

Manuscript Number: BJOMS-D-17-00417R2

Title: A Randomised Feasibility Study of Therabite versus Wooden Spatula
in the Amelioration of Trismus in Head and Neck Cancer Patients.

Article Type: Full Length Article

Keywords: Trismus; Head and Neck cancer; Randomised trial; Feasibility;
Health economics; Exercises

Corresponding Author: Ms. rana lee, M.Phil

Corresponding Author's Institution: Christie NHS Trust

First Author: rana lee, M.Phil

Order of Authors: rana lee, M.Phil; Seow Tien Yeo, MSc; Simon N Rogers,
MD; Ann-Louise Caress, PhD; Alex Molassiotis, PhD; Rhiannon Tudor-
Edwards, PhD; David Ryder, BSc; Paul Sanghera, MD; Colin Lunt, BSc; Barry
Scott, MPhil; Philip Keeley, PhD; Nick Slevin, MD

Manuscript Region of Origin: UNITED KINGDOM

Abstract: The main aim of this study was to assess the efficacy of
Therabite® compared to current standard treatment using wooden spatulas
in relieving or preventing trismus. Secondary aims were to assess the
feasibility and the impact of proactive exercise on health-related
quality of life and post-treatment clinical management/health care
utilisation.

Materials and Methods. Randomised, open-label, controlled, three-centre
feasibility study, to assess the effectiveness and cost-effectiveness of
Therabite use compared with wooden spatula in ameliorating trismus in
patients treated for stage 3 and 4 oral and oropharyngeal cancer treated
with radiotherapy. Compliance with exercises and health-related quality
of life were examined and 3 health economics measures were assessed.

Results. 37 patients were randomised to receive the Therabite device and
34 the wooden spatulas for jaw exercises. All patients had some sense of
jaw tightening prior to study entry. Mean mouth opening after 6months
increased in both groups following the exercise intervention, with non-
significant differences between the two arms ($p=0.39$). Completion rates
of the 3 health economic measures were good. There was no significant
difference between the two groups in frequency of contact with care
services nor in quality of life .

Conclusions. Proactive exercises during and after radiotherapy can
ameliorate trismus for stage 3 and 4 oral, oropharyngeal cancers ,but we
found no statistically significant difference between use of Therabite
and wooden spatulas (control) in efficacy, compliance, quality of life or
hospital/community health services utilisation.

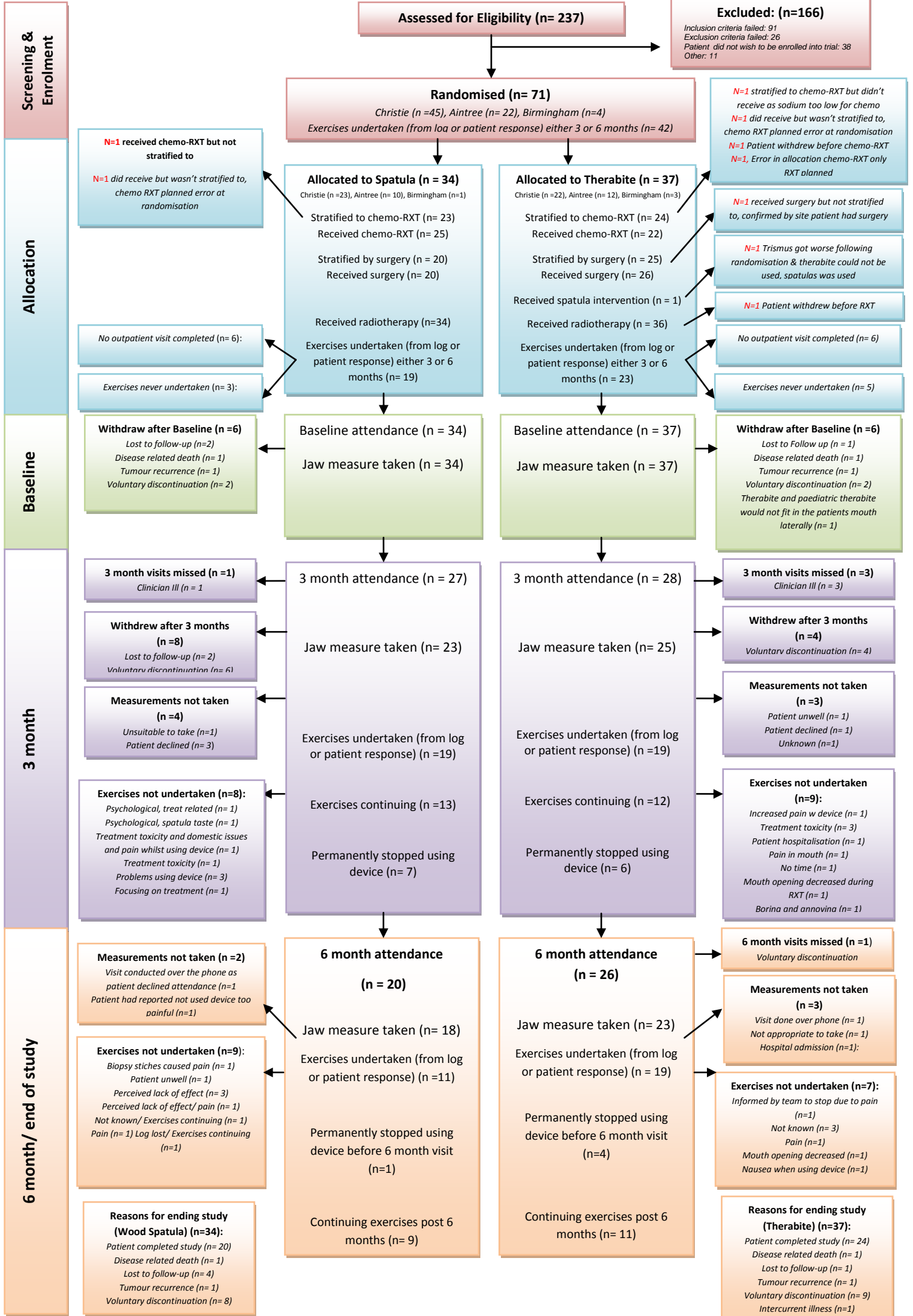
A Randomised Feasibility Study of Therabite versus Wooden Spatula in the Amelioration of Trismus in Head and Neck Cancer Patients.

Dear Editor,

Please find enclosed this article which we would be grateful for consideration of publication in BJOMS. We feel this to be the most appropriate journal as it is a cross disciplinary scientific medical journal which is read widely by the whole MDT. We feel this paper will be of interest to your readers as we have established that prophylactic exercises can ameliorate post radiotherapy trismus, that the trismus exercise regime needs to be flexible to improve compliance and that the use of health economics questionnaires are feasible in the context of further trials. We still don't know if there is any therapeutic advantage to using Therabite over wooden spatulas and would advocate a larger national trial to resolve this; the learning from this study would greatly facilitate successful recruitment and compliance in a larger trial.

We look forward to your comments.

Table 2





The British Journal of Oral & Maxillofacial Surgery
CONFIRMATION OF AUTHORSHIP

TITLE: *A randomised feasibility study of Therabite versus wooden spatula in the amelioration of Trismus in Head and Neck cancer patients.*
REFERENCE NO:

We, the undersigned, confirm that we are the joint authors of the above paper.

