Chemoradiation versus Oesophagectomy for Locally Advanced Oesophageal Cancer in Chinese Patients: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Surgery is the gold standard treatment for local advanced disease, while definitive concurrent chemoradiotherapy (DCRT) is recommended for those who are medically unable to tolerate major surgery or medically fit patients who decline surgery. The primary aim of this trial is to compare the outcomes in Chinese oesophageal squamous cell cancer patients with locally advanced resectable disease who have received either surgery or DCRT.

Methods/design: One hundred ninety-six patients with T1bN+M0 or T2-4aN0-2M0 oesophageal squamous cell cancer will be randomized to the DCRT group or the surgery group. In the DCRT group, patients will be given intensity modulation radiation therapy (IMRT) with 50 Gy/25 fractions and basic chemotherapy with 5-fluorouracil (5-FU) regimens. In the surgery group, patients will receive neoadjuvant chemoradiotherapy (NCRT) and standard oesophagectomy. Five years of follow-up will be scheduled for patients. The primary endpoints are 2-year/5-year overall survival; the secondary endpoints are 2-year/5-year progression-free survival, treatment-related adverse events and the patients' quality of life. The main evaluation methods include oesophagoscopy, endoscopic ultrasonography and biopsy, oesophageal barium meal, CT, PET-CT, blood tests, and questionnaires.

Discussion: The preponderant oesophageal cancer pathology type is dramatically different in western Caucasian and Asian oesophageal cancer patients: Caucasian patients present with 80% adenocarcinomas, and Asians patients present with 95% squamous cell carcinomas. This phenomenon needs more in-depth studies to elucidate the differences in these populations. Based on the results of this study, we will show whether DCRT will benefit patients more than oesophagectomy. It will contribute more evidence to the management of oesophageal squamous cell cancer.

Background

Oesophageal cancer (EC) is the eighth most common cancer worldwide and the sixth leading cause of cancer-related death [1]. In 2012, 456,000 EC cases occurred, and 400,000 people died from EC worldwide. It's remarkable that almost half of them came from China, with 223,000 EC cases and 197,000 death cases in 2012. Both the highest incidence and mortality were in Henan, China (including Linzhou, Anyang and Huixian cities, 379/100,000, and 150/100,000 respectively). Additionally, it is the fourth most deadly cancer among men in China; it is responsible for 9.8% of all cancer deaths annually [2].

Worldwide, approximately half of these patients present with locally advanced disease [3]. Radical oesophagectomy remains the most popular treatment for this disease, but the long-term survival is still barely satisfactory [4, 5]. The mortality in perioperative period is approximately 5% at renowned centres. The 5-year survival in patients with oesophageal carcinoma treated by surgery alone is just 10–20% [6]. Numerous clinical studies in past decades have used adjuvant or neoadjuvant chemotherapy and radiotherapy as a tool to improve the clinical outcome of surgery [7]. However, the results from

prospective randomized trials on neoadjuvant radiotherapy or chemotherapy alone were not satisfactory [8]. There was no survival benefit associated with these approaches [9].

Concurrent chemoradiotherapy as a neoadjuvant therapy has preferable clinical efficacy and has become the standard treatment for local advanced oesophageal cancer with recognized guidelines [10-12]. Compared with chemotherapy or radiation alone, CRT has outstanding advantages not only in achieving a higher rate of complete pathologic regression of oesophageal tumours but is also associated with a significant survival benefit [12]. The complete tumour response was frequently observed after NCRT, and this has prompted investigations on the role of DCRT in locally advanced oesophageal carcinoma. However, most of those studies came from western, developed countries, and the majority of patients had adenocarcinomas. Different cell pathologies of the tumours could influence the clinical outcome following the same treatment strategy. In recent studies, neoadjuvant or adjuvant chemotherapy was associated with survival benefits in patients suffering from adenocarcinomas of the oesophagus. A prospective clinical study from Hong Kong University investigated the efficacy of CRT (three-dimensional conformal radiation therapy (3DCRT) combination with 2 cycles of 5-FU and cisplatin) compared with surgery in oesophageal squamous cell cancer. Though this trial had shown no significant difference in the 2-year overall survival (OS) between the two study arms, a superior 5-year OS was found in the CRT arm, but with no statistical significance [13, 14].

