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Prehabilitation is feasible in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy and may minimize physical deterioration: results from The REx trial

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Additional Information

Authors' Contributions.

SJM, ASA, NM, RJCS, SJEB, CBu and GM led the development and design of the study.

SJM and GM led the data collection.

CB and SJEB analysed the data.

SJM, SJEB, ASA and NM interpreted the data.

SJM, SJEB, NM, RJCS, GM, CBu and ASA led the drafting and final submission

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Conflicts of interests.

The authors declare no conflicts of interest.

Interim findings were presented as a poster abstract at ISBNPA, Edinburgh 2015.

What does this paper add to the literature?

This is the first study to show that performing prehabilitation in patients with rectal cancer undergoing neo-adjuvant chemoradiotherapy is feasible, safe and well tolerated by patients. With no reported interruption to each participant's planned clinical management, these findings support progression to a large powered multi-centred trial.

Abstract

Background. Rectal cancer patients undergoing NACRT (neo-adjuvant chemoradiotherapy) experience physical deterioration and reductions in their quality of life. This feasibility study assessed pre-habilitation (a walking intervention) before, during and after NACRT to inform a definitive multi-centred RCT (REx Trial) .

Methods. Patients planned for NACRT followed by potentially curative surgery were approached (August 2014 - March 2016) (www.isrctn.com; 62859294). Prior to NACRT, baseline physical and psycho-social data were recorded using validated tools.. Participants were randomised to either the intervention (exercise counselling session followed by 13-17 weeks telephone-guided walking programme) or control group (standard care). Follow-up testing was undertaken 1-2 weeks before surgery.

Results. Of 296 screened patients, 78(26%) were eligible and 48 (61%) were recruited. N=31 (65%) were male with a mean age 65.9 years (SEM ? rather than range? range 33.7-82.6). Mean intervention duration was 14 weeks with 75% adherence. n=40 (83%) completed follow-up testing. Both groups recorded reductions in daily walking but the reduction was less in the Intervention group although not statistically significant. Participants reported high satisfaction and fidelity to trial procedures.

Conclusion. This study demonstrates that prehabilitation is feasible in rectal cancer patients undergoing NACRT. Good recruitment, adherence, retention and patient satisfaction rates support the development of a fully powered trial. The effects of the intervention on physical outcomes were promising.

Introduction

Earlier diagnosis and advances in surgery and chemo-radiotherapy are improving long-term survival for rectal cancer [1]. Long-course neo-adjuvant chemoradiotherapy (NACRT) can down-stage locally advanced rectal cancer optimising the chance of an R0 resection or in the event of a complete response, removing the immediate need for major pelvic surgery [2,3,4,5]. However, 5-6 weeks of NACRT can be challenging. About 22% of patients experience severe acute side effects such as haematological toxicity, sepsis, enteritis, radiological dermatitis and cardiotoxicity [6]. These can lead to deteriorations in physical and social functioning, accompanied by increased levels of incontinence, embarrassment and fatigue that can persist for many months or years [7,8,9]. Whilst many patients have low levels of physical fitness prior to starting neo-adjuvant treatment, NACRT has the potential to make a patient physically vulnerable prior to undergoing surgery [10].

Patients approaching major surgery with poorer physical fitness (aerobic capacity, muscular strength, endurance, flexibility and body composition) are at greater risk of post-operative morbidity and mortality [11,12,13,14,15]. Prehabilitation, an intervention to enhance the functional capacity of the individual to enable him or her to withstand a stressful event, has become an evolving area of interest. Studies have been published which have assessed feasibility of such an intervention and influence on post-operative outcomes vary in their methodology and patient population[16,17,18]. However, arecent systematic review of 9 studies (435 patients) in (n=435) patients undergoing major abdominal surgery concluded that prehabilitation decreased the incidence of post-operative major complications (OR: 0.59, 95%CI: 0.38-0.91), especially pulmonary [19].

For rectal cancer patients, current standard care creates a minimum timeframe of 2 months from completion of NACRT to potential surgery and this provides a window for prehabilitation,

which is unavailable to patients going straight to surgery given the current local target of 31 days [20].

One non-randomised study of 39 patients reported a reduction in physical fitness [using cardiopulmonary exercise testing (CPET)] on completion of long-course NACRT. Only the intervention group who went on to receive three supervised aerobic sessions per week for six weeks, compared to the standard care control group, returned to baseline fitness levels raising the possibility that prehabilitation could minimise the anticipated NACRT decline. [17].

A Canadian study anticipated this decline and recruited 18 patients to undergo prehabilitation during and after NACRT [21]. This consisted of a supervised aerobic exercise programme (three sessions per weeks during NACRT) followed by an unsupervised programme (target of 150 minutes plus per week for 6-8 weeks after NACRT). There were no serious adverse events within the authors concluding that the next step should be a feasibility study.

The aim of our study was to assess the feasibility of performing a physical activity intervention prior to, during and after NACRT in patients with rectal cancer. The primary aim was to assess feasibility of delivering such an intervention with indicative outcomes also recorded to inform design of a definitive randomised controlled trial (RCT).

Methods

The study ran from August 2014 to March 2016 (20 months). Patients (age>18 years) presenting with a new diagnosis of rectal cancer in one NHS trust (Greater Glasgow and Clyde, GGC) between August 2014 and March 2015 were considered eligible for the REx Trial if they satisfied the following: a histological confirmation of adenocarcinoma; pre-operative MRI staging determined the tumour was margin-threatening and/ or anatomically low in the pelvis; CT of chest, abdomen and pelvis showed no evidence of metastatic disease and finally, MDT recommendation for long-course neo-adjuvant chemo-radiotherapy (NACRT) followed by potentially curative surgery. Patients were excluded for the following: metastatic disease; their mobility prevented them from performing a walking intervention; they were already achieving their recommended government guidelines for physical activity per week (using The Scottish Physical Activity Screening Questionnaire)[22] or they had any physical, mental or psychological impairment that prevented signed informed consent.