We confirm that all the authors have had material input into the submission.

We confirm that, to our knowledge, all the claims, statements and conclusions are true and are our jointly held opinions.

We confirm that we all accept the terms of publication of the publisher.

Signed:

Name: *NICK SUEVIN*

Signature: *Nick Suevin*

Name: *RANA LEE*

Signature: *R. Lee*

Name:

Signature:

Name:

Signature:

Name:

Signature:

Name:

Signature:

This form must be signed by all the authors of the above paper and the original scanned and emailed to the journal office (BJOMS@elsevier.com) or uploaded with the PDF of the manuscript.

If your paper is accepted, publication will not proceed until the fully completed form is received.



The British Journal of Oral & Maxillofacial Surgery
CONFIRMATION OF AUTHORSHIP

TITLE: *A randomised feasibility study of Therabite versus wooden spatulas in the amelioration of Trismus in Head and Neck patients*
REFERENCE NO:

We, the undersigned, confirm that we are the joint authors of the above paper.

We confirm that all the authors have had material input into the submission.

We confirm that, to our knowledge, all the claims, statements and conclusions are true and are our jointly held opinions.

We confirm that we all accept the terms of publication of the publisher.

Signed:

Name: *Prof S. Rogers*

Signature: *S. N. Rogers*

Name:

Signature:

Name:

Signature:

Name:

Signature:

Name:

Signature:

Name:

Signature:

This form must be signed by all the authors of the above paper and the original scanned and emailed to the journal office (BJOMS@elsevier.com) or uploaded with the PDF of the manuscript.

If your paper is accepted, publication will not proceed until the fully completed form is received.



The British Journal of Oral & Maxillofacial Surgery
CONFIRMATION OF AUTHORSHIP

TITLE: *A randomised feasibility study of Therabite versus wooden spatulas in the amelioration of Trismus in Head and Neck cancer patients.*
REFERENCE NO:

We, the undersigned, confirm that we are the joint authors of the above paper.

We confirm that all the authors have had material input into the submission.

We confirm that, to our knowledge, all the claims, statements and conclusions are true and are our jointly held opinions.

We confirm that we all accept the terms of publication of the publisher.

Signed:

Name: Signature:

Name: Signature:

Name: Signature:

Name: *Prof. Alex MOLASSIOTIS* Signature: *[Handwritten Signature]*

Name: Signature:

Name: Signature:

This form must be signed by all the authors of the above paper and the original scanned and emailed to the journal office (BJOMS@elsevier.com) or uploaded with the PDF of the manuscript.

If your paper is accepted, publication will not proceed until the fully completed form is received.



The British Journal of Oral & Maxillofacial Surgery
CONFIRMATION OF AUTHORSHIP

TITLE:..... A Randomised Feasibility Study of Theobite
vs Wooden Spatula in The Amelioration of Tissues
REFERENCE NO: Head+Neck Cancer Patients
Ref:

We, the undersigned, confirm that we are the joint authors of the above paper.

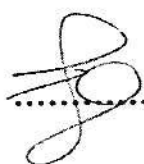
We confirm that all the authors have had material input into the submission.

We confirm that, to our knowledge, all the claims, statements and conclusions are true and are our jointly held opinions.

We confirm that we all accept the terms of publication of the publisher.

Signed:

Name: Ann-Louise CARESS

Signature: 

Name:

Signature:

Name:

Signature:

Name:

Signature:

Name:

Signature:

Name:

Signature:

This form must be signed by all the authors of the above paper and the original scanned and emailed to the journal office (BJOMS@elsevier.com) or uploaded with the PDF of the manuscript.

If your paper is accepted, publication will not proceed until the fully completed form is received.



The British Journal of Oral & Maxillofacial Surgery

CONFIRMATION OF AUTHORSHIP

TITLE: *A Randomised ^{Feasibility} Study of Therabite versus wooden spatula
in the Amelioration of Trismus in Head and Neck Cancer Patients*

REFERENCE NO:

We, the undersigned, confirm that we are the joint authors of the above paper.

We confirm that all the authors have had material input into the submission.

We confirm that, to our knowledge, all the claims, statements and conclusions are true and are our jointly held opinions.

We confirm that we all accept the terms of publication of the publisher.

Signed:

Name: *SEOW TIEN YEO* Signature: *[Signature]*

Name: *RHIANNON TUDOR EDWARDS* Signature: *[Signature]*

Name: Signature:

Name: Signature:

Name: Signature:

Name: Signature:

This form must be signed by all the authors of the above paper and the original scanned and emailed to the journal office (BJOMS@elsevier.com) or uploaded with the PDF of the manuscript.

If your paper is accepted, publication will not proceed until the fully completed form is received.



The British Journal of Oral & Maxillofacial Surgery
CONFIRMATION OF AUTHORSHIP

A RANDOMISED ~~BLIND~~ STUDY OF THERABITE VERSUS WIGGON
TITLE: SPATULAS IN THE AMELIORATION OF TRISMS IN HEAD AND NECK
CANCER PATIENTS.

REFERENCE NO: NCT01733797

We, the undersigned, confirm that we are the joint authors of the above paper.

We confirm that all the authors have had material input into the submission.

We confirm that, to our knowledge, all the claims, statements and conclusions are true and are our jointly held opinions.

We confirm that we all accept the terms of publication of the publisher.

Signed:

Name: BARRY SCOTT Signature: BSCOTT

Name: Signature:

Name: Signature:

Name: Signature:

Name: Signature:

Name: Signature:

This form must be signed by all the authors of the above paper and the original scanned and emailed to the journal office (BJOMS@elsevier.com) or uploaded with the PDF of the manuscript.

If your paper is accepted, publication will not proceed until the fully completed form is received.



The British Journal of Oral & Maxillofacial Surgery
CONFIRMATION OF AUTHORSHIP

TITLE: A randomised ^{Feasibility} ~~Study~~ Study of Therabite versus Warton's spatula in the amelioration of trismus in head and neck cancer patients
REFERENCE NO:

We, the undersigned, confirm that we are the joint authors of the above paper.

We confirm that all the authors have had material input into the submission.

We confirm that, to our knowledge, all the claims, statements and conclusions are true and are our jointly held opinions.

We confirm that we all accept the terms of publication of the publisher.

Signed:

Name: PHILIP KEENE Signature: P. Keene

Name: Signature:

Name: Signature:

Name: Signature:

Name: Signature:

Name: Signature:

This form must be signed by all the authors of the above paper and the original scanned and emailed to the journal office (BJOMS@elsevier.com) or uploaded with the PDF of the manuscript.

If your paper is accepted, publication will not proceed until the fully completed form is received.



The British Journal of Oral & Maxillofacial Surgery
CONFIRMATION OF AUTHORSHIP

TITLE: *A randomised feasibility study of Therabite versus wooden spatula in the amelioration of Trismus in Head and Neck Cancer Patients.*
REFERENCE NO:

We, the undersigned, confirm that we are the joint authors of the above paper.

We confirm that all the authors have had material input into the submission.

We confirm that, to our knowledge, all the claims, statements and conclusions are true and are our jointly held opinions.

We confirm that we all accept the terms of publication of the publisher.

