a variable cumulative arc length, expected to be 360 degrees or more.

Geometric and dosimetric accuracy of the treatment plan must be independently verified by the local physics department using phantom dosimetric measurements. The physics QA dosimetry report will be submitted with the treatment plan for QA technical review. This report shall include details of absolute dose verification and the relative dose fluence check. The in-house QA protocol forms part of the credentialing requirements, and therefore the TROG QA team must be alerted to any changes to the in-house QA processes prior to submitting patient reports.

8.5.4 Field Size and Shielding Margin

Treatment must be delivered conformally using a multileaf collimator. The use of fields with jaw settings of less than 3.0 x 3.0 cm is discouraged to maintain accuracy of dose modelling. Shielding using multileaf collimation within field sizes smaller than this should be verified wherever possible by using dose measurements within a phantom.
8.6 Respiratory Gating

Respiratory gating of the treatment is allowed but not recommended. This may be beneficial in participants with tumours which demonstrate large tumour excursion due to respiratory motion at the time of 4DCT simulation. Respiratory gating comprises modulation of the beam delivery to limit irradiation only to times when the PTV is thought to be within the field. This method may reduce the volume of normal lung parenchyma irradiated.

When respiratory gating is employed, an anisotropic ITV to PTV expansion is recommended, with an axial expansion of 5mm, and a craniocaudal expansion between 5mm to 10mm.

9 TREATMENT DELIVERY

9.1 Treatment delivery equipment

Isocentre tolerance for quality assurance must be within a 2mm diameter spherical volume in the planes of gantry, couch and collimator rotations.

9.2 Treatment Delivery Imaging Requirements

The linear accelerator must be also equipped with verification imaging that allows visualization of the target volume. This must be on board kV quality imaging, which is expected to be cone beam CT or superior technology. If 4D cone-beam CT becomes available and is validated, this may be employed. The coincidence of imaging and treatment isocentre and repositioning uncertainty must be verified to be ≤ 1 mm [9].

Treatment with respiratory gating is allowed, though not routinely recommended.

9.3 Target delivery verification

Verification imaging must be capable of visualising the target with soft tissue matching as well as bone alignment. In general, this would necessitate imaging with a Cone Beam CT (CBCT) or superior pre-treatment imaging modality. The use of fiducial markers with kV planar imaging would be considered a suitable alternative. Online soft tissue matching will ensure that the target is within the simulated safety margin or PTV on three occasions:

- Prior to delivery
- Half-way through the delivery (may be omitted for some rapid delivery techniques), please contact qa@trog.com.au.
- After completion of therapy. This may be omitted in instances of single fraction delivery, or on the last fraction of a multi-fraction delivery.

A radiation oncologist must be present to perform the online soft tissue matching. A 0mm tolerance should be considered standard for target position taken with pre-treatment imaging. Tolerances for surrounding bony and soft tissue anatomy will be defined as that which is demonstrated to be acceptable by individual trial sites, and should take into consideration dose gradients in the region of relevant critical structures for each case. All shifts should be actioned to a 0mm tolerance based on the match to the soft-tissue target. Repeat pre-treatment image verification is necessary when required shifts are ≥ 3mm in any direction.

It is recommended that one ‘dummy run’ is conducted on the treatment unit for each participant prior to commencement of treatment. This dummy run shall include imaging (including up to two CBCT scans) and simulation of treatment in all beam directions to ensure clearance of all non-coplanar beams so that the treatment can be delivered as planned. If it is apparent that the proposed plan cannot be technically delivered due to gantry collision, then
nearest possible angles to the planned angles will be used, and the computer data revised accordingly and reviewed to ensure the new plan meets established criteria. If the tumour cannot be visualised adequately on the cone-beam CT, either at the dummy run or at treatment, then the radiation oncologist will be responsible for determining the management plan. If treatment is performed using alternate online matching techniques, then the radiation oncologist must report this event to the principal investigator as a protocol violation. Once a participating centre deems that their own expertise with the technique is sufficient, the dummy run may be omitted as a separate procedure. If a dummy run has not been performed for a particular participant, clearance of all treatment beams must be established at the first treatment appointment prior to delivery of any treatment field.