In recent studies, both oxaliplatin and capecitabine have been shown to be at least equivalent to cisplatin and 5-FU in the treatment of advanced upper GI cancer or oesophageal cancer and can be given as a convenient 2-hour infusion and oral administration and has a more favourable toxicity profile compared to cisplatin and 5-FU [15, 16]. Based on these previous findings, in this randomized, open-label, multicentre clinical trial, aimed to compare outcomes in Chinese patients with locally advanced resectable oesophageal squamous cell cancer (ESCC) who have received either NCRT plus surgery or DCRT. The primary endpoints will be 2-year/5-year OS, and the second endpoints will be 2-year/5-year progression-free survival (PFS), treatment-related adverse events (AEs) and the patients' quality of life (QoL). Additionally, in the subgroup analysis of CRT, we will also investigate the effect and AEs between the different chemotherapy regimens: Xelox (capecitabine + oxaliplatin), PF (cisplatin + 5-FU) and single capecitabine. This is the first head to head clinical trial to compare CRT with radical operation in Chinese mainland people with locally advanced ESCC.

Methods And Design

Aim

The primary aim of this trial is to compare the outcomes in Chinese oesophageal squamous cell cancer patients with locally advanced resectable disease who have received either surgery or DCRT.

Design

A multicentre, open, prospective, randomized controlled trial will be conducted that includes 3 regional hospitals in Henan, which is the area with the highest incidence of ESCC in the world, including the First Affiliated Hospital of Henan University of Science and Technology (HUST), Anyang Tumour Hospital of HUST, and Nanyang Centre Hospital. A total population of 216 x 105 is served by these three hospitals (Fig. 1).

Settings

The First Affiliated Hospital of Henan University of Science and Technology (HUST), Anyang Tumour Hospital of HUST, and Nanyang Centre Hospital.

Participants' characteristics

Patients

A total of 196 ESCC patients with T1bN+M0, T2-4aN0-2M0 will be randomized to the CRT group or the surgery group.

Inclusion criteria

1. Age: 18-75 years;

2. Mainland Chinese;

3. Oesophageal squamous cell cancer is confirmed by histology;

4. Tumour is resectable;

5. Clinical stage: cT1bN+Mo, or cT2-4aN0-2M0

6. Performance status score: 0-2

Exclusion Criteria:

1. Patient had distant metastasis to solid visceral organs or local invasion into the trachea, descending aorta, or recurrent laryngeal nerve.

2. Patient had a serious premorbid condition or a poor physical status that compromised the thoracotomy.

3. Compromised cardiac function or creatinine clearance less than 50 ml/min.

4. MVV of pulmonary function test is less than 30%.

Withdrawal criteria

Patients will be withdrawn from the study if they withdraw informed consent and decline to continue treatment or follow-up.

Recruitment

Recruitment will be from cancer centres of The First Affiliated Hospital of Henan University of Science and Technology (HUST), Anyang Tumour Hospital of HUST, and Nanyang Centre Hospital, Henan province, China. Research staff will regularly check the inpatient registry Information System and identify any potentially eligible patients. They will liaise with an oncologist to ensure the patient's history and screening results are clear for study commencement. Eligible participants who present at cancer center when research staff are present will complete informed consent documentation after discussion with the oncologist, fill out baseline measures, then be randomly allocated to DCRT or NCRT plus surgery group.

Randomisation

The randomisation codes will be generated by the study statistician using computer-generated random numbers. Participants will be randomly allocated to DCRT or NCRT plus surgery group in 1:1 order. Then in each group, participants will be secondary randomly allocated to subgroups with one of three different chemotherapy regimens in 1:1:1 order.