Signed:

Name: *COLIN LUNT* Signature: *Colin Lunt*

Name: Signature:

Name: Signature:

Name: Signature:

Name: Signature:

Name: Signature:

This form must be signed by all the authors of the above paper and the original scanned and emailed to the journal office (BJOMS@elsevier.com) or uploaded with the PDF of the manuscript.

If your paper is accepted, publication will not proceed until the fully completed form is received.



The British Journal of Oral & Maxillofacial Surgery

CONFIRMATION OF AUTHORSHIP

TITLE: *Advanced Voxel Study of Throat*
we've been studying in the
REFERENCE NO: *Archives of Otolaryngology*
Neurology, 2013, 161, 1045

We, the undersigned, confirm that we are the joint authors of the above paper.

We confirm that all the authors have had material input into the submission.

We confirm that, to our knowledge, all the claims, statements and conclusions are true and are our jointly held opinions.

We confirm that we all accept the terms of publication of the publisher.

Signed: *[Signature]* Signature: *[Signature]*

Name: Signature:

Name: Signature:

Name: Signature:

Name: Signature:

Name: Signature:

Name: Signature:

This form must be signed by all the authors of the above paper and the original scanned and emailed to the journal office (BJOMS@edmgr.com) or uploaded with the PDF of the manuscript.

If your paper is accepted, publication will not proceed until the fully completed form is received.

BRITISH JOURNAL OF ORAL & MAXILLOFACIAL SURGERY
 Author contribution

Manuscript Title: A Randomised Feasibility Study of Therabite versus Wooden Spatula in the Amelioration of Trismus in Head and Neck Cancer Patients.

Please provide details in the table below of each author(s) contribution to the submitted manuscript

AUTHORS	Conception and design of study/review/case series	Acquisition of data: laboratory or clinical/literature search	Analysis and interpretation of data collected	Drafting of article and/or critical revision	Final approval and guarantor of manuscript
R. LEE	✓	✓	✓	✓	
N. SLEVIN	✓			✓	✓
S.N. ROGERS	✓			✓	
A.L. CARESS			✓	✓	
A. MOLASSIOTIS	✓			✓	
D. RYDER			✓	✓	
S. SANGHERRA				✓	

BRITISH JOURNAL OF ORAL & MAXILLOFACIAL SURGERY

Author contribution

Manuscript Title: A Randomised Feasibility Study of Therabite versus Wooden Spatula in the Amelioration of Trismus in Head and Neck Cancer Patients.

Please provide details in the table below of each author(s) contribution to the submitted manuscript

AUTHORS	Conception and design of study/review/case series	Acquisition of data: laboratory or clinical/literature search	Analysis and interpretation of data collected	Drafting of article and/or critical revision	Final approval and guarantor of manuscript
S. T. YEO		✓	✓	✓	
R. T. EDWARDS		✓	✓	✓	
C. LUNT		✓		✓	
B. SCOTT		✓		✓	
P. KEELEY			✓	✓	

Table 1: Baseline characteristics

	Wooden spatulas	Therabite
Centre		
Liverpool	10	12
Birmingham	1	3
Manchester	23	22
Surgery		
No	14	11
Yes	20	26
Chemoradiation		
No	9	14
Yes	25	23
Gender		
Male	24	25
Female	10	12
Alcohol use		
Current heavy	4	2
Previous heavy	8	16
Never heavy	22	19
Smoking status		
Current smoker	4	4
Ex smoker	17	25
Never smoked	13	8
Site of disease		
Oral	11	15
Oropharyngeal	23	22
Stage		
T1/2 N+ M0	14	16
T3/4 N0 M0	5	4
T3/4 N+ M0	15	17

Table 3: Frequency of contacts with primary and secondary care health services use by 30 participants in the Trismus feasibility trial at 6 month post-baseline

	Therabite (n = 16) Total; Mean, median (min, max)	Wooden spatulas (n = 14) Total; Mean, median (min, max)	Mann Whitney p-value¹
<i>NHS Primary Care Sector:</i>			
Cancer nurse	10; 0.63, 0 (0, 4)	6; 0.43, 0 (0, 6)	0.313
General practitioner	51; 3.19, 2 (0, 13)	32; 2.29, 2 (0, 5)	0.697
Practice nurse	25; 1.56, 0 (0, 14)	7; 0.50, 0 (0, 3)	0.637
Community nurse	128; 8.00, 1 (0, 56)	47; 3.36, 1 (0, 22)	0.667
Physiotherapist	2; 0.13, 0 (0, 2)	18; 1.29, 0 (0, 9)	0.294
Speech and language therapist	43; 2.69, 2 (0, 14)	36; 2.57, 2 (0, 9)	1.000
Occupational health therapist	0; 0.00, 0 (0, 0)	0; 0.00, 0 (0, 0)	1.000
Dietician	41; 2.56, 1 (0, 16)	51; 3.64, 2 (0, 11)	0.637
Other healthcare professional	81; 5.06, 1 (0, 52)	28; 2.00, 1 (0, 10)	0.667
<i>NHS Secondary Care Sector:</i>			
Oncology inpatient ward (bed days)	256; 16.06, 9 (0, 78)	217; 15.50, 6 (0, 74)	0.790
Medical inpatient ward (bed days)	31; 1.94, 0 (0, 14)	51; 3.64, 0 (0, 30)	0.854
Intensive care inpatient ward (bed days)	0; 0.00, 0 (0, 0)	0; 0.00, 0 (0, 0)	1.000
Other inpatient ward (bed days)	6; 0.38, 0 (0, 6)	0; 0.00, 0 (0, 0)	0.790
Physiotherapist inpatient consultation	62; 3.88, 0 (0, 55)	3; 0.21, 0 (0, 2)	1.000
Speech and language therapist inpatient	4; 0.25, 0 (0, 2)	4; 0.29, 0 (0, 2)	0.918

consultation			
Dietician inpatient consultation	56; 3.50, 1 (0, 25)	38; 2.71, 1 (0, 20)	0.822
Occupational health therapist inpatient consultation	2; 0.13, 0 (0, 2)	0; 0.00, 0 (0, 0)	0.790
Other inpatient consultation	3; 0.19, 0 (0, 2)	0; 0.00, 0 (0, 0)	0.580
Outpatient visits	76; 4.75, 1 (0, 30)	74; 5.29, 1 (0, 58)	1.000
Accident and emergency	1; 0.06, 0 (0, 1)	18; 1.29, 0 (0, 12)	0.154

¹ = significant at 5% significance level

Table 4: Mean costs of all contacts with NHS primary and secondary care services use by 30 participants in the Trismus trial (£) over the six-month follow-up period