It is recommended that all participants should have a pre-treatment dosimetric analysis using a patient phantom with film dosimetry. In vivo dosimetry is not mandatory but recommended. Dosimetry and target verification information will be recorded and assessed after each treatment by the investigative team.

10 TROG ON-TRIAL QUALITY ASSURANCE PROGRAM

In accordance with TROG Policy Statement TP E6 (Quality Assurance Guidelines), a QA technical review will be conducted for this trial. Remote technical audits will be conducted by an independent reviewer.

Radiotherapy on-trial quality assurance for the trial will consist of two phases:

1. Pre-Treatment Radiotherapy QA Technical Review
2. Post-Treatment Radiotherapy QA Technical Review

To complete the QA requirements you will need access to CQMS and the TROG website. Please email qa@trog.com.au to arrange access.

Timely feedback will be provided to participating centres regarding the outcome of QA technical reviews; via the TROG QA office.

10.1 Pre-Treatment QA Technical Reviews

All participants enrolled must undergo real-time review. The treatment plan will be required for review at least one week prior to treatment commencement. If the review results are acceptable the participant will proceed to treatment.

Data Submission: A checklist of the source data required for each RT QA case will be provided by the TROG QA Office with specifications of timelines for data submission included. Please refer to Appendix C. This checklist can also be accessed via the TROG website www.trog.com.au

10.2 Post-Treatment QA Technical Reviews

All participants enrolled will undergo post-treatment review to confirm treatment delivery and imaging was performed as per protocol.

Data Submission: A checklist of the source data required for each RT QA case will be provided by the TROG QA Office with specifications of timelines for data submission included. Please refer to Appendix D. This checklist can also be accessed via the TROG website www.trog.com.au
10.3 Additional Guidelines to assist with QA Submissions

Additional documents are available on the TROG website [www.trog.com.au](http://www.trog.com.au) (Professionals → QA program), which will assist you to submit the data required for QA. The following resources are available:

- **TROG Guidelines for Exporting Treatment Plan Data for Clinical Trial QA Reviews.**
  For BrainLab, Eclipse, Monaco, Oncentra, Pinnacle, RayStation, TomoTherapy and Xio.

- **TROG CQMS Data Upload Guidelines.** A guide on how to upload data into CQMS.

- **Overview of Quality Assurance Data Submission for TROG Trials.** A guide on the types of source documentation required for trials. This is a general document; *please refer to the trial specific checklist for what is required for the SAFRON II trial.*

**Please Note:** De-identification of the treatment plan files is now automatic at the point of upload to CQMS.
11 REFERENCES

APPENDIX A: CYBERKNIFE ROBOTIC STEREOTACTIC RADIATION THERAPY SYSTEM

12.1 RADIOTHERAPY SUMMARY

12.1.1 Trial Regimen Summary

As per section 1.1 Trial Regimen Summary (Radiotherapy Planning, Delivery and QA guidelines).

12.2 TROG PRE-TRIAL QUALITY ASSURANCE PROGRAM

All participating centres must successfully complete pre-trial quality assurance procedures prior to enrolling patients to the study. This will consist of an initial credentialing phase involving the following activities:

1. Phantom Dosimetry Audit
2. Facility Questionnaire
3. Benchmarking
4. Site Staff Training

As part of the credentialing process, all sites wishing to use Cyberknife must seek explicit approval by TROG.

To complete the QA requirements you will need access to CQMS and the TROG website (password protected documents). Please email qa@trog.com.au to arrange access.

12.2.1 Phantom Dosimetry Audit

Each participating centre must have completed a TROG-approved dosimetry study. Contact TROG QA, qa@trog.com.au for further information.

12.2.2 Facility Questionnaire

All centres wishing to use CyberKnife must complete a facility questionnaire pertaining to this treatment modality. Documentation outlining centre practice for IGRT and immobilisation will be requested. The facility questionnaire can be accessed on the TROG website (www.trog.com.au).

12.2.3 Benchmarking exercise

Sites must complete a benchmarking exercise for a single lesion case only. Two tumours in the same lung would have to be so close together that they could be reasonably assumed to be the same tumour. If they were not, they would need to be planned and treated as separate lesions. It is not possible to export the summed plan from Multiplan (CK TPS). As a result only single lesions will be treated on the study.