The trial was approved by the West of Scotland Research Ethics Service (14/WS/0079) and registered with ISRCTN (www.isrctn.com; 62859294; 17th March 2014). The trial was reported using the CONSORT 2010 Guidelines [23]. This study was funded by the Chief Scientist Office (CZH/4/986). www.cso.scot.nhs.uk

Trial Design. This was a two-arm randomised controlled feasibility study (RCT). Potentially eligible patients were screened by the trial team and then approached by the patient's colorectal cancer nurse specialist at the time of one of their surgical or oncological consultations. The study co-ordinator then followed up interested participants by telephone and scheduled for consent and baseline testing. Informed written consent was taken by participating colorectal surgeons.

Primary Outcomes. The primary outcomes were feasibility and acceptability of the research procedures, as assessed by eligibility and recruitment rates (including reasons for non-

participation), participant acceptability of randomisation, data collection and physical intervention and rates of retention and adherence to the physical activity intervention. Acceptability of randomisation was estimated from the percentage of participants attending baseline measurements who gave informed consent to take part in the feasibility trial. The number of telephone calls planned and subsequently received by each participant in the intervention group during the physical activity intervention measured adherence to the intervention. Trial satisfaction was assessed by asking each participant how much they were in agreement with the following 4 questions using a Likert scale from 1 (not at all in agreement) to 5 (very much in agreement): how satisfied were you with the REx Trial, how convenient did you find coming up to the hospital for trial appointments, how easy did you find the pedometer to use (intervention group only) and how likely would you be to recommend the REx trial to other people with rectal cancer?

At the weekly telephone call to each participant in the intervention group, the research assistant was asked to grade the fidelity of the intervention using a Likert score (1- poor to 5 – high). Any protocol deviations were recorded.

Secondary Outcomes. The primary efficacy outcome was median step count per day. Other secondary outcomes included physical, psychological and peri-operative variables. All outcomes were assessed at baseline testing pre-intervention (Baseline Test 1 prior to undergoing NACRT) and repeated post-intervention (1-2 weeks pre-surgery, Test 2) with peri-operative variables collected within the first few weeks after surgery [Figure 1].

In addition to demographic and clinico-pathological characteristics the following physical measurements were taken: weight, height, hip and waist circumference, sit-to-stand test and 6 minute walking test (6MWT). Waist circumference was measured with a measuring tape, with

participants in the standing position and the tape positioned midway between the lateral lower rib margin and the iliac crest [24]. If these landmarks could not be identified, the measurement was taken at the level of the umbilicus. Hip measurement was taken around the widest portion of the buttocks. Both measurements were taken twice. Weight and height allowed calculation of Body Mass Index (BMI): weight (kg)/[height $(m)^2$]. Sit-to-stand test was administered over 30 seconds, during which each participant crossed their arms and moved from sitting to full standing position (body straight). This was repeated as many times as possible during the timeframe to allow assessment of functional lower extremity strength that has been validated in many groups, especially older adults [25]. The 6MWT is an objective measurement of functional exercise capacity that in addition to being safe in a variety of populations, has shown good correlation with 12 minute walk test and cycle ergometer and treadmill exercise tests [26,27]. A flat, indoor surface was selected with markers placed 12.5m apart. Participants were then requested to walk as far as they could in the 6 minutes with the final distance (m) being recorded.

At the end of the baseline testing each participant was instructed on how to use the accelerometer to record data for 3-5 days. The activPAL (activPAL3, PAL Technologies, Glasgow, UK) is a small (53 x 35 x 7mm) lightweight (15g) triaxial accelerometer that was gently placed over their anterior thigh with an adhesive dressing, allowed anonymous data collection. Data were uploaded using the activPAL software fora sedentary time, active time and average steps walked per day.. Mean daily step counts were categorised as follows: sedentary (<5000steps/day); mildly active (5000-6999); moderately active (7000- 10999) and very active (≥11000 steps) [28]. Each participant repeated this after Test 2.

Questionnaires. Each participant completed the following at pre-NACRT and post-NACRT testing: Becks Depression Inventory (BDI-II), FACT-C, PANAS, EORTC-QLQ CR29 and C30. The existence and severity of symptoms of depression was measured using BDI-II [29]. A total of 21

items are summed to give a single point score: 0-13 normal or minimal depression; 14-19 mild; 20-28 moderate and 29-63 severe. Colorectal cancer specific quality of life was measured using the Functional Assessment of Cancer Therapy – Colorectal (FACT-C). This includes 27 items from the FACT-General (FACT-G) and adds in 11 items specific to colorectal cancer, with a higher score indicating a better quality of life and a change of at least 2 being stated as clinically relevant [30]. The Positive and Negative Affect Schedule (PANAS) is a 20-item self-reported measure of two scales, one to measure positive affect (where higher scores represent higher levels of positive affect) and the other, negative affect (where lower levels represent lower levels of negative affect) [32]. EORTC QLQ-C30 is the widely used and validated quality of life questionnaire for all cancer patients by the European Organisation for Research and Treatment of Cancer. It comprises nine multi-item scales and six single item scales. EORTC QLQ-C29 specifically assesses quality of life in colorectal cancer patients and was administered alongside the C-30 [32].

Randomisation. Participants were randomised 1:1 to either the physical intervention or control group (standard care) using block size 4 and no stratification. Randomisation was performed using an interactive voice response (IVR) telephone system provided by the Robertson Centre for Biostatistics. After each participant had completed pre-NACRT testing, the research assistant received the group allocation via the IVR system and provided it to the participant. The testers were blinded to the group allocation throughout as were their surgeons, nurse specialists and hospital staff involved in their care.