	Therabite (n=16)	Wooden spatulas	Mean difference in £
	Mean (SD) in £	(n=14)	(95% CI bootstrapped)
		Mean (SD) in £	
NHS Primary Care			
Cancer nurse	60.47 (139.12)	38.57 (144.32)	21.90
General practitioner	188.91 (210.35)	190.82 (194.58)	-1.91
Practice nurse	18.22 (34.96)	11.99 (26.24)	6.23
Community nurse	307.66 (704.63)	113.14 (223.99)	194.52
Physiotherapist	4.50 (18.00)	27.85 (56.46)	-23.35
Speech and language therapist	45.56 (47.64)	46.93 (48.14)	-1.37
Occupational health therapist	0.00 (0.00)	0.00 (0.00)	0.00
Dietician	37.77 (49.38)	95.58 (122.89)	-57.81
Other healthcare professional	172.48 (316.27)	135.57 (246.80)	36.91
Total NHS primary care costs	835.56	660.46	175.10
	(974.13)	(637.13)	(-358.51 to 759.77)
NHS Secondary Care			
Oncology inpatient ward	9678.00 (12783.29)	9001.93 (12641.66)	676.07
Medical inpatient ward	1110.19 (2532.19)	2087.36 (4797.26)	-977.17
Intensive care inpatient ward	0.00 (0.00)	0.00 (0.00)	0.00
Other inpatient ward	120.75 (483.00)	0.00 (0.00)	120.75
Physiotherapist inpatient consultation	164.00 (579.91)	10.43 (27.76)	153.57
Speech and language therapist inpatient consultation	24.13 (54.54)	27.57 (57.71)	-3.44
Dietician inpatient consultation	216.19 (388.57)	169.14 (316.15)	47.05
Occupational health therapist inpatient consultation	8.50 (34.00)	0.00 (0.00)	8.50
Other inpatient consultation	16.94 (48.06)	0.00 (0.00)	16.94
Outpatient visits	513.56 (1000.97)	466.29 (1205.24)	47.27

Accident and emergency	6.56 (26.23)	134.88 (332.85)	-128.32
Total NHS secondary care costs	11858.81 (14055.02)	11897.60 (13421.63)	-38.79 (-9463.46 to 9446.84)
Total NHS primary and secondary care costs	12694.37 (14136.93)	12558.06 (13675.36)	136.31 (-9419.24 to 9791.03)
Intervention cost (Intervention – ‘Therabite’ and Control – ‘Wooden spatula’)	251.94 (0.00)	2.84 (0.00)	249.10
Total cost	12946.31 (14136.93)	12560.90 (13675.36)	385.41 (-8916.37 to 10013.82)

NHS: National Health Service

Table 5 : Mean EQ-5D-3L index scores, mean QALYs and incremental mean QALYs at 6 months post-baseline by group (n=30)

Measure	Therabite (n = 16)				Wooden spatulas (n = 14)				Incremental mean QALYs between groups [®] (bootstrapped 95% CI)
	Mean (SD)				Mean (SD)				
	Baseline	3 months	6 months	QALY over 6 months	Baseline	3 months	6 months	QALY over 6 months	
EQ-5D-3L index	0.6914 (0.1863)	0.6209 (0.2806)	0.6935 (0.2523)	0.3283 (0.1082)	0.6232 (0.3599)	0.6824 (0.2999)	0.7481 (0.1844)	0.3420 (0.1330)	-0.0137 (-0.0978 to 0.0706)

[®] Incremental mean QALYs between groups=mean QALYs for intervention group minus mean QALYs for control group

Table 6: Mean ICECAP-A capability index scores, change in mean ICECAP-A index score between study time points and difference in mean change scores between groups at 6 months post-baseline by group (n=19<30)[∞]

Measure	Therabite (n = 8) [∞]				Wooden spatulas (n = 11) [∞]				Difference in mean change scores between groups [‡] (bootstrapped 95% CI)
	Baseline	3 months	6 months	Change in mean ICECAP-A index score between baseline and 6 months	Baseline	3 months	6 months	Change in mean ICECAP-A index score between baseline and 6 months	
ICECAP-A capability index scores	0.8733 (0.1092)	0.8095 (0.1967)	0.8551 (0.1209)	-0.0182 (0.0873)	0.8914 (0.1524)	0.9175 (0.0927)	0.9079 (0.1506)	0.0165 (0.2029)	-0.0347 (-0.1726 to 0.0828)

[‡] Difference in mean change scores between groups = (Mean change score for intervention) minus (Mean change score for control)

[∞] ICECAP-A analysis was conducted on 19 out of 30 participants who had complete ICECAP-A data (n=8 Therabite group, n=11 wooden spatulas group).

R. Lee¹, S.T. Yeo⁵, S.N. Rogers², A.L. Caress³, A. Molassiotis^{3,4}, D. Ryder¹, P. Sanghera⁶, C. Lunt¹, B. Scott⁷, P. Keeley⁸, R.T.Edwards⁵, N. Slevin⁹. 

¹The Christie, Research and Development, Manchester, United Kingdom.

²University Hospital Aintree, Maxillofacial Unit Directorate, Liverpool, United Kingdom.

³University of Manchester, School of Nursing and Midwifery, Manchester, United Kingdom.

⁴The Hong Kong Polytechnic University, School of Nursing, Hong Kong, China.


⁵Bangor University, Centre for Health Economics and Medicines Evaluation (CHEME), School of Healthcare Sciences, Bangor, United Kingdom.

⁶University of Birmingham, Clinical Oncology, Birmingham, United Kingdom

⁷University Hospital Aintree, Clinical Lead Therapist, Liverpool, United Kingdom

⁸The University of Huddersfield, Department of Health Sciences, Huddersfield, United Kingdom

⁹The Christie, Clinical Oncology, Manchester, United Kingdom.

 Corresponding author. Address: Department of Oncology, The Christie NHS Foundation Trust. Wilmslow Road, Manchester M20 4BX. Telephone 0161 4463000.

E-mail address; nick.slevin@christie.nhs.uk (N.Slevin).

[“The Christie NHS Foundation Trust Hospital acknowledges the support of the National Institute of Health Research Clinical Research Network \(NIHR CRN: Trismus RfPB trial \(portfolio ID 13415\)\)”](#)

Trial registration with clinicaltrials.gov NCT01733797

Acknowledgements

We would like to thank the dedicated clinical, research and allied health professional teams in helping running of this study. Special thanks for all patients for their participation help and time in assisting with this study.

Ethics statement/confirmation of patients permission

The study was approved by the North Manchester Ethics committee (12/NW/0414) and all patients gave written informed consent prior to study commencement.



The British Journal of Oral & Maxillofacial Surgery
CONFIRMATION OF AUTHORSHIP

TITLE: *A randomized feasibility study of Therabite versus wooden Spatula in the amelioration of Trismus in Head & Neck Cancer patients*

REFERENCE NO: *BJOMS - D - 17 - 00417R1*

We, the undersigned, confirm that we are the joint authors of the above paper.

We confirm that all the authors have had material input into the submission.

We confirm that, to our knowledge, all the claims, statements and conclusions are true and are our jointly held opinions.

We confirm that we all accept the terms of publication of the publisher.

Signed:

Name: *David Ryder*

Signature: *D. Ryder*

Name:

Signature:

Name:

Signature:

Name:

Signature:

Name:

Signature:

Name:

Signature:

This form must be signed by all the authors of the above paper and the original scanned and emailed to the journal office (BJOMS@elsevier.com) or uploaded with the PDF of the manuscript.

Original signatures and required and photocopies are not acceptable. If your paper is accepted, publication will not proceed until the fully completed form is received.

A Randomised Feasibility Study of Therabite versus Wooden Spatula in the Amelioration of Trismus in Head and Neck Cancer Patients.

Dear Editor, please find enclosed actioned, reviewers comments including stats comments.