CK does not plan on an AVG scan but a breath-hold CT scan. As a result, an anonymised dataset from a previously treated patient will be used and a single lesion plan will be produced that complies with the protocol. This will be submitted for review.
12.2.4 Site Staff Training

All staff will have completed either the Accuray or in-house training for target tracking volume (TTV) delineation, simulation, soft tissue matching using X-Sight Lung Tracking (XLT) and XLT treatment delivery prior to participating in this study.

12.2.5 Submitting Data For QA

Plans and additional source data are to be submitted to the TROG Central Office via CQMS. A checklist of the required source documentation will be provided by the TROG QA Office. Please refer to Appendix B. This checklist can also be accessed via the TROG website (www.trog.com.au). For additional support submitting data please see Section 10.3 Additional Guidelines to assist with QA Submissions.

12.3 RADIOTHERAPY TREATMENT SCHEDULE

As per Section 2. Radiotherapy Treatment Schedule.

12.4 PLANNING SIMULATION

12.4.1 Patient Positioning

Patients will be positioned supine with arms by sides and a bolster under their knees. Patient wears a tight fitting top that moves as one with their body as they breathe. Tattoos are not used.

12.4.2 Immobilisation

A half body vacuum immobilisation device will be used.

12.4.3 CT scan

In order to accurately track the target during treatment, breath-hold CT scans are required to eliminate motion from the DRR. Slice thickness will be 1.0mm and patient will be scanned approximately 17cm superior and inferior to tumour to include anatomy required for beam avoidance areas e.g. chin. Two non-contrast breath-hold CT scans will be performed, the first at end of normal exhale and the second at end of normal inhale. If contrast is required an additional contrast scan at end of normal exhale must also be performed. A 4DCT is not necessary.

12.4.4 Motion Management

The management of respiratory motion using the CyberKnife (CK) system is unique. LED markers are attached to the patients’ chest or abdomen and external respiratory motion is tracked using an infrared camera suspended from the ceiling above the treatment couch. Pairs of kV images are then taken at different points on the respiratory cycle to identify and align the internal tumour position at each point. The CK system is able to track soft tissue lung targets without the need for fiducials. It relies on two things to do this, the ability of the CK system to accurately detect the soft tissue target on one or both of the kV images repeatedly and the radiation therapists also need to be confident they can see the soft tissue target on the same.

The CyberKnife Robotic Stereotactic Radiotherapy System can treat patients by tracking soft tissue, as described below (or if this is not possible, by implanted fiducial markers or spine tracking and using suitable ITV margins). Only patients suitable for soft tissue tracking will be treated on this trial. To determine that patients are suitable for soft tissue tracking a simulation will be performed using the CK system. A tumour tracking volume is defined by a suitably trained radiation therapist on the exhale and inhale CT scans. The patient will have their
external respiratory motion aligned with the internal position of the tumour. During the simulation the radiation therapists determine whether the tumour can be accurately identified by them and the tracking software on one (1-view) or both (2-view) kV images. If 1-view, in the untracked plane the motion will be accounted for by taking into consideration the variation in tumour position between the inhale and exhale CT scans. For 2-view, all motion is tracked during treatment and hence this is planned using the exhale CT scan only.

12.4.5 Simulation procedure

If 4DCT is required as part of the trial the only amendment is that the patient will be positioned with their arms by their sides to avoid collision with the CK.

12.5 STANDARDISED NAMING

As per section 5 Standardised Naming (Radiotherapy Planning, Delivery and QA guidelines).

12.6 TARGET VOLUME DEFINITIONS

12.6.1 Target Volumes

Target volumes must be defined as per ICRU 50, 62 and 83, with clear definitions, individual contouring and specific labelling. These include:

Gross Target Volume (GTV) – The GTV will encompass the visible gross tumour.

Internal Target Volume (ITV) – The ITV will be used to take into account the tumour excursion in the untracked plane for patients tracked using 1-view method. This will be determined using both exhale and inhale CT scans and will result in an anisotropic expansion of the GTV.

Planning Target Volume (PTV) – For 2-view tracked targets the GTV – PTV expansion will be 5mm in all directions. For 1-view tracked targets the GTV – PTV expansion will be 5mm in the tracked directions and 8mm in the untracked.

