LITEFORM

A Randomised Controlled Trial of the Clinical and Cost Effectiveness of Low Level Laser Therapy in the Management of Oral Mucositis in Head and Neck Cancer Irradiation

IRAS: 209809

Economic Analysis Plan

Version 1.0

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1. Summary of the LiTEFORM study

Background: Around 4000 patients per year in England and Wales undergo chemotherapy (CT) or radiotherapy (RT) for head and neck cancer (HNC) [1]. 97% of these patients will develop Oral Mucositis (OM) [2]. OM is a debilitating, painful complication characterised by inflammation of the mucous membranes, erythema and ulceration [3]. There is emerging evidence of the efficacy of Low Level Laser Therapy (LLLT) as a treatment for OM, which is the most significant cause of acute morbidity of HNC (C)RT. However, there is inadequate evidence of the effectiveness of LLLT for it to be recommended as standard of care. LLLT remains unavailable to NHS patients undergoing HNC apart from, at the time of writing, a small pilot involving one centre. There is a lack of evidence as to whether LLLT is cost effective and how it is most efficiently delivered.

Summary of Trial Design: A multicentre, blinded, randomised controlled trial of low-level laser versus sham low-level laser therapy (LLLT) in the prevention and management of OM in head and neck cancer irradiation

Summary of Participant Population: Adults (≥18 years), referred for head and neck cancer irradiation

Planned Sample Size: 380 adults (190 per arm)

Planned Number of Sites: Up to 10 sites (including 7 pilot sites)

Intervention Duration: 6 weeks after first LLLT

Follow Up Duration: 12 weeks after last LLLT, 4 months after last LLLT, 14 months after last LLLT

Final Follow Up Visit: 14 months post LLLT and CRT (for patients who started laser therapy after 6th July 2018, the final follow-up visit will be 4 months)

Planned Trial Period: 47 months (including 9 months pilot phase)

Intervention: Low Level Laser Therapy (LLLT)

Primary Outcome: Oral Mucositis Weekly Questionnaire-Head and Neck Cancer (OMWQ-HN) score at week 6 following start of LLLT treatment.

Primary Objective: To compare the clinical effectiveness and cost effectiveness of LLLT plus standard care vs standard care alone as measured by the OMWQ-HN in adult HNC patients receiving (C)RT.

2. Outline of the economic analysis

The objective of this economic analysis plan is to outline the economic evaluation that will be conducted as part of the LiTEFORM study. Given that the original proposed analysis is no longer appropriate given the achieved sample size, the economic evaluation initially has three primary components:

(i) A micro-costing analysis of the intervention
(ii) Presentation of health service utilisation data in the form of summary statistics
(iii) Presentation of health economic quality of life data in the form of summary statistics

Additionally, if the data is of sufficient quality, we will extend the analysis to summarise the costs and effects in the two trial arms. Due to the sample size, no formal statistical testing will be undertaken as part of the analysis.

The design, conduct and analysis will follow guidelines for best practice throughout [4]. The economic evaluation will be from the perspective of the UK National Health Service (NHS) and personal and social care services.

2.1 Micro-costing of the intervention

All relevant costs associated with the intervention will be measured using study specific estimates and routine data sources. As the time horizon for the study is now less than a year, discounting will not be applied to costs.

The resources used for the intervention will be estimated for each trial participant. This requires ascertaining the number of laser therapy sessions attended during the intervention period. These data will be based on session attendance from the electronic associated case report forms (eCRF).

Intervention costs for those randomised to receive the laser therapy session will include:

- Equipment required for each laser therapy session
- Maintenance fee for the laser therapy system

- Estate/facilities costs for use of a treatment room, including storage of the laser therapy system
- Staff cost (per minute) for set up and preparation for each therapy session
- Staff costs (per minute) of the staff members(s) who deliver the session
- Staff costs (per minute) of the staff member (s) who provide administrative support
- Staff costs (per minute) of the staff member(s) who supervises the session

Assumptions for the intervention costs will be based on:

- Usual lifespan of the laser is 5 years
- Patients will receive LLLT 3 times weekly by a non-contact method for a period of 6 weeks
- Each session will last approximately 20-30 minutes
- The equipment will be serviced annually
- LLLT will be delivered to the patient by trained doctors, nurses or allied healthcare professionals
- Laser costs will include the capital investment + maintenance costs + estate and facilities costs. The allocation of these capital costs will be carried out following the "equivalent annual cost" methodology.