Reviewer 1

Actions:

Maximum mouth opening measurements

Six month mouth opening measurements were supplied by 41/71 participants. These tentatively indicate that mouth opening in both groups had not deteriorated following the exercise intervention. There was no statistically significant difference between the two interventions though the power of the study was low due to failing to achieve the target recruitment and a higher than anticipated attrition rate. The estimated difference in average 6 month mouth opening (**Wooden spatula versus Therabite**) after adjustment for baseline, centre, surgery and chemoradiation in an analysis of covariance model was **2.43mm** with 95% CI (-8.15 to 3.29). This is not a statistically significant difference (p=0.39).

Exercise compliance rates were poor particularly at the end of radiotherapy but not markedly different between the two trial arms; this data was obtained from the patients logs.

Reviewer 2

Actions:

Limitations of the study:

Pre- radiotherapy patients who indicated subjective tightening of the jaw were included in the study, omitting those patients who, during radiotherapy may have developed tightening of the jaw. This could be captured by a more adaptive study design such as a stepped wedge design whereby patients are randomised as soon as jaw tightening develops.

A larger group of patients and more study specific follow up may also have provided greater representative data on both the quantitative and qualitative aspects of the study. A larger telephone interview pool of patients may also have provided richer insight to day to day living with trismus. Patients' suggestions of rewording the exercise regime to 'up to 5 times a day', when exercises were more likely to be performed 3 times a day have not been validated to test for frequency effects. The dose-effect analysis of a new therapy protocol would be required in future studies.

The attrition rate for this study was set at 25% which is in agreement with other head and neck cancer toxicity intervention studies, but was higher in this study than expected. The likely explanations include the demands of the prescribed exercise regimen as well as the difficulty in compliance in the presence of severe mucositis.

It would be useful to employ a more sensitive scale to measure trismus-specific symptoms, such as the Gothenburg Trismus Questionnaire (which was not available at the start of our trial), for a full scale trial as it can be used to track changes in trismus specific symptoms [25].

All stats comments have been actioned and shown in red on the submitted manuscript.

A Randomised Feasibility Study of Therabite versus Wooden Spatula in the Amelioration of Trismus in Head and Neck Cancer Patients

Abstract

The main aim of this study was to assess the efficacy of Therabite® compared to current standard treatment using wooden spatulas in relieving or preventing trismus. Secondary aims were to assess the feasibility and the impact of proactive exercise on health-related quality of life and post-treatment clinical management/health care utilisation.

Materials and Methods. Randomised, open-label, controlled, three-centre feasibility study, to assess the effectiveness and cost-effectiveness of Therabite use compared with wooden spatula in ameliorating trismus in patients treated for stage 3 and 4 oral and oropharyngeal cancer treated with radiotherapy. Compliance with exercises and health-related quality of life were examined and 3 health economics measures were assessed. Semi-structured patient interviews were also conducted.

Results. 37 patients were randomised to receive the Therabite device and 34 the wooden spatulas for jaw exercises. All patients had some sense of jaw tightening prior to study entry. Mean mouth opening after 6 months increased in both groups following the exercise intervention, with non-significant differences between the two arms ($p=0.39$). Completion rates of the 3 health economic measures were good. There was no significant difference between the two groups in frequency of contact with care services nor in quality of life.

Conclusions. Proactive exercises during and after radiotherapy can ameliorate trismus for stage 3 and 4 oral, oropharyngeal cancers, but we found no statistically significant difference between use of Therabite and wooden spatulas (control) in efficacy, compliance, quality of life or hospital/community health services utilisation.

Keywords: Trismus; Head and Neck cancer; Randomised trial; Feasibility; Health economics; Exercises

Introduction

Around 7,600 patients were diagnosed with lip, oral cavity and oropharynx cancer in the UK in 2013 (CRUK 2013). Standard treatments for these patients involve a variable combination of surgery, radiotherapy and chemotherapy. Patients can develop trismus, a condition affecting the jaw muscles and making mouth opening difficult, from their disease or treatment. Trismus is underreported as a significant deleterious impact from treatment [1] with radiotherapy being reported as one of the most frequent causes of this condition. Dijkstra's (2006) definition of trismus as a maximum mouth opening of 35mm or less is now widely accepted [2]. Trismus can impair chewing, swallowing, speaking, oral health, dental integrity and overall quality of life [3,4,5,6]. Psychological difficulties can include low self-esteem, depression and suicidal tendencies [7].

Previously published work by Van der Molen and Carnaby-Mann in the area of proactive jaw exercises for head and neck patients receiving chemoradiotherapy have shown less of a decline in mouth opening compared to standard post treatment rehabilitation techniques; however both studies had small numbers, only 10 week follow up and no economic evaluations [8, 9]. Current standard post- treatment interventions such as wooden spatulas, Therabite, Dynasplint and swallowing therapies have only shown a modest effect once trismus is established [10,11,12,13,14]. A recent systematic review alternatively suggested that jaw exercise therapy can have a positive impact on mouth opening in established radiotherapy-induced trismus [12]. In view of these conflicting opinions, there is consensus on the need for a rigorous, controlled study to provide clearer evidence regarding the value

of proactive exercise devices in patients with pre-radiotherapy trismus or at high risk of developing radiotherapy-induced trismus [10].

This was a feasibility study to establish whether there is an indication of benefit to proactive exercises and to inform the design of a future larger study, in line with the MRC Framework for complex interventions [15].

The main aim was to assess the efficacy of Therabite® as compared with current standard treatment using wooden spatulas in relieving or preventing trismus.

Secondary aims were to assess the feasibility and the impact of proactive exercise on health-related quality of life, post-treatment clinical management and healthcare resource use along with completion rates of the health economic outcome measures (CSRI, EQ-5D-3L and ICECAP-A).

Materials and Methods

This was a randomised, open-label controlled, three-centre feasibility study comparing Therabite with wooden spatulas in ameliorating trismus in patients treated for stage 3 and 4 oral and oropharyngeal cancer. The study was approved by the [REDACTED] Ethics committee [REDACTED] and all patients gave written informed consent prior to study commencement.

Patients & Settings

Patients with stage 3 and 4 oral and oropharyngeal cancer managed either by primary (chemo)radiotherapy or surgery followed by (chemo)radiotherapy were recruited from three

tertiary referral centres in England. Patients who self reported a sense of jaw tightening prior to radiotherapy were offered study entry. All patients were prescribed a dose of 60-70 Gy in 30-35 fractions over 6 to 7 weeks using IMRT to the region of the jaw muscles.

To detect a minimum of 5mm **difference in mean** change from the baseline mouth opening level, with a common standard deviation **of 8mm (previously estimated from patients that have had no intervention and have had radiotherapy)** with 80% power required 42 cases per group. With a predicted 25% attrition rate, 112 patients were required in total.

Randomisation was performed using the minimisation method **with a random element (allocation was with probability 0.75 to the arm yielding a lower imbalance score or 0.5 if scores were tied) . Factors controlled for were:** surgery or no surgery, centre and synchronous chemotherapy given or not given.

After patients had been randomly assigned to receive wooden spatulas or Therabite they were instructed to perform their mouth exercises according to a set protocol.

Patients were excluded if mouth opening was <12mm (cannot fit Therabite), were anatomically unable to use Therabite due to being partially dentate and patients who had a past history of previous surgery or radiotherapy to the head and neck.