In the instance of two tumours in close proximity, then a single isocentre and single target volume may be considered when the sum of the cumulative largest diameter of the tumours and the intervening normal lung is \( \leq 5 \) cm. In these cases, both tumours may be considered a single target and treated simultaneously. For simultaneous treatment to be considered, each lesion must have identical tumour motion. If they do not, each lesion must be planned and treated separately and the two plans summed to attain the total doses to OARs.

12.6.2 Field Borders

The CK system will use cones or collimators to deliver treatment non-isocentrically to the target volume and hence field border parameters do not apply.

12.7 ORGANS AT RISK (OAR) DEFINITIONS

OAR, except for both normal lungs, must be contoured and labelled as in Table 2. Please refer to Section 7 ORGANS AT RISK (OAR) DEFINITIONS. As treatment is planned on a breath-hold exhale CT scan, both normal lungs will be labelled “BilatLung-GTV” where an ITV is not used and “BilatLung-ITV” if one has.
12.8 TREATMENT PLANNING AND DOSIMETRY

12.8.1 Planning System

The dose calculation algorithm will be Monte Carlo. As per Section 8.1 Planning System.

12.8.2 Dose Prescription, Fractionation and Duration

As per Section 8.2 Dose Prescription, Fractionation and Duration.

12.8.2.1 Stereotactic radiation therapy prescription

For both arms the total dose (TD) is prescribed to the covering isodose, which is expected to be between 70-80% of the maximum dose. The Dmax will be within the PTV and is described as 100% and will represent approximately 125% of the TD. The maximum dose should be between 125 – 143%, outside this range is unacceptable.

The CK is a non-isocentric treatment using 100-200 beams to deliver the dose to the PTV therefore standard practice of normalising the dose to the ICRU reference point is not applicable. For each PTV the following criteria must be adhered to:

- The maximum dose will be contained within the GTV.
- The dose outside the PTV will be minimised.
- D99% - The near-minimum dose, defined as the dose to 99% of the PTV, shall be ≥ 100% of the prescribed dose (i.e. either 28 Gy or 48 Gy).
- Max doses below 125% are not acceptable. Maximum doses >143% constitute a minor violation.

12.8.3 Target Volume Dose Reporting

As per main document Radiotherapy Planning, Delivery and QA guidelines (section 8.3 Target Volume Dose reporting) except if an ITV is not required then a DVH will not be provided.

The CK is a non-isocentric treatment using 100-200 beams to deliver the dose to the PTV therefore standard practice of normalising the dose to the ICRU reference point is not applicable however, the dose at the centroid of the PTV will be reported.

12.8.3.1 Conformity indices

As per section 8.3.1 Conformity indices (Radiotherapy Planning, Delivery and QA guidelines), although CK is made to treat small volumes so meeting the conformality ratio of 1.2 should ideally be achieved.

12.8.3.2 Intermediate dose spillage

As per section 8.3.2 Intermediate dose spillage (Radiotherapy Planning, Delivery and QA guidelines).

12.8.4 Organ At Risk Dose Constraints

During treatment the CK system will image the target every 15s for the first 10 minutes then every 30 – 60s for the remainder of the treatment fraction. The average number of pairs of kV images taken each treatment is 94 and the average skin dose per image pair is 0.18mGy. Hence, for each fraction the imaging dose is estimated at 0.17cGy to the skin. For this reason the imaging dose will not be taken into account when considering dose constraints.

Dose constraints listed in Table 3, unless stated otherwise, are applicable to clinically meaningful volumes. Maximum dose refers to D0.03cc (30mm3).
12.8.4.1 Constraints for retreatment of irradiated lung

As per Section 8.5 Constraints for retreatment of irradiated lung.

12.8.5 Treatment Techniques

12.8.5.1 Beam shaping

The CK system has photon energy of 6MV and utilises a range of cones or collimators that vary in size from 5 – 60mm. Treatment is delivered using 100-200 non-isocentric beams from a variety of angles and planes. Cones must be used for diameters of 10mm or smaller.

12.8.5.2 Beam Arrangements

The CK system has photon energy of 6MV and utilises a range of cones or collimators that vary in size from 5 – 60mm. Treatment is delivered using 100-200 non-isocentric beams from a variety of angles and planes.

12.8.6 Respiratory Gating

Not Applicable.