Pretreatment Investigations

Patients will receive further staging workup, including oesophagoscopy, endoscopic ultrasonography (EUS), computer tomography (CT) of the thorax and abdomen with contrast, and ultrasonography of the cervical region with fine needle aspiration cytology for any suspicious nodes. PET-CT will be used when the disease stage is difficult to confirm by general imaging examination, but it is not compulsory.

Interventions

Standard Oesophagectomy

Standard oesophagectomy surgery will be performed for patients by specialists. The surgical approach to the mid or lower thoracic oesophagus was standardized to two-stage oesophagectomy to achieve a 5-cm minimum proximal margin. For tumours located over the proximal mid thoracic oesophagus where a 5-cm proximal margin could not be achieved, a three-stage oesophagectomy was performed. We performed a two-field lymphadenectomy in situations of either cervical or thoracic anastomosis. All the oesophagectomies were performed through the thoracoscopy operation or an open approach. A radical surgical resection was defined as macroscopic clearance of the oesophageal tumour with no residual disease left (R0). Patients in the standard oesophagectomy group received postoperative adjuvant chemotherapy if the resection was considered to be R1 as if microscopic disease is left behind.

Chemoradiotherapy

Radiotherapy

IMRT radiotherapy was performed for patient in the DCRT group with 50 Gy/25 F and in the surgery group with 42 Gy/21 F for NCRT, at 2 Gy/day, 5 times/week, until disease progression or unacceptable toxicity was found. The dosage for the individual patients was governed by the dose constraints of the normal organs. Target volume length included 5 cm on each side of the imaged visible tumour and malignant nodes. Radiotherapy was delivered in two consecutive phases. Phase I started with anterior-posterior opposing portals to 30 Gy, while phase II was given with three fields to another 20 Gy (or 12 Gy in surgery group for NCRT), which is subject to the limiting radiation dose of the heart, lung, and spinal cord.

Chemotherapy

Patients will be randomized given one of three regimens below:

Xelox: oxaliplatin 65 mg/m2, d1, 8, 22, 29, plus capecitabine, 625 mg/m2, bid, d1-5; 6 weeks in total.

Single capecitabine: capecitabine, 625 mg/m2, bid, d1-5; q1w, 6 weeks in total.

PF: cisplatin, 75 mg/m2, d1, 29, 5-Fu, 750 mg/m2, CIV 24 h, d1-4, d29-32.

Outcome measures

The primary outcome measures are 2-year/5-year overall survival (OS).

The secondary outcomes are 2-year/5-year disease-free survival (DFS), treatment-related adverse events (AEs) and QoL. The recurrence of the disease is defined as either endoscopic recurrence confirmed with biopsy or distant metastasis. The operative mortality is defined as an in-hospital death within 30 days of perioperative period.

Follow-up

All patients will be followed in the hospital where they received treatment at the 16th week after random allocation, then, at 3-month intervals in the first 2 years, and 6-month intervals for the next 3 years thereafter. Local or systemic recurrences and any AEs will be recorded. For the DCRT group, patients could be treated with salvage oesophagectomy if the disease doesn't reach complete remission at the 16th week follow-up. As well as for the surgery group, patients could be treated with radiation or chemotherapy if R0 is impossible to take or there is local recurrence at the 16th week of follow-up.

QoL was evaluated in all patients using the quality of life-core 30 questionnaire (QLQ-C30; ver. 3.0, in Chinese) and the supplemental quality of life-oesophageal module 18 questionnaire (QLQ-ES18, in Chinese) for patients with oesophageal cancer, both of which were developed by the European Organization for Research and Treatment of cancer (EORTC). For this evaluation, each patient was visited in person during hospitalization 1 week before and 1 week after surgery, and contacted by telephone at 12 and 24 weeks postoperatively (Fig. 2) [17].

Data management

This trial will be conducted in accordance with ICH Guidelines for Good Clinical Research Practice and relevant local ethical regulations. Study data will be collected and managed using a regulatory approved electronic data capture system.