Physical Activity Intervention. Participants randomized to the intervention group had an initial face-to-face consultation with the study co-ordinator who had been trained in the application of two behavioural theoretical frameworks: self-regulatory theory (providing techniques to

improve impulse control allowing walking targets to be reached) and the health action process approach (replacing behaviours that compromise health with those that enhance health) [33,34].

The walking programme started prior to NACRT and was of minimum 13 weeks duration: 5 weeks of NACRT followed by minimal time interval of 8 weeks prior to surgery determined by individual surgeon's usual practice. The programme was based on targeted stepping counts: the first 8 weeks consisted of graduated goals calculated from the baseline stepping count (identified from the pre-NACRT accelerometer result) with that behaviour then maintained or increased over the remaining weeks up to surgery. Each participant was given a weekly walking diary (targets and motivational material included) and the use of the pedometer explained. Participants then received follow-up telephone calls (weeks 1,3,5,7,9,12,16) where new stepping targets were set, motivational techniques applied and any issues discussed. All participants were asked to engage a support person (e.g. spouse) to assist in their adherence with the programme.

The target was for the participants to increase their average daily step count by 3000 accumulated above their baseline value which is a protocol that has been used successfully by this research team before and other researchers [28,35,36,37,38]. This is based on the assumption that an adult walking at a moderate pace produces 100 steps/ minute. Therefore an increase of 3000 steps in one day is equal to 30 minutes extra activity that if performed on five days of the week would correspond to approximately 150 minutes of moderate physical activity over the course of the week which is the recommended physical activity level for adults in Scotland [22].

Below is an example:

Weeks 1-2: extra 1500 steps on at least 3 days a week.

Weeks 3-4: extra 1500 steps on at least 5 days a week.

Weeks 5-6: extra 3000 steps on at least 3 days a week.

Weeks 7-8: extra 3000 steps on at least 5 days a week.

Weeks 9-17: maintenance of weeks 7-8 or individually increased.

Control Group. The control group received standard care with no contact from the trial team except at the two test sessions. When informed of their allocation to the control group, they were told to maintain their normal level of physical activity. They were offered a voluntary exercise counselling session and information pack from the trial team after their surgery and on completion of the trial.

Neo-Adjuvant Chemoradiotherapy (NACRT). Radiotherapy dose was standardised at 4500 cGY in 25 fractions on weekdays only accompanied by oral Capecitabine 900mg/ m^2 bd on the same days or 5FU 350 mg/m2 iv on weeks 1 and 5.

Peri-operative Outcome Variables. For each participant that underwent surgery the following were recorded: length of hospital stay; surgery type; number of post-operative complications [39]. In addition, pathology of the resected specimen was recorded.

Sample Size. This was a phase 1 feasibility study to test practical aspects of the study design and to help inform the calculation of effect sizes for a subsequent definitive fully powered RCT. From The West of Scotland Colorectal Cancer Managed Clinical Network 2013 - 2014 data, approximately one hundred patients per year were deemed eligible for inclusion in this study. We estimated that we could recruit 80 patients during the planned 18-month trial recruitment period (40 intervention and 40 control), and this would provide sufficient data to determine feasibility.

Statistical Analysis. The main aim was to assess feasibility of intervention delivery to inform design of a main trial, thus the indicative outcomes are underpowered for statistical interpretation. Descriptive tables to summarise the feasibility measures by each group were performed, with means and standard deviations or medians and interquartile ranges (IQR) calculated for continuous variables, depending on whether or not they were normally distributed; and counts and percentages for categorical variables. Wilcoxon tests were used to compare satisfaction scores between study groups.

The most relevant physical outcome (measured average daily step count) was compared between groups using a linear regression model fitted to change from baseline, adjusting for the number of steps per day at baseline, age and gender, and presented as a mean estimate of the group difference with a corresponding 95% confidence interval. Study group comparisons of change from baseline in other physical and psychological outcome measures were carried out using two-sample t-tests and within-group comparisons for all measures of within-patient change from baseline to follow-up using paired t-tests, and both were presented as mean estimates and corresponding 95% confidence intervals. The EORTC-C29 embarrassment measure was compared from baseline to follow-up within groups using multinomial tests, and change from baseline between groups was assessed using a Fisher's exact test.

All statistical analysis was undertaken using R for Windows version 3.4.1 or the SAS application software (version 9.3, SAS Institute Inc., Cary, NC, USA).

Results

Feasibility.

During the trial's timeframe a total of 296 patients were diagnosed with rectal cancer. 78 patients were put forward by their MDT for NACRT (26%) [Figure 1, Consort Diagram]. Screening showed that all 78 patients were eligible for the trial and were approached, with 48 patients attending for baseline testing and consent (recruitment rate 62%). The main reasons given for not participating were: 'too much going-on' and 'overwhelmed by diagnosis'. No patients were excluded for achieving the recommended government guidelines for physical activity per week.

All participants completed baseline testing and randomisation with 24 participants randomised to the intervention group [Table 1]. Median walking intervention duration of 14 weeks (IQR 13-17) was completed with 80% of planned telephone calls to the intervention group being achieved and 75% completing the intervention [Table 1].

Overall, a total of 8 participants did not complete the study: 6 from the intervention group and 2 controls (retention rate 83%). Two of the intervention group withdrew prior to starting the intervention and of the remaining 6 drop-outs, 4 were for medical reasons {Figure 1]. There were no serious adverse events reported and no treatment pathways were modified as a consequence of trial participation.

At the end of the trial, participants from both groups reported high levels of satisfaction with the trial and would recommend prehabilitation to other patients [Table 1]. Intervention fidelity assessments found an overall mean score of 4.0 (range 1-5) for the telephone-guided intervention. Deviations from the protocol included several attempts by the research assistant to contact participants on their telephone and modifying the weekly target step count depending on the participant's weekly clinical status.

