PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for the Isotoxic Intensity Modulated Radiotherapy (IMRT) in stage III non-small cell lung cancer (NSCLC) - A feasibility study
AUTHORS	Haslett, Kate; Franks, Kevin; Hanna, Gerard; Harden, Susan; Hatton, Matthew; Harrow, Stephen; McDonald, Fiona; Ashcroft, Linda; Falk, Sally; Groom, Nicki; Harris, Catherine; McCloskey, Paula; Whitehurst, Philip; Bayman, Neil; Faivre-Finn, Corinne

VERSION 1 - REVIEW

REVIEWER	David Palma London Health Sciences Centre, Canada
REVIEW RETURNED	18-Nov-2015

GENERAL COMMENTS	This is a well-written, well-rationalized clinical trial exploring the feasibility of isotoxic radiation dose escalation in the setting of sequential chemo-radiation for Stage III NSCLC. RT will be delivered twice daily, with an attempt to escalate to a dose of 79.2 Gy, with IMRT used to help achieve OAR constraints. OAR doses are appropriate. This trial is already underway and recruiting, and in my opinion requires no revision prior to publication of this protocol. The authors may wish to consider two issues going forward, in case the protocol needs to be refined in the future: First, the PTV margins appear somewhat large in a setting where 4D-CT is already used and setup error is the only residual error. Second, radiation pneumonitis is a key factor in determining trial outcome/continuation. However, RP can be quite difficult to diagnose and can be difficult to distinguish from other entities such as COPD exacerbations. A clear definition of RP (or scoring 'dyspnea' as the outcome of interest rather than RP) may be preferable.

REVIEWER	Ursula Nestle Universitaetsklinikum Freiburg, Germany, Dpt. of Radiation Oncology
REVIEW RETURNED	23-Dec-2015

GENERAL COMMENTS	Minor points: - Throughout the protocol, it was not so clear (for me) until page 9, that the study actually has started a while ago. - It is stated that late radiation toxicity will be scored according to CTCAE v 4.0. How is early radiation toxicity scored? - Table 1: pre-specified normal tissue doses: The OAR “Mediastinal envelope” comprises a variety of different organs, with a different radiation sensitivity and reaction profile. Perhaps, for a consecutive study protocol (and also after evaluation of reported toxicities in this

	trial), a refined pre-specified normal tissue dose would be worthwhile. Additionally, the lung constraints could be augmented (e.g.V5) - Page 7 : statistical considerations The design of Bryant and Day is mentioned. Please, could you add a reference? Also, the statistical methods for the estimation of local control and overall survival are not depicted, and when is the starting point (e.g. start of irradiation or inclusion in the trial?) of these end points? - For me it is not quite clear, if the PET/CT is mandatory (should be)? - It could be stated that preferably a MR head should be performed

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

1. The PTV margins appear somewhat large in a setting where 4D-CT is already used and setup error is the only residual error.

2. Radiation pneumonitis is a key factor in determining trial outcome/continuation. However, RP can be quite difficult to diagnose and can be difficult to distinguish from other entities such as COPD exacerbations. A clear definition of RP (or scoring 'dyspnea' as the outcome of interest rather than RP) may be preferable.

We thank reviewer 1 for his comments which will be taken into account when developing a future protocol.

Reviewer 2:

1. Throughout the protocol, it was not so clear (for me) until page 9, that the study actually has started a while ago.

Added to page 5, 'The study started recruitment in June 2014'.

2. It is stated that late radiation toxicity will be scored according to CTCAE v 4.0. How is early radiation toxicity scored?

It has been clarified on page 10 that CTCAE v4.0 is used for the scoring of both early and late toxicity. Acute and late radiation toxicities continue to be recorded at each follow-up visit (according to the CTCAE v4.0 grading system).

3. Table 1: pre-specified normal tissue doses: The OAR “Mediastinal envelope” comprises a variety of different organs, with a different radiation sensitivity and reaction profile. Perhaps, for a consecutive study protocol (and also after evaluation of reported toxicities in this trial), a refined pre-specified normal tissue dose would be worthwhile. Additionally, the lung constraints could be augmented (e.g.V5).

We thank reviewer 2 for these comments, which we will take into account when developing a future protocol.

4. Page 7: statistical considerations
The design of Bryant and Day is mentioned. Please, could you add a reference? Also, the statistical methods for the estimation of local control and overall survival are not depicted, and when is the starting point (e.g. start of irradiation or inclusion in the trial?) of these end points?

The following reference has been added 'Bryant J, Day R. Incorporating toxicity considerations into the design of two-stage phase II clinical trials. Biometrics. 1995; 51(4):1372-83'.

Local control and overall survival are calculated from date of registration. The following sentence is amended on page 8. Percentage of patients who are deemed suitable to receive isotoxic IMRT, withdrawal rates, recruitment rates, incidence of toxicity, incidence of serious adverse events (SAEs), estimation of local control and estimation of overall survival (calculated from date of registration) will be reported.

5. For me it is not quite clear, if the PET/CT is mandatory (should be)? It could be stated that preferably a MR head should be performed.

Both points have been clarified on page 5. The following sentence has been added:
'Mandatory investigations prior to registration included: a Contrasted computerised tomography (CT) scan of the thorax and upper abdomen (within 4 weeks prior to registration), Contrast-enhanced CT (or magnetic resonance imaging) brain scan (within 4 weeks prior to registration if patients have not had imaging of the brain prior to starting induction chemotherapy), fluorodeoxyglucose positron emission tomography (FDG PET) CT within 4 weeks prior to registration if patients have not had a PET-CT prior to starting induction chemotherapy and lung function tests.'

Correction: *Protocol for the isotoxic intensity modulated radiotherapy (IMRT) in stage III non-small cell lung cancer (NSCLC): a feasibility study*

Haslett K, Franks K, Hanna GG, *et al*. Protocol for the isotoxic intensity modulated radiotherapy (IMRT) in stage III non-small cell lung cancer (NSCLC): a feasibility study. *BMJ Open* 2016;6:e010457. This paper was published under an incorrect license. The correct license is CC BY and the following statement should be applied:

BMJ Open 2016;**6**:e010457corr1. doi:10.1136/bmjopen-2015-010457corr1