Data quality will be assured through range checks for data values. Integrity of trial data will be monitored by regularly scrutinising data for omissions and errors. In order to protect confidentiality before, during and after the trial, personal information about potential and enrolled participants will remain secure in a locked research office at The First Affiliated Hospital of Henan University of Science and Technology. Study data will be retained, securely password protected, for a minimum of 15 years from completion. Details of data management procedures can be found in the protocol.

Data analyses

Because of participant numbers and the aims of the study, we will report descriptive analyses. Recruitment rate (number of patients approached, number consenting to participate and number eligible to be randomised) will be reported, as will frequencies and proportions of missing data and participant attrition, both during intervention and follow-up periods.

Sample Size Estimation and Statistical Analysis

Sample size calculation is based on the 5-year OS in patients treated with oesophagectomy of 29.4% and 50% in DCRT group [18]. We used the log-rank test to compare the survival rate difference between the surgery and DCRT group. We defined the α as 0.05, and β as 0.2. We supposed that the rate of loss to follow-up per year is 2.5% and 12.5% in 5 years. A sample size of 96 patients was determined to be required for each group.

The baseline data of the patient characteristics and the primary and secondary outcome measures will be compared using the Student's t-test for the parametric data and the Mann-Whitney U test for the nonparametric data. For the data in proportions, a X2 test or the Fisher's exact test (if one of the expected values is less than 5) will be used. The provision of a 95% confidence interval will be calculated with the relative risk for cancer recurrence, morbidities and mortalities related to each therapy. We will use the Kaplan-Meier curve to represent the probability of survival within 2 years and 5 years after the initial diagnosis, and compare the two groups using the log-rank test. A value of $P < 0.05$ is considered to be statistically significant. The statistical analysis will be performed with the SPSS software (version 13.0; SPSS Inc., Chicago, IL, United States).

Monitoring

Collecting, assesing, reporting and managing adverse events

The most common side effects of CRT are myelosuppression, oral mucositis, hand-foot syndrome and peripheral neuritis. More severe side effects are rare. Information about solicited and spontaneously reported adverse events will be sought from all participants during telephone reviews by the trial GP. If a

participant reports an adverse event, the trial GP will determine appropriate action, which may include dose alteration or withdrawal. If an adverse event is identified more serious than grade 4, the trial GP will forward this information immediately to the Principal Investigator and Data Safety Monitoring Board. All of the serious AEs (SAEs), suspected adverse reactions and serious unexpected suspected adverse reactions will be recorded immediately in the source documents, and on the adverse event case report form. Each event will be followed until resolution, stabilisation or until it has been determined that the study treatment is not causal. SAEs still on going at the end of the study will be followed up to determine final outcome. Any SAE will be recorded and reported immediately that occurring after the study considered to be possibly related to study treatment. Economic compensation will be provided by the trial sponsor that to who suffer harm from trial participation.

Dissemination

Authorship eligibility guidelines will follow ICMJE guidelines. The final trial dataset will be available to the investigative team and on reasonable request.

Discussion

This is the first registered prospective head to head clinical trial to compare the outcomes between radical operation and DCRT in ESCC patients in the highest incidence area worldwide. In the current international guidelines for oesophageal cancer, DCRT is recommended as an effective intervention approach only for patents with local advanced disease but whose are not suitable for oesophagectomy. The reasons could be the patient's willingness, poor performance status, concomitant cardiopulmonary disease and so on. Some studies reported that patients received a survival benefit from DCRT. However, the prospective clinical trials that compare DCRT and NCRT plus surgery through a head to head method is still limited. And the participants were reported in published studies were mainly western Caucasian with oesophageal adenocarcinoma. Sjoquist et al. reported that the oesophageal cancer patients with adenocarcinoma pathology had a higher disease regression rate than squamous cell cancer after neoadjuvant CRT [18]. The long-term survival status of oesophageal squamous cell carcinoma after the DCRT or NCRT plus surgery treatment is unclear.