Baseline Participant Characteristics.

Participants had a mean age of 65.9 years (range 33.7-82.6) and were: predominately male (65%) and of white ethnicity (96%) and all were educated to at least completion of secondary education. 38% of participants were from the two most deprived socioeconomic groups. Co-morbidities were present in 57%, with hypertension (present in 59% of those with co-morbidities) and arthritis (30%) most commonly recorded [Table 2].

Most (60%) participants currently or had previously smoked, 88% reported current alcohol consumption, 71% were overweight (BMI≥25) with 19% obese (≥30). The majority of participants (90%) stated they could complete a flight of stairs without stopping; however, on average were only active for 1.6 hours a day (6.6% of their week). The mean number of steps per day of all participants was 7392 (range 1151 to 17422) with 54% classified as sedentary or only slightly active [Table 3]. In relation to psychological testing, participants did not report being depressed [BDI mean score 7.2 (6.6)] and had a reasonable quality of life although fatigue and embarrassment were commonly reported [Table 3].

Follow-up Testing.

Results from follow-up testing are displayed in Table 4. For the primary efficacy outcome (mean of the median daily step count), both groups recorded a reduction in step count: the intervention group dropped by a mean of 1105 steps (15% reduction from baseline), whilst the control group reported a greater drop of 1853 steps (24% reduction from baseline) [Figure 2]. This difference between groups in change from baseline of 785 [95% CI -1194,2765] was not significant (adjusted for baseline median daily step count, age and gender).

A higher percentage of the intervention group achieved step count improvements at 12 weeks (23.5 versus 15.8%). The intervention group also documented a non-significant mean increase of

13.7m in their 6MWT scores, while the control group showed a mean 54.8m reduction, which resulted in a non-significant between-group difference of 68.5m (95% CI [-27.2,164.2]).

There were no statistically significant changes within and between groups in relation to any of the psychological questionnaires.

Peri-operative Outcome Variables.

Table 5 describes the clinico-pathological factors in all participants finding the majority successfully completed NACRT (98%). Most participants (36 out of 40) underwent surgery with 33 being of curative intent, 2 local excision due to poor fitness and 1 had a defunctioning stoma performed. Of the 4 patients that did not undergo surgery, 3 had progressive disease on their post-NACRT imaging with the other participant having a complete response to NACRT on follow-up imaging.

The majority of surgery was performed electively (97%), by an open approach (72%) with a permanent end-colostomy formed in 61%. All grades of post-operative complications were recorded in 67% of cases with T3 N0 being the most commonly recorded pathological TNM staging. The tumour was completely resected (R0) in 86% of surgical procedures.

Discussion

This is the first RCT to assess the feasibility of performing a walking intervention (prehabilitation) in patients with rectal cancer undergoing NACRT and with good recruitment, good retention and high participant satisfaction with trial procedures, all without compromise to the planned treatment pathway, these results support proceeding to a future definitive multi-centred RCT.

The demographics of the participants shows that performing a walking intervention is feasible in groups that can be considered challenging in both recruitment and adherence; older adults (40% were over 70), those with high levels of socioeconomic deprivation (38%) and in patients with co-morbidities, including potentially activity limiting conditions, such as arthritis. Furthermore many participants reported smoking, alcohol consumption and being overweight, in addition to high levels of sedentary behaviour. Many of these factors either by themselves or in combination are traditionally associated with a patient potentially being labelled as 'high risk' for treatment morbidity and mortality, a statement that is supported by the reported complication rate of 67% in this study. Indeed, previous work has found that such patients account for 85% of peri-operative complications making them a key area to target. Despite this many prehabilitation protocols have excluded such patients [40]. One recently published RCT supports our findings by recruiting only high-risk patients going straight to major abdominal surgery. This study defined "high-risk" as age > 70 years and/ or American Society of Anaesthesiologists score III/ IV [41]. With a mean intervention time of 6 weeks to perform a multimodal prehabilitation programme (lifestyle counseling, nutrition assessment, iron therapy as appropriate accompanied by a physical activity programme), the authors reported that 54 out of 73 completed the intervention (73%) without any serious adverse events. In addition, these authors found a significant reduction in post-operative complications in the prehabilitation group compared to the usual care controls (31% versus 62%; p=0.001).

These results suggest that not only is prehabilitation feasible in high-risk patients, but that their risk of complications can be modified.

The reduction in daily step counts of the participants confirms the previously reported negative effect that NACRT has on physical function in patients with rectal cancer [17]. Instituting a walking intervention is a proactive approach that may offset this decline and this is supported by the intervention group step count results from this study. However, a definitive trial needs be powered for daily step count as its primary aim. Consideration must be given to delivering the optimal intervention that leads to the majority of participants in the intervention group achieving improved step counts. Individualized walking programmes have achieved success in older adults and over a shorter time frames than in this study highlighting that there is no obvious reason why this patient population cannot achieve similar targets [35,36,37,42]. Previous focus group work has mentioned the role of an exercise counselor and how increased contact time (either by phone or face to face) could increase motivation and adherence to step targets. The role of motivational feedback also needs to be established as does the exact timing of treatment and testing after, including immediately upon completion of NACRT. Specific strategies for dealing with patient reported fatigue need to be identified as this was a commonly reported barrier to patients undergoing prehabilitation. Consideration must also be given to educating all the health professionals that are involved in each patient's care to ensure that each participant is encouraged through their prehabilitation as they would be in all aspects of their treatment. This need for both health care professional and patient education is suggested by the two main refusal reasons for participation in this study: 'too much going-on' and 'overwhelmed by diagnosis'.