2.2 NHS Resource and social care resource use

Data are primarily being collected on resource use in the two trial arms based on a health service use questionnaire administered to all participants at 4 months post baseline. This questionnaire asks about resource use in the preceding 4 months. This data will be used to calculate the use of health care resources from baseline to the 4 month follow up in the two trial arms.

The health service utilisation (HSU) questionnaire will gather data on:

- Inpatient and day-case resource use
- Outpatient resource use
- A&E resource use
- Primary and community-based NHS resource use

- Private health care/personal care
- Work affected by illness

The data collected through the health service use questionnaire will be supplemented with data collected via the eCRF. Specifically, the eCRF will collect data regarding patient visits to the oral hygienist, and the use of painkillers, mouth washers and other medications. We will initially report the competition rates for the HSU (Table 1).

Table 1 - Summary of the health service use questionnaire completeness at 4 months in the intervention and control arms		
Intervention Arm (n=)		
Missing	Partial	Complete
Control Arm (n=)		
Missing	Partial	Complete

2.2.1 Inpatient costs

The health service utilisation questionnaire will gather data on the number of inpatient stays (including the duration of stay) experienced by each participant in the time since their last laser session. These relate to an illness/injury, not just visits related to their cancer, and include data on whether or not inpatient stay resulted from A&E assessment, as this may incur additional resource use.

The reported length of stay (per day) will be basis of identifying the resource use per patient. For both trial arms, a point estimate and range for the mean number of inpatient days will be reported. Data on resource use per day during each inpatient and/or day-case stay will be estimated from routine sources to calculate a unit cost per inpatient day.

Inpatient costs vary widely depending on the reason for admission, type of admission and the severity of the situation. However, these data will not be collected within the health service utilisation questionnaire, as these responses could be subject to recall bias.

Table 2 – Inpatient costs				
Type of cost	**Unit of measurement**	**Cost (£) per unit**	**Price year**	**Source**
Accident and Emergency Visit(s)	per visit			NHS Reference Costs data
Inpatient stay(s)	per night			NHS Reference Costs data
Total Cost Σ"Units used" x Σ"Cost (£) per unit" (Standardised Price Year)	Per participant			

2.2.1 Medications

The cost of medication per patient will also be captured for each trial arm. Trial participants may be prescribed medications as inpatients, outpatients or from their GP at any point during the trial. The eCRF will collect data on the drug name, dosage, frequency and start date of medication prescribed to each participants each week (for the first 6 weeks) and for the previous six weeks (at the 12 week time period).

The unit cost of each medication will be taken from the British National Formulary (BNF), and the cost per patient in terms of medication will be calculated by multiplying the unit costs by the number of units consumed for each patient, as taken from the health service utilisation questionnaire. A medication cost will be calculated for each patient and then averaged across each trial arm to obtain the mean cost of medications in each trial arm.

Table 3 – Medication costs					
Drug name	**Duration on drug (days)**	**Unit of measurement**	**Cost (£) per unit**	**Price year**	**Source**
Drug A		Dose per day			BNF
Drug B		Dose per day			BNF
Drug C		Dose per day			BNF
Total Units used (Days x dose per day)					

2.2.2 Outpatient costs

The number of outpatient visits at baseline and 4 months post randomisation for trial arm will be obtained from the HSU.