Researchers from Hong Kong University initiated an excellent prospective clinical trial to compare the long-term outcome between DCRT and surgery for ESCC patients. In this study, the overall 5-year survival favours CRT, but the difference did not reach statistical significance (surgery 29.4% and CRT 50%, $P = 0.147$) [13, 14]. The intervention of chemoradiotherapy used in this study is: Cisplatin 60 mg/m2 with hydration therapy given on days 1 and 22, whereas 5-FU was administered as a continuous infusion at 200 mg/m2/day from day 1 to 42. Radiotherapy was delivered as three-dimensional conformal radiation therapy (3DCRT) with a total of 50–60 Gy given in 25–30 fractions over 5–6 weeks. It is inconvenient for patients to be administered 5-FU continuously for 42 days, while IMRT has been reported as more effective and tolerable than 3DCRT. Therefore, we designed this study to investigate the role of definitive CRT compared with neoadjuvant CRT followed by radical operation in locally advanced ESCC patients in the highest incidence area worldwide using IMRT (50 Gy/25 F) and different chemotherapy regimens

(capecitabine, Xelox, PF, randomized delivery). In the pilot trial, 86 patients finished 16-weeks of follow-up with at least these three regimens in the DCRT group (capecitabine: Xelox: PF = 24: 37: 25) [19, 20]. The incidence of grade 3-5 ATEs were 25%, 32.4%, and 64% (p = 0.03) and the pCR rate were 50%, 48.6%, and 48% in the three sub-groups, respectively (p = 0.99). Additionally, an ORR of 87.5% (21/24), 83.8% (31/37), and 100% (25/25) (p = 0.133) was observed. No differences were seen in the CR and ORR between the three sub-groups. Therefore, it is worth exploring the roles of both the definitive CRT and single capecitabine in CRT in advanced ESCC patients with a larger sample size.

Trial status

The trial began recruitment in April 2017. Participants will be recruited until December 2020, if necessary.

Declarations

Ethics approval and consent to participate

Ethics: This study has been approved by the Ethics Committee of The First Affiliated Hospital of Henan University of Science and Technology. The approval number is 2016110201.

Informed consent: Written informed consent will be collected from each study participant prior to enrolment.

Consent for publication

The authors certify that they will obtain all the appropriate patient consent forms. In the form the patient(s) will give his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request, and in ClinicalTrials.gov identifier NCT02972372.

Competing interests

The authors declare that they have no conflicts of interest.

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Authors' contributions

RJ was responsible for patients' recruitment in all participated center, and carried out the trial design and drafted the manuscript. SL carried out the pilot study and sample size estimation. RL participated in the patient recruitment. JY performed the statistical analysis. TS conceived of the study, and participated in its design and coordination. DZ participated in the patient recruitment. WW participated in the patient recruitment too. LW was responsible for one local center patients' management. FZ was responsible for other local center patients' management. SG carried out the trial design and financial supervision. All authors read and approved the final manuscript.