Therabite/Wooden Spatula Protocol and measurement of Mouth Opening.

Patients randomised to either wooden spatula or Therabite use were asked to follow the 5-5-30 protocol which comprised 5 sessions per day for 6 months, with 5 opening/closing per session, each opening for a 30 second stretch [16, 17]. Patients commenced Therabite or

spatula use approximately 3 weeks post surgery and /or 1-3 weeks pre radiotherapy. Patients recorded the maximum mouth opening at the end of each day using a Platon Therabite motion scale and documented the readings on a log, to capture compliance to exercises. Additional readings from the bottom of the nose to the chin with the mouth closed and open were also taken using a Willis bite calliper at baseline and again at 3 and 6 months post intervention.

Demographic Information

Baseline patient, tumour and treatment characteristics are documented in Table 1.

Quality of Life.

Quality of Life (QoL) assessments were performed at baseline, 3 and 6 months post intervention. QoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C 30) and Head and Neck (H&N) module (EORTC QLQ H&N 35) [18]. Data was collected using QoLproforma sheets.

Health Economics Assessments:

The following assessments were used:

EQ-5D-3L (**European Quality of Life-5 Dimensions-3 Levels**) (baseline, 3, 6 months) - This is a validated generic, health-related, preference-based measure [19], comprising five domains: mobility; self-care; usual activities; pain and discomfort; anxiety and depression.

Each domains has three levels: no problem, some problems and major problems, thus giving a total of 243 possible health states [20] . The reported health-related quality of life states were converted into EQ-5D-3L index a single utility scores anchored at 0 for death and 1 for

perfect health. Negative score is also possible when patient values their health worse than death [21,20]. The EQ-5D-3L index scores were then translated into quality-adjusted life years (QALYs) by weighting them with quantity of life (the aggregated number of years lived), using the area-under-the-curve method [22, 23]. QALYs a common unit of effect is a measure of utility, which has been advocated by the National Institute for Health and Care Excellence (NICE) in the UK for the evaluation of cost-effectiveness [24].

ICECAP-A (ICEpop CAPability measure for Adults) (baseline, 3, 6 months) This is a more encompassing quality of life measure [25]. There are 5 domains: attachment, security, role, enjoyment and independence.

CSRI - A Client Service Receipt Inventory [26]. Patients' contacts with primary and secondary care services were collected retrospectively at 3 and 6 months by interview. This included their contacts with services such as speech and language therapy, dietary and nutritional advice and/or artificial feeding and orthodontic interventions including surgery.

Nested qualitative study

Semi-structured telephone interviews were conducted up to 6 months post study completion to explore the experience of the patient taking part in the study and their experience of daily living with trismus. Items discussed included compliance with the protocol and whether pain had affected their compliance with the intervention so as to consider such variables in a future phase III trial. Data was transcribed verbatim; data analysis was conducted using the framework analysis reported by Richie and Spencer [27].

Data analysis

Analysis was undertaken using Stata (version 13) SPSS (version 16). The null hypothesis for the primary analysis was that there is no difference in the amount of mouth opening at six months between the two arms of the trial.

Descriptive statistics were used to identify prevalence of trismus between the two groups and their respective mouth openings. Similarly descriptive statistics were used to calculate the number of patients completing different parts of the study and the amount of missing data.

The original power calculation was based on a t-test of change scores but a more efficient analysis method is analysis of covariance (ANCOVA). An ANCOVA model was fitted with the six month mouth opening measurement as the response and the trial arm as the variable of primary interest after adjustment for baseline, centre, surgery and chemo-radiation.

Economic analysis was undertaken using Microsoft Excel 2013 and SPSS (IBM SPSS Statistics 22). Confidence intervals (CIs) for costs and health-related quality of life were estimated using non-parametric bootstrapping methods [28, 29]. A simulation of 5000 non-parametric bootstrapping iterations were run to construct 95% CIs around estimates of costs and quality of life scores using Microsoft Excel 2013.

Results

Seventy one of 237 patients screened in three UK centres were randomised to the study.

Main reasons for screening failure included no subjective tightening of the jaw or declined participation.

Thirty-seven patients were allocated to the Therabite intervention and 34 received Wooden spatulas (Table 2 CONSORT diagram). Median baseline maximum mouth opening readings were 24.0mm (range 12.0-58.0), for the Therabite group and 21.8mm (range 12.5–48.0) for the wooden spatula group. Recorded baseline characteristics (age, gender, prior surgery, (chemo)radiation, disease site, disease stage, alcohol use and smoking status) were broadly similar between the two intervention groups. This was made possible by using the priori stratification factors to minimise differences at baseline (Table 1 Baseline Characteristics).

Maximum mouth opening measurements

Six month mouth opening measurements were supplied by 41/71 participants. These tentatively indicate that mouth opening in both groups had not deteriorated following the exercise intervention. There was no statistically significant difference between the two interventions though the power of the study was low due to failing to achieve the target recruitment and a higher than anticipated attrition rate. The estimated difference in average 6 month mouth opening (**Therabite versus Wooden spatula**) after adjustment for baseline, centre, surgery and chemoradiation in an analysis of covariance model was **-2.43 mm** with 95% CI (-8.15 to 3.29). This is not a statistically significant difference ($t_{35} = -0.86$, 2-tail $p = 0.39$). **There was no formal evidence against two key assumptions of the fitted model: Normality of the residuals (Shapiro-Wilk W test, $Z = 0.6$, 1-tail $p = 0.27$) and homogeneity of the variance (Cook-Weisberg test for heteroskedasticity, $X_5^2 = 7.90$, 1-tail $p = 0.16$)**

Exercise compliance rates were poor particularly at the end of radiotherapy but not markedly different between the two trial arms; this data was obtained from the patients logs.

Health related quality of life

Subscales (taken from the EORTC QLC-C30) around 'eating', 'weight loss', 'pain', and 'mouth opening' were predicted to be more sensitive to changes than others in trismus patients. However, there was no marked difference in the observed mean change scores from baseline to 6 months between the wooden spatula and Therabite groups for any of these items.

Telephone interviews: The consequences and possible effects of the exercises on pain and compliance with the exercise protocol were explored as well as the nature, acceptability and impact of the exercises in terms of motivation and perceived gain in maximum mouth opening. From the 15 telephone interview participants there was a mix of compliant and non-compliant participants at both 3 and 6 month follow up periods. The trend seemed to be greater compliance in the Therabite group at both 3 and 6 months. Patients felt they had to stop or reduce exercises towards the end of the course of radiotherapy until approximately 4 weeks post radiotherapy due to painful mucositis. Exercises were then restarted when side effects had abated.

Key feasibility and acceptability messages were: change the wording of the exercise regimen to at 'least 3 times a day' rather than 5 times a day; have a scheduled break from the exercises when radiotherapy side effects are at their worst; more regular contact with healthcare professionals is needed.

Health Economics Assessments:

Completion rates of the three health economics measures (CSRI, EQ-5D-3L and ICECAP-A) were evaluated: CSRI had completion rates of 89% and 100% at 3 and 6 months respectively; EQ-5D-3L had 90% at baseline, 78% at 3 months and 87% at 6 months; ICECAP-A had 59%, 49% and 74% at baseline, 3 and 6 months respectively. Across the study time-points,

completion rates for CSRI, EQ-5D-3L and ICECAP-A were overall, on average, 95%, 85% and 61% respectively.