Table 4 – Outpatient costs				
Type of cost	**Unit of measurement**	**Cost (£) per unit**	**Price year**	**Source**
Outpatient episode (e.g. head and neck ward)	per new visit or follow up visit			NHS Reference Costs data
Total Cost Σ"Units used" x Σ"Cost (£) per unit" (Standardised Price Year)	Per participant			

2.2.3 Primary and community-based NHS costs

The number of visits to primary care services and other community based NHS services will be obtained from the HSU.

Table 5 – Primary and Community Care Costs				
Type of cost	**Unit of measurement**	**Cost (£) per unit**	**Price year**	**Source**
GP Consultation at Practice	per visit			NHS Reference Costs data
Nurse Consultation at Practice	per visit			NHS Reference Costs data
Other Consultation at Practice	per visit			NHS Reference Costs data
GP Consultation at Home	per visit			NHS Reference Costs data
Nurse Consultation at Home	per visit			NHS Reference Costs data
Other Consultation at Home	per visit			NHS Reference Costs data
GP Telephone Consultation	per minute			NHS Reference Costs data
Nurse Telephone Consultation	per minute			NHS Reference Costs data
Other Telephone Consultation	per minute			NHS Reference Costs data
GP Out-of-Hours Consultation	per visit			NHS Reference Costs data
Nurse Out-of-Hours Consultation	per visit			NHS Reference Costs data

Hospital Doctor Out-of-Hours Consultation	per visit			NHS Reference Costs data
NHS Call Centre Out-of-Hours Consultation	per minute			NHS Reference Costs data
Other Out-of-Hours Consultation	per visit			NHS Reference Costs data
Consultation with Nurse from Cancer Support Organisation	per visit			NHS Reference Costs data
Consultation with Other Health Care Professional from Cancer Support Organisation	per visit			NHS Reference Costs data
Total Cost Σ"Units used" x Σ"Cost (£) per unit" (Standardised Price Year)	per participant			

2.2.4 Patient and carer-borne costs

Certain patient borne costs will be obtained from the HSU and the eCRF.

Table 6 – Patient and carer-borne costs				
Type of cost	**Unit of measurement**	**Cost (£) per unit**	**Price year**	**Source**
Private health care episode 1	per visit			
Private health care episode 2	per visit			
Private health care episode 3	per visit			
Lost income due to illness	per day			

2.2.5 Total costs

Once the total health service cost per patient has been calculated, we will report the total average cost for the two trial arms (Table 7). Due the curtailment of the trial, no information on patient and carer costs will be analysed from the time and travel questionnaire due to be issued at 14 months post baseline.

Table 7 – Average total cost per patient for trial arm			
Resource use (mean costs per patient)	**Intervention (Mean)**	**Control (Mean)**	**Mean Difference (Intervention vs Control)**
Intervention costs *		**N/A**	**N/A**
Inpatient costs			
Medication costs			
Outpatient costs			
Primary and community-based NHS costs			
Patient and carer costs			
Total average cost			
* We will not present intervention cost for the sham arm of the trial			

2.3 Cost effectiveness: EQ-5D-5L and QALY values

2.3.1 EQ-5D-5L

The EQ-5D-5L questionnaire will be completed by participants at baseline, 6 weeks and 4 months post-randomisation. The EQ-5D-5L measure divides health status into five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each of these dimensions has five levels, so 3,125 possible health states exist. Given that original proposed analysis is no longer appropriate, we will initially report the completion rates and domain scores for the EQ-5D-5L (Table 8 and Table 9) and Visual Analogue Scores (VAS) (Table 10) for the two trial arms. If the quality of the data is sufficient, we will also convert the responses to the EQ-5D-5L into EQ-5D utility scores. We will follow current NICE guidelines [5] and use the mapping/cross-walk algorithm to map the responses to the EQ-5D-3L, and then convert these values into health state utility values at each time point for each patient based on a representative sample of the UK population (Table 11) [6].