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Figures

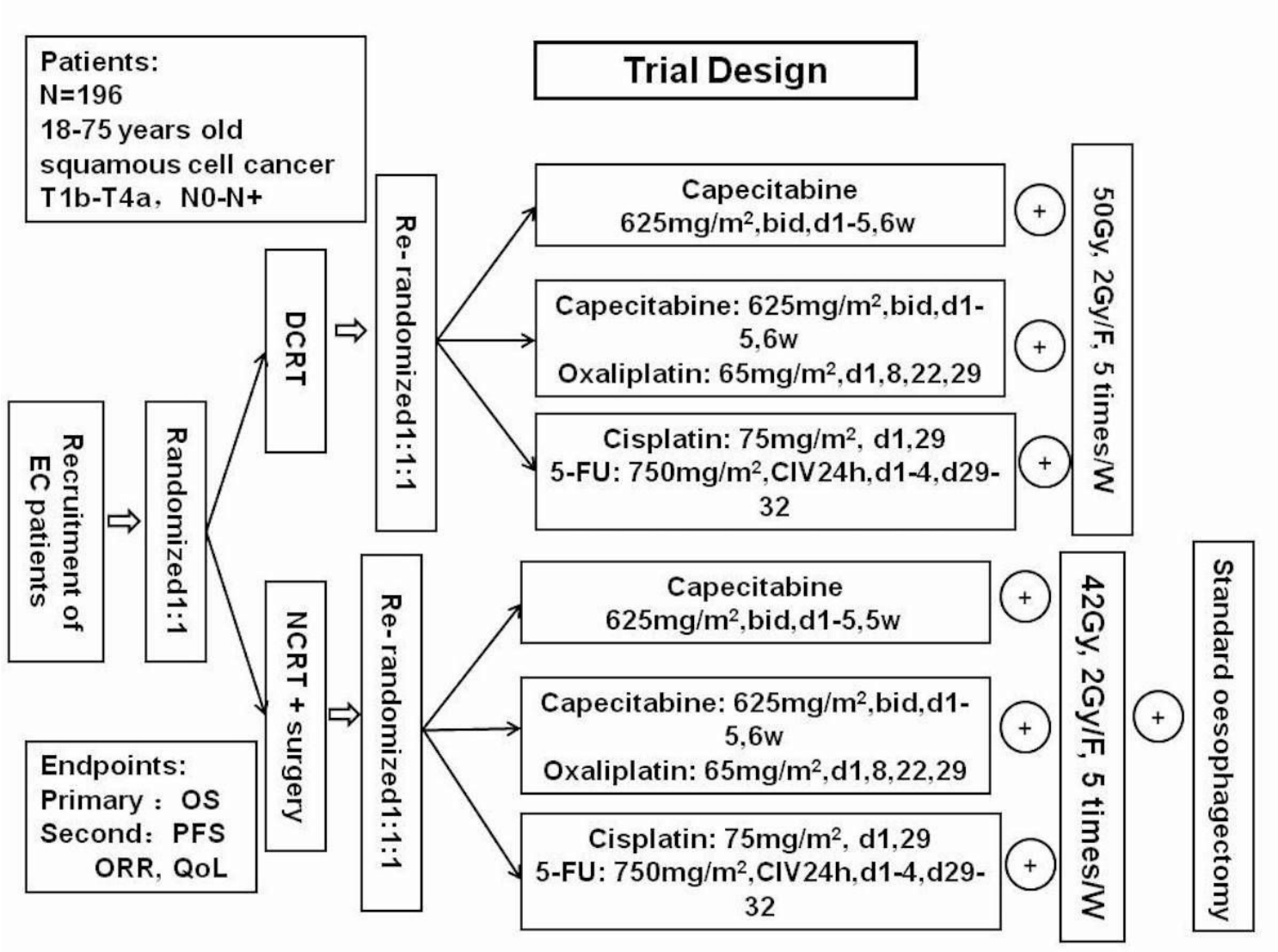

Figure 1

Flow chart of the trial

	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				Close-out
TIMEPOINT	$-t_1$	0	t_1	t_2	t_3	t_4 .	t_x
			CRT step1: d1-29	*CRT step 2: d29-35*	*Perioperative period week 8-12*	*Follow-up 16week*	*Follow-up 2/5 years*
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Baseline assessment	x						
Randomization		X					
INTERVENTIONS:							
Definitive concurrent chemoradiotherapy (DCRT)			←	→			
Neoadjuvant chemoradiotherapy (NCRT) + surgery			X		X		
ASSESSMENTS:							
Primary outcome: Overall survival (OS)			X	X	X	X	X
Secondary outcome : Progression-free Survival (PFS)			X	X	X	X	X
Treatment-related adverse events (TAEs)			X	X	X	X	
Quality of life (QoF)			X	X	X	X	X

Figure 2

Schedule of enrolment, interventions, and assessments

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.doc
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