In addition, although not a core feasibility objective, an exploratory cost consequences analysis was conducted on the participants that had complete cost and outcome data (n=30). The exploratory cost consequences analysis was undertaken from an NHS perspective, the results are presented in Table 3, 4, 5 and 6.

Table 3 shows frequency of contacts with primary and secondary care health services at 6 month post-baseline. Results show that there is no significant difference between the two groups in the frequency of contacts with primary and secondary care services.

Table 4 shows mean costs of all contacts with NHS primary and secondary care services use by participants in the Therabite and wooden spatulas groups over the six-month follow-up period. The Therabite intervention cost £251.94 per patient as compared with £2.84 for patients receiving wooden spatulas. Taking account of the cost of Therabite intervention and wooden spatulas, the mean total cost per patient was £12,946 (SD £14,137) in the Therabite group and £12,561 (SD £13,675) in the wooden spatulas group. This shows that the Therabite group costs £385 (bootstrapped 95% CI: -£8,916 to £10,014) higher than the wooden spatulas group.

Table 5 shows mean EQ-5D-3L index scores, mean **quality-adjusted life years** (QALYs) and incremental mean QALYs between Therabite and wooden spatulas groups over the six-month follow-up period. The mean QALY was 0.3283 (SD 0.1082) for the Therabite intervention group and 0.3420 (SD 0.1330) for the wooden spatulas group.

Change in mean ICECAP-A index score between study time-points and the difference in mean change ICECAP-A index scores between groups over the 6-month study period were assessed on the 19 out of the 30 participants who had complete ICECAP-A data. Table 6 shows the change in mean ICECAP-A index score between baseline and 6 months for the Therabite group was -0.0182 (SD 0.0873) and for the wooden spatulas group was 0.0165 (SD 0.2029). This yielded a difference of -0.0347 (bootstrapped 95% CI: -0.1726 to 0.0828) between groups.

Discussion

A recent systematic review has shown that post treatment exercise therapy with jaw mobilizing devices yields better results than no exercise, in radiotherapy induced trismus in head and neck cancer patients [12]. Our study has shown that proactive exercises with Therabite or wooden spatulas, prior, during and after radiotherapy treatment can ameliorate radiation induced trismus in head and neck cancer patients. Melchers and colleagues have described a positive increase in mouth opening with increased exercise adherence. This group also found that self-discipline and clear setting of objectives are important factors for maintaining exercises. The main factor which negatively affected exercise adherence was painful mucositis, as in this study. Other factors such as anxiety, ill fitting Therabite pads and the lack of goal setting during treatment also had a negative effect [30]. Tang *et al.*, also showed that rehabilitation training can slow down the progress of trismus in nasopharyngeal carcinoma patients after radiotherapy [31]. Several studies which performed exercises after radiotherapy have shown that Therabite exercises were no more effective than wooden spatulas or active range of motion exercises [32, 33]. Pauli *et al* have reported that Therabite exercises were more effective in increasing mouth opening compared to Engstrom (a wooden

clothespin with an attached rubber band), although compliance to exercise was comparable [34]. An earlier study by Buchbinder showed the Therabite to be more efficient than unassisted stretching or stretching using wooden spatulas although this study had small numbers of patients [35].

Limitations of the study:

Pre- radiotherapy patients who indicated subjective tightening of the jaw were included in the study, omitting those patients who, during radiotherapy may have developed tightening of the jaw. This could be captured by a more adaptive study design such as a stepped wedge design whereby patients are randomised as soon as jaw tightening develops.

A larger group of patients and more study specific follow up may also have provided greater representative data on both the quantitative and qualitative aspects of the study. A larger telephone interview pool of patients may also have provided richer insight to day to day living with trismus. Patients' suggestions of rewording the exercise regime to 'up to 5 times a day', when exercises were more likely to be performed 3 times a day have not been validated to test for frequency effects. The dose-effect analysis of a new therapy protocol would be required in future studies.

The attrition rate for this study was set at 25% which is in agreement with other head and neck cancer toxicity intervention studies, but was higher in this study than expected. The likely explanations include the demands of the prescribed exercise regimen as well as the difficulty in compliance in the presence of severe mucositis.

It would be useful to employ a more sensitive scale to measure trismus-specific symptoms, such as the Gothenburg Trismus Questionnaire (which was not available at the start of our trial), for a full scale trial as it can be used to track changes in trismus specific symptoms [36].

This is the first study of its kind to provide both an exercise regimen proactively, pre radiotherapy and to include a health economics aspect within the study design to enable healthcare professionals to make evidence-based decisions about patient management and resource use. The overall response rates for all the three health economics measures were good. In line with a study by Clarke and colleagues, our findings have shown that it is feasible to collect health economics information in a definitive randomised trial in this population group [37].

Conclusions

This feasibility study has shown that mouth openings had in fact increased on average in both groups following the exercise intervention. Proactive exercises during and after radiotherapy treatment can ameliorate trismus for stage 3 and 4 oral and oropharyngeal cancers.

Conflict of Interest

None

Ethics statement/confirmation of patients permission

The study was approved by the Ethics committee and all patients gave written informed consent prior to study commencement.

References

[1] Lee R, Slevin N, Musgrove B, Swindell R, Molassiotis A. Prediction of post-treatment trismus in head and neck cancer patients. *B J. Oral Maxillofac. Surg* 2012; **50**(4):328–32.

- [2] Dijkstra, PU, Huisman, PM, Roodenburg, JLN. Criteria for trismus in head and neck oncology. *Int. J. Oral Maxillofac. Surg.* 2006;35: 337-342.
- [3] Weber C, Dommerich S, Pau H.W, Kramp B. (2010). Limited mouth opening after primary therapy of head and neck cancer. *Oral Maxillofac Surg.*14(3):169-73.
- [4] Scott, B., Butterworth, C., Lowe, D. and Rogers, S.N. (2008) Factors associated with restricted mouth opening and its relationship to health-related quality of life in patients attending a maxillofacial oncology clinic. *Oral Oncol* 2008; 44, 430-438
- [5] Kent L, Brennan MT, Noll JL, Fox PC, Burri SH, Hunter JC, et al. (2008). Radiation-induced trismus in head and neck cancer patients. *Support Care Cancer* **16**(3): 305–9.
- [6]. Scott B, D'Souza J, Perinparajah N, Lowe D, Rogers SN. Longitudinal evaluation of restricted mouth opening (trismus) in patients following primary surgery for oral and oropharyngeal squamous cell carcinoma. *B J. Oral Maxillofac. Surg* ; 2011;**49**(2):106–11.
- [7] Zeller JL. High suicide risk found for patients with head and neck cancer. *JAMA* 2006; 296:1716-1717.
- [8] van der Molen L, van Rossum MA, Burkhead LM, Smeele, LE, Rasch CR, Hilgers FJ. A randomized preventive rehabilitation trial in advanced head and neck cancer patients treated with chemoradiotherapy: feasibility, compliance, and short-term effects. *Dysphagia* 2011;**26**(2):155–70.
- [9] Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. "Pharyngocise": randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. *Int J Radiat Oncol Biol Phys.* 2012 1;83(1):210-9.