2.3.2 QALYs

If the quality of the data is sufficient, the calculation of health state utilities using the EQ-5D-5L will allow us to estimate mean QALYs for both trial arms. This will be done using the "area under the curve" method, which allows us to take into account differences in the rate of recovery following the interventions. As per NICE's current guidelines the EQ-5D-5L results will be converted ("cross-walked") into EQ-5D scores. As we are collecting quality of life data from each participant at baseline, we will adjust the analysis to account for any imbalance in the characteristics of the two trial arms.

2.3 Cost utility analysis

If the quality of the data is sufficient, we will compare the incremental cost-per QALY for each trial arm at 4 months. An adjusted analysis will be used to estimate the point estimates of the mean incremental costs, effects and cost-effectiveness using seemingly unrelated regression (SUR). SUR permits the simultaneous estimation of costs and effects, calculated at an individual level, while accounting for unobserved individual characteristics that could affect both costs and effects and lead to potential correlation between these two variables.

Cost effectiveness acceptability curves (CEACs) will then be created with the calculated ICERs to show whether the assessed interventions are cost effective at different threshold values for society's willingness to pay for a QALY. The CEACs will summarise the uncertainty in estimates of cost-effectiveness by graphically representing the probability of the interventions of being cost-effective at each willingness-to-pay (WTP) threshold (Table 12). As part of this threshold evaluation, we will include £20,000 and £30,000 since these are used as reference points for NICE policy recommendations [4].

2.4.1 Sub-group analysis

Given the reduced sample size, no sub-group will be undertaken.

Table 8 - Summary of EQ-5D-5L completeness as baseline and 4 months in the intervention and control arms					
Intervention Arm					
Baseline			4 Months		
Missing	Partial	Complete	Missing	Partial	Complete
Control Arm					
Baseline			4 Months		
Missing	Partial	Complete	Missing	Partial	Complete

Table 9 - EQ-5D-5L Responses by Intervention Arm										
Mobility										
	Intervention					**Control**				
	No	Slight	Moderate	Severe	Unable to do	No	Slight	Moderate	Severe	Unable to do
Baseline										
6 Weeks										
4 Months										
Self-Care										
	Intervention					**Control**				
	No	Slight	Moderate	Severe	Unable to do	No	Slight	Moderate	Severe	Unable to do
Baseline										
6 Weeks										
4 Months										
Usual Activities										
	Intervention					**Control**				
	No	Slight	Moderate	Severe	Unable to do	No	Slight	Moderate	Severe	Unable to do
Baseline										
6 Weeks										
4 Months										
Pain & Discomfort										
	Intervention					**Control**				
	No	Slight	Moderate	Severe	Extreme	No	Slight	Moderate	Severe	Extreme
Baseline										
6 Weeks										
4 Months										
Anxiety & Depression										
	Intervention					**Control**				
	No	Slight	Moderate	Severe	Extreme	No	Slight	Moderate	Severe	Extreme
Baseline										
6 Weeks										
4 Months										

Table 10 – Mean VAS Score by Intervention Arm		
	Intervention	**Control**
Baseline		
6 Weeks		
4 Months		

Table 11 – EQ-5D-5L and QALYs		
Score	**Intervention**	**Control**
Baseline mean (SD) EQ-5D-5L		
Baseline median (IQR) EQ-5D-5L		
6 weeks EQ-5D-5L mean (SD) score		
6 weeks median (IQR) EQ-5D-5L		
4 months EQ-5D-5L mean (SD) score		
4 months EQ-5D-5L median (IQR) score		
QALYs mean (SD)		
QALYs median (IQR)		

Table 12 – Cost-effectiveness/utility analysis								
						Probability that intervention is cost-effective for different threshold values for society's WTP for a QALY		
Treatment	**Cost (£)**	**Δ Cost* (95% CI)**	**QALY**	**Δ QALYs* (95% CI)**	**ICER**	**£0**	**£20,000**	**£30,000**
Control								
Intervention								

* estimated using adjusted analysis

References

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4. NICE. Guide to the methods of technology appraisal 2013. National Institute for Health and Care Excellence; 2013

5. NICE. Position statement on use of the EQ-5D-5L valuation set. 2017.

6. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35.