Colorectal nurse specialists performed the initial approach and, at the outset, many were unaware or uncertain about the definition of prehabilitation and its potential role whilst undergoing treatment and its influence on long-term cancer related outcomes [43,44,45]. With

education through face-to-face meetings and invited presentations at colorectal nurse meetings, in addition to their own patients' feedback, a culture change occurred. With nurse specialists documented as a preferred source of information for cancer patients, consideration to education for these specialists should be integrated in the future trial protocol [46].

Limitations.

The authors acknowledge limitations of this predominately single-centred feasibility study. Selection bias cannot be excluded because motivated patients are more likely to participate in prehabilitation . Furthermore, adherence to the walking intervention was self-reported and future work could consider including objective measures to monitor. In addition, the target of 80 patients was not achieved in this feasibility trial, primarily because the total number of rectal cancer patients suitable for NACRT had declined slightly from the previous year reflecting the natural diagnostic variation that could potentially be overcome with a large multi-centred trial. In addition, with the interest in defining 'complete responders' to NACRT (no residual disease on post-NACRT imaging), it is entirely possible that in the coming years, the number of patients being referred for NACRT will increase due to early rectal cancers (stages I or II) also being considered for NACRT.

Conclusion.

This is the first RCT to assess the feasibility of performing a walking intervention (prehabilitation) in rectal cancer patients undergoing NACRT followed by potentially curative surgery. In addition to integrating around the multi-modal and sometimes rapidly changing treatment pathway, prehabilitation was found to be feasible in a predominately inactive, co-morbid, older adult population. With good recruitment, adherence and retention rates and the possibility of reducing the physical deterioration of NACRT, these results support the

development of a fully powered trial to investigate the influence of prehabilitation on optimising physical function and patient related outcomes.

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Table 1: Feasibility outcomes in the REx Trial: Subject Participation and satisfaction scores.

Participation		
All Participants		
Recruited		48
Screening visit and Test 1 completed		48 (100%)
Randomisation visit completed		48 (100%)
Test 2 completed		40 (83%)
Intervention group (n=24)		
Diary and walking intervention completed		18 (75%)
Number of completed intervention weeks	Median (IQR)	14 (13-17)
	Range	0-17
Total number of Telephone calls	Planned	116
	Performed	93 (80%)
No of telephone calls per participant	Median (IWR)	5(4-6)
	Range	1-6

Satisfaction Scores	**ALL**	**Intervention**	**Control**	
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**P value**
How satisfied were you with The REx Trial	5.0 (4.0-5.0)	5.0 (5.0-5.0)	4.5 (4.0-5.0)	0.019
How convenient did you find coming up to the hospital for trial appointments?	4.0 (4.0–5.0)	4.0 (4.0-5.0)	4.0 (3.0-5.0)	0.120
For the intervention group: How easy did you find the pedometer to use?	5.0 (5.0-5.0)	5.0 (5.0-5.0)		
How likely would you be to recommend The REx Trial to other people with a diagnosis of rectal cancer	5.0 (4.0–5.0)	5.0 (4.0–5.0)	5 (4.0.5.0)	0.230

*****_Scored using Likert scale from 1 (not at all in agreement) to 5 (very much in agreement)._

Table 2: Comparison of Demographics, Co-morbidities and Lifestyle Factors of Participants with Rectal Cancer recruited to the REx Trial: Intervention group versus Control group.