12.9 TREATMENT DELIVERY

The CK system uses kV imaging that is capable of visualising the target for soft tissue matching as well as bone alignment. Initially, the patient will be aligned using bony matching to match the spine position to the DRR. The offsets should be as close to zero as possible. Once the spine is aligned the soft tissue visualisation is confirmed and matching the target tracking volume (TTV) to the soft tissue target is performed to build the synchrony model. The CK system automatically performs the soft tissue match on each pair of orthogonal images under the supervision of the treatment team who have undergone specific training. The radiation oncologist is available to assist if needed.

The soft tissue target will be tracked during treatment and a pair of kV images will be taken every 15-60s. The robot will correct for a mismatch in the translational planes as long as within tolerance of 25mm. Outside of this the system will stop treatment and wait for intervention by the radiation therapists to get the patient position back within tolerance before continuing.

Once the patient is aligned and prior to each treatment a safety check will be performed to ensure the entire patient lies within the safety zone and hence the linac and robot will not touch them during treatment. This will involve passing a bar at a set height over the patient and visually inspecting that they lie beneath it.

Treatment and soft tissue matching will be performed by suitably trained radiation therapists. Should the radiation therapists be unable to visualise the soft tissue target as simulated and planned then treatment will not proceed and the radiation oncologist will be contacted to determine the management plan.

A dosimetric analysis using a patient phantom with film dosimetry will be conducted for each patient prior to treatment and submitted for QA plan review. The results of this and the verification images will be made available for QA plan review if required.

12.10 ON-TRIAL QUALITY ASSURANCE PROGRAM

As per Section 10 On-Trial Quality Assurance Program.

If more beam data is required, the plan can also be provided in XML format. The CK system does not have CBCT capability.
APPENDIX B: SOURCE DOCUMENTATION CHECKLISTS FOR QA TECHNICAL REVIEW

TROG 13.01
SAFRON II: Stereotactic Ablative Fractionated Radiotherapy versus Radiosurgery for Oligometastatic Neoplasia to the Lung: A Randomised Phase II Trial

QA REVIEW
Benchmarking-RT Checklist [QA1]

ALL INFORMATION LISTED IS REQUIRED FOR BENCHMARKING REVIEW AND SHOULD BE SUBMITTED USING CQMS

RADIOThERAPY: BENCHMARKING SOURCE DATA VERIFICATION

- As per protocol, the following information is required for submission of the benchmarking exercise.
- Information should be submitted via CQMS (Central Quality Management System)
- Copies of all information/documents should not reveal any personal identifying information, and should be labelled with the patient's initials and trial registration number.
- Electronic versions of documents should be sent in DICOM, pdf or jpeg format.

The following files are to be uploaded using the [RT Plan Upload] function listed in CQMS

RT Treatment Plans (Export):

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning CT data set (CT files)</td>
<td>Please ensure the plan is calculated and approved by RO</td>
</tr>
<tr>
<td>Planning file (RP file)</td>
<td>Please ensure the plan is calculated and approved. There will be one plan file for each phase</td>
</tr>
<tr>
<td>Structure Files (RS file)</td>
<td>Please ensure all structures are contoured and named as per the protocol</td>
</tr>
<tr>
<td>Dose Files (RD file)</td>
<td>Separate dose files are required for each PTV to allow assessment of target volume dose and conformity indices.</td>
</tr>
</tbody>
</table>

Please note: CQMS has inbuilt anonymisation software, which occurs at the point of upload. Please do not use any other anonymisation software.

The following files are to be uploaded using the [Other Upload] function listed in CQMS.

TROG QA Verification Images:

- De-identified JPEG image/s from the planning system demonstrating the composite isodose distribution. This image must include all 3 viewing planes, i.e. sagittal, axial and coronal planes, at the intersection of a relevant arbitrary point (e.g. ICRU reference point, isocentre, CT reference) within the central part of each PTV. The CT coordinates of the point/s (x, y, z) must be visible. Isodose lines must be in absolute dose (Gy) and clearly identifiable (no colourwash). Each JPEG image must demonstrate the absolute maximum dose (Gy) of the composite plan. Alternatively a separate JPEG must be created to demonstrate the maximum dose.
- Dose Volume Histogram (DVH) 'screen capture' (from treatment planning system or record and verify system) - Demonstrating in COLOUR all structures specified in the protocol. This image is required to verify accurate import and display of DVH data in the review software. The screen capture must be large enough to assess each structure.
- RT Prescription – including dose, fractionation and schedule
- Treatment Plan Summary - including field information and beam parameters

CQMS can be accessed via www.trog.com.au. If you are a new user, please contact the Helpdesk on qa@trog.com.au for a CQMS account.