- [10] Carvalho APV, McNeely ML, Vital FMR. Interventions for preventing and treating trismus in patients with head and neck cancer. *Cochrane Database of Systematic Reviews* 2016, Issue 8. Art. No.: CD012316. DOI: 10.1002/14651858.CD012316
- [11] Rapidis A.D, Dijkstra P.U, Roodenburg J.L.N., Rodrigo J.P., Rinaldo A., Strojan P, Takes R.P., Ferlito A. Trismus in patients with head and neck cancer: etiopathogenesis, diagnosis and management. *Clinical Otolaryngology* 2015;40, (6),516-526.
- [12] Scherpenhuizen A , van Waes A, Janssen L, Van Cann E , Stegeman E. The Effect of Exercise Therapy in Head and Neck Cancer Patients in the Treatment of Radiotherapy-Induced Trismus: A Systematic Review. *Oral Oncol* 2015; 51 (8), 745-750.
- [13] Looorents V, Rosell J, Karlsson C, Lidback M, Hultman K, Borjeson S. Prophylactic training for the prevention of radiotherapy-induced trismus- a randomised study. *Acta Oncol* 2014; 53:530-538.
- [14] Kamstra JI, Roodenburg JL, Beurskens CH, Reintsema H, Dijkstra PU TheraBite exercises to treat trismus secondary to head and neck cancer. *Support Care Cancer*. 2013; 21:951–957
- [15] (<https://www.mrc.ac.uk/documents/pdf/complex-interventions-guidance/>).
- [16] Atos Medical AB (2009) Therabite® jaw motion rehabilitation system [online]. Atos Medical AB, [accessed on 24th Jan 2017]. Available from the World Wide Web: http://www.atosmedical.com/Corporate/Focus_areas/~media/Files/Mouth_Jaw/Catalog
- [17] Bandy WD, Irion JM. The effect of time on static stretch on the flexibility of hamstring muscles. *Phys Ther*. 1994; 9:845-50.
- [18] <http://groups.eortc.be/qol/eortc-qlq-c30>
- [19] EuroQoL Group (2017). EQ-5D-3L. Available from: <https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/> (Last accessed: 18th May 2017).

- [20] Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D, Discussion Paper No. 172. Centre for Health Economics, University of York: York, 1999.
- [21] Dolan P, Gudex C, Kind P, and Williams A. A social tariff for EuroQoL: Results from a UK general population survey, Discussion Paper No. 138. Centre for Health Economics, University of York: York, 1995.
- [22] Morris S, Devlin N, Parkin D. Economic analysis in health care. John Wiley & Sons Ltd: Chichester, UK, 2007.
- [23] Drummond MF, Sculpher MJ, Claxton K, Stoddart GL and Torrance GW. Methods for the economic evaluation of health care programmes (4th Ed.). Oxford University Press: Oxford, UK, 2015.
- [24] National Institute for Health and Clinical Excellence (NICE). *Process and methods guides: Guide to the methods of technology appraisal 2013*.
<https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781> (Last accessed 23rd May 2017).
- [25] Flynn TN, Huynh E, Peters TJ, Al-Janabi H, Clemens S, Moody A and Coast J. Scoring the ICEFCAP-A capability instrument: Estimation of a UK general population tariff. Health Economics, 2013, DOI: 10.1002/hec
- [26] DIRUM (Database of Instruments for Resource Use Measurement) Available from: <http://www.dirum.org/> (Last accessed: 22nd May 2017).

- [27] Ritchie J and Spencer L. Qualitative data analysis for applied policy research. In *Analysing Qualitative Data* (Bryman A., Burgess R., eds), Routledge, London, 1994. pp.172-194.
- [28] Gray, AM, Clarke, PM, Wolstenholme, JL, Wordsworth, S. *Applied Methods of Cost-effectiveness Analysis in Health Care*. Oxford University Press: Oxford, UK, 2011.
- [29] Russell IT, Edwards RT, Gliddon AE, Ingledew DK, Russell D, Whitaker R, Yeo ST, Attwood SE, Barr H, Nanthakumaran S and Park KGM. Cancer of Oesophagus or Gastric-
New Assessment of Technology of Endosonography (COGNATE): report of pragmatic randomised trial. *HTA*, 2013, 17(39). DOI: 10.3310/hta17390.
- [30] Melchers, I.J., Van Weert, E., Beurskens, C.H.G., Reintsema, H., Slagter, A.P., Roodenburg, J.L.N. and Dijkstra, P.U. Exercise adherence in patients with trismus due to head and neck oncology: a qualitative study into the use of the Therabite®. *Int J Oral Maxillofac Surg* 2009;38(9):947-54
- [31] Tang Y, Shen Q, Wang Y, Lu K, Wang Y, Peng Y. A randomised prospective study of rehabilitation therapy in the treatment of radiation-induced dysphagia and trismus. 2011; *Strahlenther Onkol: No 1*.
- [32] Ren WH, Ao HW, Lin Q, Xu ZG, Zhang B. Efficacy of mouth opening exercises in treating trismus after maxillectomy. *Chin Med J (Engl)* 2013;126(14):2666-9.
- [33] Hogdal N, Juhl C, Aadahl M, Gluud C. Early preventative exercises verses usual care does not seem to reduced trismus in patients treated with radiotherapy for cancer in the oral cavity or oropharynx: A randomised clinical trial. *Acta Oncol*, 2014; 1-8
- [34] Pauli N, Andrell P, Johansson M, Fagerberg-Mohlin B, , Finizia C. Treating trismus-a prospective study on effect and compliance to jaw exercise therapy in head and neck cancer. *Head and Neck* 2014.doi:10.1002/hed.23818

[35] Buchbinder D, Currivan R, Kaplan A, Urken M. Mobilisation regimens for the prevention of jaw hypomobility in the radiated patient: a comparison of three techniques. *J Oral Maxillofac Surgery* 1993; 51:863-867

[36] Johnson J, van As-Brooks CJ, Fagerberg-Mohlin B, Finizia C. Trismus in head and neck cancer patients in Sweden: incidence and risk factors. *Med Sci Monit.* 2010 Jun;16(6):CR278-82

[37] Clarke M, Hogan V, Buck D, Shen J, Powell C, Speed C, Tiffin P, Sloper J, Taylor R, Nassar M, Joyce K, Beyer F, Thomson R, Vale L, McColl E and Steen N. An external pilot study to test the feasibility of a randomised controlled trial comparing eye muscle surgery against active monitoring for childhood intermittent exotropia [X(T)]. *Health Technol Assess*, 2015;19(39).

Legends

Table 1: Baseline characteristics

Table 2 Consort diagram

Table 3: Frequency of contacts with primary and secondary care health services use by 30 participants in the Trismus feasibility trial at 6 month post-baseline

Table 4: Mean costs of all contacts with NHS primary and secondary care services use by 30 participants in the Trismus trial (£) over the six-month follow-up period

Table 5 : Mean EQ-5D-3L index scores, mean QALYs and incremental mean QALYs at 6 months post-baseline by group (n=30)

Table 6: Mean ICECAP-A capability index scores, change in mean ICECAP-A index score between study time points and difference in mean change scores between groups at 6 months post-baseline by group (n=19<30)^o