	Statistic	All (N = 48)	Intervention (N = 24)	Control (N = 24)
Age (years)	N_{obs} (N_{miss})	46 (2)	24 (0)	22 (2)
	Mean (SD)	65.9 (10.5)	65.2 (11.4)	66.5 (9.6)
Sex	N_{obs} (N_{miss})	48 (0)	24 (0)	24 (0)
Male	N (%)	31 (65%)	18 (75%)	13 (54%)
Female	N (%)	17 (35%)	6 (25%)	11 (46%)
Ethnicity	N_{obs} (N_{miss})	48 (0)	24 (0)	24 (0)
White	N (%)	46 (96%)	22 (92%)	24 (100%)
Asian, Asian Scottish or Asian British	N (%)	1 (2%)	1 (4%)	0 (0%)
African	N (%)	1 (2%)	1 (4%)	0 (0%)
Education level	N_{obs} (N_{miss})	44 (4)	20 (4)	24 (0)
Secondary Education	N (%)	21 (48%)	11 (55%)	10 (42%)
Higher/Further Education	N (%)	19 (43%)	8 (40%)	11 (46%)
Other	N (%)	4 (9%)	1 (5%)	3 (12%)
SIMD	N_{obs} (N_{miss})	47 (1)	23 (1)	24 (0)
1 (most deprived)	N (%)	9 (19%)	4 (17%)	5 (21%)
2	N (%)	9 (19%)	6 (26%)	3 (12%)
3	N (%)	13 (28%)	7 (30%)	6 (25%)
4	N (%)	10 (21%)	4 (17%)	6 (25%)
5 (least deprived)	N (%)	6 (13%)	2 (9%)	4 (17%)
ASA	N_{obs} (N_{miss})	47 (1)	23 (1)	24 (0)
1	N (%)	0 (0%)	0 (0%)	0 (0%)
2	N (%)	32 (68%)	18 (78%)	14 (58%)
3	N (%)	15 (32%)	5 (22%)	10 (42%)
4	N (%)	0 (0%)	0 (0%)	0 (0%)
5	N (%)	0 (0%)	0 (0%)	0 (0%)
Co-morbidities	N_{obs} (N_{miss})	47 (1)	24 (0)	23 (1)
No	N (%)	20 (43%)	12 (50%)	8 (35%)
Yes	N (%)	27 (57%)	12 (50%)	15 (65%)
Diabetes	N_{obs} (N_{miss})	27 (0)	12 (0)	15 (0)
No	N (%)	25 (93%)	10 (83%)	15 (100%)
Yes	N (%)	2 (7%)	2 (17%)	0 (0%)
BMI	N_{obs} (N_{miss})	48 (0)	24 (0)	24 (0)
<20	N (%)	2 (4%)	2 (8%)	0 (0%)
20-24.9	N (%)	12 (25%)	8 (33%)	4 (17%)
25-29.9	N (%)	25 (52%)	12 (50%)	13 (54%)
30-34.9	N (%)	8 (17%)	2 (8%)	6 (25%)
35+	N (%)	1 (2%)	0 (0%)	1 (4%)
Hypertension	N_{obs} (N_{miss})	27 (0)	12 (0)	15 (0)
No	N (%)	11 (41%)	5 (42%)	6 (40%)
Yes	N (%)	16 (59%)	7 (58%)	9 (60%)
COPD	N_{obs} (N_{miss})	27 (0)	12 (0)	15 (0)
No	N (%)	25 (93%)	11 (92%)	14 (93%)
Yes	N (%)	2 (7%)	1 (8%)	1 (7%)
MI	N_{obs} (N_{miss})	27 (0)	12 (0)	15 (0)
No	N (%)	24 (89%)	10 (83%)	14 (93%)
Yes	N (%)	3 (11%)	2 (17%)	1 (7%)
CVA	N_{obs} (N_{miss})	27 (0)	12 (0)	15 (0)
No	N (%)	26 (96%)	11 (92%)	15 (100%)
Yes	N (%)	1 (4%)	1 (8%)	0 (0%)
Arthritis	N_{obs} (N_{miss})	27 (0)	12 (0)	15 (0)
No	N (%)	19 (70%)	9 (75%)	10 (67%)
Yes	N (%)	8 (30%)	3 (25%)	5 (33%)
Other co-morbidities	N_{obs} (N_{miss})	27 (0)	12 (0)	15 (0)
No	N (%)	22 (81%)	10 (83%)	12 (80%)
Yes	N (%)	5 (19%)	2 (17%)	3 (20%)
Weight (kg)	N_{obs} (N_{miss})	48 (0)	24 (0)	24 (0)
	Mean (SD)	76.2 (11.4)	75.4 (13.4)	77.0 (9.1)
Smoking	N_{obs} (N_{miss})	48 (0)	24 (0)	24 (0)
Current	N (%)	7 (15%)	4 (17%)	3 (12%)
Ex (<12 months)	N (%)	10 (21%)	7 (29%)	3 (12%)
Ex (>=12 months)	N (%)	12 (25%)	4 (17%)	8 (33%)
Never smoked	N (%)	19 (40%)	9 (38%)	10 (42%)
Alcohol consumption	Nobs (Nmiss)	48 (0)	24 (0)	24 (0)
Excess	N (%)	4 (8%)	1 (4%)	3 (12%)
Previous excess	N (%)	4 (8%)	2 (8%)	2 (8%)
Within limits	N (%)	34 (71%)	18 (75%)	16 (67%)
None	N (%)	6 (12%)	3 (12%)	3 (12%)
Physical activity: Climb flight of stairs:-	Nobs (Nmiss)	48 (0)	24 (0)	24 (0)
Unable	N (%)	2 (4%)	0 (0%)	2 (8%)
With stopping	N (%)	3 (6%)	2 (8%)	1 (4%)
Without stopping	N (%)	43 (90%)	22 (92%)	21 (88%)

Table 3: Comparison of Baseline Physical and Psychological Measurements of REx Trial Participants: Intervention group versus Control group.

		All (N = 48)	Intervention (N = 24)	Control (N = 24)
Median steps per day	N_{obs} (N_{miss})	46 (2)	23 (1)	23 (1)
	Mean (SD)	7392 (3765)	7162 (3193)	7623 (3684)
	Range	1152, 17422	1526, 17422	1152, 16472
Sedentary	N (%)	12 (26.1%)	8 (34.8%)	4 (17.4%)
Slightly active	N (%)	13 (28.3%)	5 (21.7%)	8 (34.8%)
Moderately active	N (%)	17 (37.0%)	8 (34.8%)	9 (39.1%)
Very active	N (%)	4 (8.7%)	2 (8.7%)	2 (8.7%)
Waist circumference (cm)	N_{obs} (N_{miss})	48 (0)	24 (0)	24 (0)
	Mean (SD)	96.1 (9.4)	95.3 (11.1)	96.9 (7.6)
Sit-to-stand test (no. in 30 secs)	N_{obs} (N_{miss})	48 (0)	24 (0)	24 (0)
	Mean (SD)	11.3 (3.0)	11.3 (3.1)	11.4 (3.0)
6 minute walking tests (m)	N_{obs} (N_{miss})	48 (0)	24 (0)	24 (0)
	Mean (SD)	436.2 (79.2)	435.7 (91.7)	436.7 (66.4)
% of week spent active	N_{obs} (N_{miss})	46 (2)	23 (1)	23 (1)
	Mean (SD)	6.6 (2.8)	6.5 (2.8)	6.7 (2.9)
% of week spent sedentary	N_{obs} (N_{miss})	46 (2)	23 (1)	23 (1)
	Mean (SD)	76.4 (12.1)	77.9 (7.3)	74.9 (15.6)
EORTC-C30 Fatigue*	N_{obs} (N_{miss})	46 (2)	23 (1)	23 (1)
	Mean (SD)	23.9 (22.3)	27.5 (23.4)	20.3 (21.1)
EORTC-C29 Embarrassment*	N_{obs} (N_{miss})	47 (1)	24 (0)	23 (1)
Not at all	N (%)	27 (57.4%)	14 (58.3%)	13 (56.5%)
A little	N (%)	11 (23.4%)	4 (16.7%)	7 (30.4%)
Quite a bit	N (%)	1 (2.1%)	1 (4.2%)	0 (0.0%)
Very much	N (%)	8 (17.0%)	5 (20.8%)	3 (13.0%)
PANAS				
Positive affect score	N_{obs} (N_{miss})	47 (1)	24 (0)	23 (1)
	Mean (SD)	33.6 (9.9)	35.0 (11.5)	32.1 (7.9)
Negative affect score	N_{obs} (N_{miss})	47 (1)	24 (0)	23 (1)
	Mean (SD)	17.6 (7.0)	18.5 (7.4)	16.6 (6.5)
BDI-II	N_{obs} (N_{miss})	47 (1)	23 (1)	24 (0)
	Mean (SD)	7.2 (6.6)	7.9 (7.3)	6.5 (6.1)
Fact-C total score	N_{obs} (N_{miss})	47 (1)	24 (0)	23 (1)
	Mean (SD)	63.9 (10.9)	66.0 (8.6)	61.7 (12.8)

