

## 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

<b>TITLE (PROVISIONAL)</b>	Predictability of Recurrence using Immunohistochemistry to delineate Surgical Margins in mucosal Head and Neck Squamous Cell Carcinoma (PRISM - HNSCC): Study protocol for a prospective, observational and bilateral study in Australia and India
<b>AUTHORS</b>	Joseph, Sheela; Janakiraman, Rajinikanth; Chacko, Geeta; Jayaraj, Rama; Thomas, Mahiban; Thomas, Meera; Mukhopadhyay, Sramana

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Justin Bishop The Johns Hopkins University, USA
<b>REVIEW RETURNED</b>	08-Dec-2016

<b>GENERAL COMMENTS</b>	Nicely designed study. One thing that should be addressed is that the interpretation of p53 and IF4E is not always so straightforward, especially in the setting of normal-appearing mucosa. Strict interpretation criteria should be given, ideally accompanied by photomicrographs illustrating a positive and negative (and perhaps an equivocal) case.
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<b>REVIEWER</b>	Panagiota Economopoulou Attikon University Hospital Greece
<b>REVIEW RETURNED</b>	23-Apr-2017

<b>GENERAL COMMENTS</b>	Please correct grammar and mistakes Please clearly specify the number of patients that will participate in the study Please specify the inclusion criteria
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<b>REVIEWER</b>	Dr Omar Breik Oral and Maxillofacial Surgery Unit Royal Melbourne Hospital Melbourne, Victoria, Australia
<b>REVIEW RETURNED</b>	23-Jul-2017

<b>GENERAL COMMENTS</b>	This is a well designed project aiming to answer some important questions in relation to margin clearance in head and neck SCCs.
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	The use of VELoscope and lugol's iodine in the Vellore patients would be ideal, but not having this information available still makes for an interesting comparison of outcomes. I look forward to seeing the results of this study once recruitment and follow up is completed.
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## VERSION 1 – AUTHOR RESPONSE

### Reviewer 1 - Justin Bishop

Thanks for the comments on the design of the study. I agree interpretation of immunohistochemistry may not always be straight forward. Standardisation and interpretation particularly with e IF4E has been quite a challenge. After several attempts we have just managed to standardise the stain for e IF4E antibody. Since I live in Australia I work on the research project in India only during periodic visits. I am yet to complete the staining of the cases selected for Immunohistochemistry. Hence I will be grateful if the photomicrographs of the positive controls with a description of the interpretation is acceptable to you at this stage, particularly as this is a protocol paper. I hope to include photomicrographs of the margins and results in a subsequent paper describing the outcomes of the research. I will at that time discuss the interpretation of the immunostained sections in greater detail.

### Reviewer: 2 - Panagiota Economopoulou

Thank you for the comments. I noticed quite a few spelling and grammar mistakes. I have attempted to address that in the revised version of the manuscript. I have elaborated on the inclusion criteria as below:

- All patients at the Royal Darwin Hospital and Christian Medical College Vellore during the recruitment period with a confirmed diagnosis of mucosal head and neck squamous cell carcinoma on initial biopsy.
  - Wide local excision biopsy with mucosal surgical margins  $\geq 5\text{mm}$  on histopathological examination.
- Addition to exclusion criteria:
- Patients who undergo postoperative radiotherapy

I have given an approximate number of around 50 participants; 6-8 from Darwin and 40- 45 from Vellore.

### Reviewer: 3 Dr Omar Breik

Thank you for the comments. I hope to complete the project soon and look forward to disseminating some useful results that can be applied in the clinical setting.