TROG 13.01_QA1 Checklist_Benchmarking_v2_2015_10_28
Radiation Therapy Planning, Delivery and Quality Assurance - SAFRON II (V2 19 Nov 2015)

TROG 13.01
SAFRON II: Stereotactic Ablative Fractionated Radiotherapy versus Radiosurgery for Oligometastatic Neoplasia to the Lung: A Randomised Phase II Trial

QA REVIEW
Pre-RT Checklist [QA2]

ALL INFORMATION LISTED IS REQUIRED FOR REAL TIME REVIEW AND SHOULD BE SUBMITTED USING CQMS AT LEAST ONE WEEK BEFORE TREATMENT COMMENCEMENT

RADIOThERAPY: PRE-TREATMENT SOURCE DATA VERIFICATION

- As per protocol, the following information is required for all patients selected for QA review.
- Information should be submitted via CQMS (Central Quality Management System)
- Copies of all information/documents should not reveal any personal identifying information, and should be labelled with the patient’s initials and trial registration number.
- Electronic versions of documents should be sent in DICOM, pdf or jpeg format.

The following files are to be uploaded using the [RT Plan Upload] function listed in CQMS:

RT Treatment Plans (Export):
- All plans must be exported from the treatment planning system (TPS) in DICOM RT (RTOG is acceptable if DICOM RT is not available) format including all relevant data relating to:

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning CT data set (CT files)</td>
<td>Please ensure the plan is calculated and approved by RO</td>
</tr>
<tr>
<td>Planning file (RP file)</td>
<td>Please ensure the plan is calculated and approved. There will be one plan file for each phase</td>
</tr>
<tr>
<td>Structure Files (RS file)</td>
<td>Please ensure all structures are contoured and named as per the protocol</td>
</tr>
<tr>
<td>Dose Files (RD file)</td>
<td>Separate dose files are required for each PTV to allow assessment of target volume dose and conformity indices.</td>
</tr>
</tbody>
</table>

Please note: CQMS has inbuilt anonymisation software, which occurs at the point of upload. Please do not use any other anonymisation software.

The following files are to be uploaded using the [Other Upload] function listed in CQMS:

TROG QA Verification Images:
- De-identified JPEG image/s from the planning system demonstrating the composite isodose distribution. This image must include all 3 viewing planes, i.e. sagittal, axial and coronal planes, at the intersection of a relevant arbitrary point (e.g. ICRU reference point, isocentre, CT reference) within the central part of each PTV. The CT coordinates of the point/s (x, y, z) must be visible. Isodose lines must be in absolute dose (Gy) and clearly identifiable (no colourwash). Each JPEG image must demonstrate the absolute maximum dose (Gy) of the composite plan. Alternatively a separate JPEG must be created to demonstrate the maximum dose.
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RT Prescription – including dose, fractionation and schedule

Treatment Plan Summary - including field information and beam parameters

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### TROG 13.01
SAFRON II: Stereotactic Ablative Fractionated Radiotherapy versus Radiosurgery for Oligometastatic Neoplasia to the Lung: A Randomised Phase II Trial

**QA REVIEW**
Post-RT Checklist [QA3]

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**ALL INFORMATION LISTED IS REQUIRED FOR REVIEW AND SHOULD BE SUBMITTED USING CQMS WITHIN 2 WEEKS OF THE END IF TREATMENT**

**RADIOThERAPY: POST-TREATMENT SOURCE DATA VERIFICATION**

- As per protocol, the following information is required for all patients selected for QA review.
- Information should be submitted via CQMS (Central Quality Management System)
- Copies of all information/documents should not reveal any personal identifying information, and should be labelled with the patient’s initials and trial registration number.

The following files are to be uploaded using the [Other Upload] function listed in CQMS.

- **RT Daily Dose Record** – including dates of treatment delivery
- **CT Verification Image Log** – To verify that daily imaging was performed

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