***** Selected results shown

Table 4: Comparison of Changes in Physical and Psychological Measurements between Intervention and Control groups (Test 2 versus baseline Test 1). * Primary efficacy outcome

** Adjusted for number of steps at baseline, age and gender.

		Intervention			Control			Group difference (Intervention – Control)
		N	Mean (SD)	Change from baseline (95% CI)	N	Mean (SD)	Change from baseline (95% CI)	Mean (95% CI)
Median steps per day*	**Baseline**	**17**	**7779 (4045)**	**-1105 (-2802, 593)**	**19**	**7773 (3975)**		**785 (-1195, 2765)****
	12 week		**6675 (3100)**			**5920 (3152)**	**-1853 (-3871, 164)**	
Weight (kg)	Baseline	18	76.7 (10.1)	1.3 (-0.4, 3.0)	20	77.3 (7.8)		0.5 (-2.1, 3.1)
	12 week		78.0 (11.6)			78.2 (8.9)	0.8 (-1.2, 2.9)	
BMI	Baseline	18	26.5 (3.0)	0.3 (-0.2, 0.8)	20	28.0 (3.4)		0.2 (-0.6, 1.1)
	12 week		26.8 (3.4)			28.1 (3.3)	0.1 (-0.6, 0.8)	
Waist circumference (cm)	Baseline	18	96.0 (9.7)	-2.2 (-8.8, 4.4)	21	97.7 (7.4)		-4.4 (-11.3, 2.5)
	12 week		93.8 (17.9)			99.9 (7.7)	2.2 (-0.1, 4.5)	
Sit-to-stand test (no.completed in 30 secs)	Baseline	18	11.5 (2.5)	-0.4 (-2.2, 1.4)	22	11.5 (3.0)		-0.6 (-3.3, 2.2)
	12 week		11.1 (4.2)			11.7 (6.1)	0.1 (-2.1, 2.4)	
6 minute walking tests (m)	Baseline	18	448.8 (64.9)	13.7 (-50.1, 77.5)	22	444.9 (59.2)		68.5 (-27.2,164.2)
	12 week		462.5 (144.3)			390.1 (159.4)	-54.8 (-130.4, 20.7)	
% of week spent active	Baseline	17	6.6 (2.9)	-0.8 (-2.1, 0.4)	19	6.9 (3.1)		0.3 (-1.7, 2.2)
	12 week		5.8 (2.6)			5.8 (2.3)	-1.1 (-2.7, 0.5)	
% of week spent sedentary	Baseline	17	76.0 (5.3)	0.4 (-2.8, 3.6)	19	74.8 (17.2)		-2.7 (-13.2, 7.9)
	12 week		76.4 (7.6)			77.9 (7.6)	3.1 (-7.1,13.3)	
EORTC-C30 Fatigue	Baseline	17	28.1 (23.6)	0.7 (-13.7, 15.0)	20	18.3 (19.8)		-6.6 (-21.7, 8.5)
	12 week		28.8 (23.9)			25.6 (16.9)	7.2 (1.8,12.6)	
Positive affect score	Baseline	18	36.2 (11.1)	-3.7 (-10.2, 2.9)	20	33.0 (8.0)		-3.7 (-11.5, 4.2)
	12 week		32.5 (7.4)			33.0 (8.0)	0.0 (-4.7, 4.7)	
Negative affect score	Baseline	18	18.9 (7.8)	1.1 (-2.0, 4.2)	20	16.1 (5.9)		1.5 (-2.8, 5.8)
	12 week		20.0 (8.3)			15.7 (6.5)	-0.4 (-3.7, 2.8)	
BDI-II	Baseline	15	7.3 (5.9)	0.7 (-1.7, 3.2)	22	5.5 (4.4)		-0.7 (-3.8, 2.5)
	12 week		8.1 (6.9)			7.0 (5.2)	1.4 (-0.7, 3.5)	
Fact-C total score	Baseline	18	66.7 (8.9)	-0.2 (-6.3, 6.0)	21	60.5 (12.7)		0.9 (-6.2, 8.0)
	12 week		66.5 (13.5)			59.4 (11.2)	-1.1 (-5.1, 2.9)	

Table 5: Comparison of Clinico-Pathological Factors in Participants with Rectal Cancer recruited to the REx Trial: Intervention group versus Control group (patients who completed test 2 only).

		All Participants N=40	Intervention N=18	Control N=22
NACRT	Started N (%)	40 (100%)	18 (100%)	22 (100%)
	Completed Yes: No	39 (98%)	18 (100%)	21 (95%)
Surgery	Yes: No	36 (90%)	17 (94%)	19 (86%)
	Elective *	35 (97%)	16 (94%)	19 (100%)
	Laparoscopic/ lap assisted:	6 (17%):	3 (18%):	3 (16%):
	lap-open : open	4 (11%): 26 (72%)	3(18%): 11 (65%)	1 (5%): 15 (79%)
Type of Surgery N (%)	Anterior Resection/ Hartmann's procedure	18 (50%)	10 (59%)	8 (42%)
	APR	15 (42%)	6 (35%)	9 (47%)
	Local Excision/ TAMIS	2 (6%)	0	2 (11%)
	Palliative stoma formation	1 (3%)	1 (6%)	0
Stoma formed	Yes: no	33:3	17:0	16:3
	Permanent: temporary	20: 13	8: 9	12:4
Complications	N (%)	24 (60%)	12 (67%)	12 (55%)
Length of stay (days)	Median (range)	10.5 (0.0 -38.2)	11.0 (6.0-37.0)	10 (0.0-38.2)
TNM Staging (post-op)**	T0	8 (23%)	4 (22%)	4 (18%)
	T1	3 (9%)	1 (6%)	2 (9%)
	T2	7 (20%)	1 (6%)	6 (27%)
	T3	16 (46%)	10 (56%)	9 (41%)
	T4	1 (3%)	0 (0%)	1 (5%)
	N0¶	20 (61%)	10 (56%)	10 (45%)
	N1	11 (33%)	5 (28%)	6 (27%)
	N2	2 (6%%)	1 (6%)	1 (5%)
No. of Lymph Nodes	Median (range)	13.0 (0-43)	17 (4.0-43.0)	13 (0.0-27.)
CRM clear¶	Yes: No	30: 3	15: 2	16: 1
R0 Resection **	Yes: No	30: 5	13: 3	17: 2

* n=1 obstruction, perforation

** n=1 no pathology resected, defunctioning stoma only; percentage expressed out of total of 35 operations.

¶ n=2 local excision where no nodal resection performed; percentage expressed out of a total of 33 operations.

Figure 1: The REx Trial Consort Diagram.

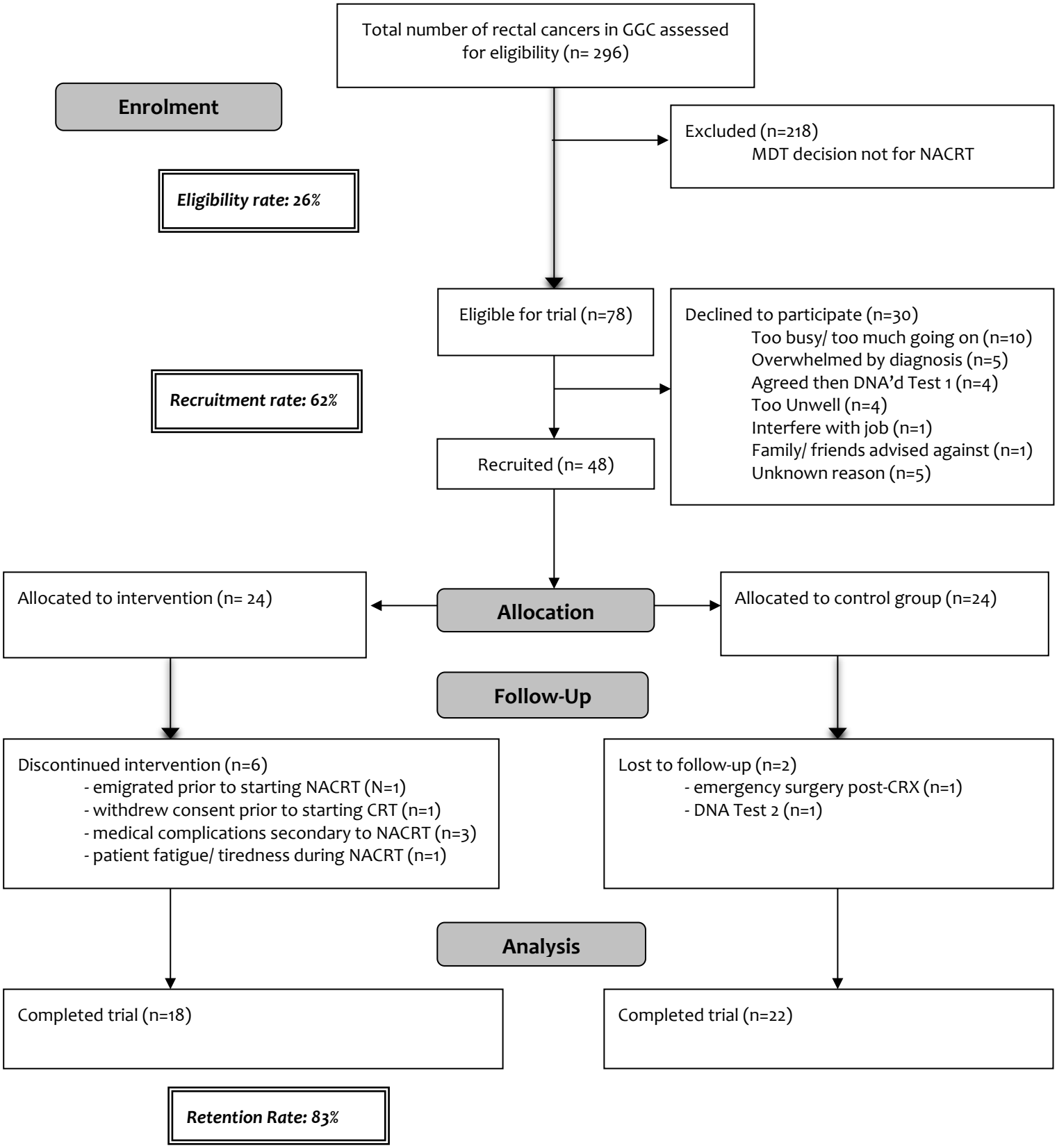

Figure 2: Comparison of change in daily step count after intervention between Intervention and Control groups.