HOTII

Randomised double-blind controlled phase III trial of hyperbaric oxygen therapy in patients suffering long-term adverse effects of radiotherapy for pelvic cancer

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HOT II Clinical Study Report – **full version 4.4**

27/10/2015

Based on data snapshot taken 20/06/2014

NOT FOR CITATION

**Document history**

| Version | Date | Changes made |
|---|---|---|
| 1.0 | 05/11/2013 | First short version of report created to circulate data to TMG prior to submission of ESTRO 2014 abstract |
| 2.0 | 21/03/2013 | Second short version of the report to circulate data to TMG prior to preparation of SPUMS 2014 abstract |
| 3.0 | 06/05/2014 | Update to results in short version of the report following corrections made to data. For preparation of SPUMS presentation. |
| 3.1 | 08/05/2014 | Correction to table 6 & A3.3 and inclusion of exploratory analysis for presentation at SPUMS as requested by CI. |
| 4 | | First full draft of report, including updates to tables included in previous versions and further analyses of secondary and exploratory endpoints. |
| 4.1 | 12/08/2014 | Updated report including data returned as a result of data queries. |
| 4.2 | 26/09/2014 | Minor updates following review by Emma Hall, Deputy Director, ICR-CTSU |
| 4.3 | 16/10/2015 | Minor updates to correct typographical errors. Inclusion of additional analysis for manuscript |
| 4.4 | 26/10/2015 | Line listings removed to ensure anonymity in preparation for publication online |

## Scope of report

### Content

This report contains the principal analysis of the primary and secondary endpoints of the HOT II trial as well as sensitivity analyses, subgroup analyses, other exploratory analyses and analysis of quality of life questionnaires.

### Author

Lauren Maynard, the trial statistician, performed the analyses and prepared this report.

### Purpose

The purpose of this report is to provide results for the principal analysis for publication.

### Data status

The data snapshot used was taken on the 20th June 2014. All data received to this date are included in the analysis; any outstanding data queries are summarised within the report.

### Data checking

Data checks performed are summarised in the report. The data represent the best knowledge of the trial team at the time of analysis.

### Validation of statistical analysis

Principal analysis of the primary endpoint was repeated by a second ICR-CTSU statistician for validation.

### Statistical analysis plan

This analysis report is based on version 4.0 of the HOT II statistical analysis plan (SAP). Any deviations from the SAP are described in section 12.

Contents

## Trial summary

**Title:** Randomised double-blind controlled phase III trial of hyperbaric oxygen therapy in patients suffering long-term adverse effects of radiotherapy for pelvic cancer.

**Trial design:** Randomised double-blind controlled phase III trial

**Aims:** To test the clinical benefits of hyperbaric oxygen therapy in reducing dysfunction in patients developing iatrogenic gastrointestinal symptoms as a result of previous radical pelvic radiotherapy for cancer, which was completed at least one year previously.

**Treatments:**

**Hyperbaric Oxygen Therapy group**

Patients were compressed to 2.4 ATA in a hyperbaric chamber and breathed 100% oxygen while at pressure following Royal Navy Therapeutic Table 66 (RNTT 66). The total time at 2.4 ATA was be 90 minutes. It was planned that participants would receive a total of 40 pressure exposures (five days per week for eight weeks).

**Control group**

Patients were compressed to 1.3 ATA in a hyperbaric chamber and breathed 21% oxygen (air) while at pressure. The total time at 1.3 ATA was be 90 minutes. It was planned that each participant would receive a total of 40 pressure exposures (five days per week for eight weeks).

**Endpoints:**

*Primary clinical endpoints*

i) Overall gastrointestinal symptoms score using the modified Inflammatory Bowel Disease Questionnaire (IBDQ), using a 3% significance level.

ii) Change in rectal IBDQ bleeding score between the two groups, using a 2% significance level.

*Secondary clinical endpoints*

i) Physician assessment of bowel dysfunction using Late Effects in Normal Tissues Subjective, Objective, Management and Analytic (LENT SOMA) scales of radiation injury.

ii) Patient self-assessments using European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and Defecation Problem Subscale of QLQ-CR38.

iii) Photographic images of rectal mucosa taken via flexible sigmoidoscopy.

iv) Physician assessment of rectal dysfunction based on the modified Common Terminology Criteria for Adverse Events (CTCAE) grading.

*Translational endpoints*

i) Rectal biopsies: Increase in blood vessel density will be investigated. This component of the research will use immunohistochemistry on tissue sections. Changes will also be investigated in proteins involved in extracellular matrix metabolism, including fibrogenic cytokines (e.g. CTGF, TGFβ1), collagen synthesis (e.g. PINP, PIIINP, prolyl-4-hydroxylase) and metalloproteinases (e.g. MMP-I).

**Randomisation:** Randomisation was by random permuted blocks. Stratification is by centre.

**Follow-up:** Clinical post-treatment assessments were performed at The Royal Marsden, London, within 14 days of completing the treatment and at 12 months after the start of hyperbaric oxygen (HBO) therapy. For patients unable to attend The Royal Marsden, assessments using the LENT SOMA and CTCAE forms were carried out by a Clinical Nurse Practitioner via a telephone interview. All patients were asked to complete self-assessment questionnaires, including Health Economics, IBDQ, EORTC QLQ-C30 and CR38, at 3, 6, 9, and 12 months after the start of HBO therapy (+ IBDQ only at 2 weeks after completion of HBO).

**Sample size:** 75

**Data collection:** Data management was undertaken by the trial coordinator, Mrs Grace Sharp, at the Royal Marsden, Sutton. The databases used for data entry and storage were Macro v3 and Macro v4 (upgrade). All analyses were conducted in Stata version 11 or subsequent versions.

**Primary endpoint analysis:** The primary endpoints have been analysed using all data completed within the timeframes specified.

# 1 Background

## 1.1 Sample size and power

The sample size was based on changes in the Modified Inflammatory Bowel Disease Questionnaire in patients who improved, remained stable or deteriorated after one month on therapy for chronic inflammatory bowel disease (Crohn's disease) [Hlavaty T, Persoons P, Vermeire S, Ferrante M, Pierik M, Van Assche G, Rutgeerts P. Evaluation of short-term responsiveness and cut off values of inflammatory bowel disease questionnaire in Crohn's disease. Inflamm Bowel Dis 2006;12(3):199-204.]. These mean ±SD changes were 15 ±10 (n=109), 3 ±7 (n=63), and -3 ±6 (n=8), respectively. We therefore used 10 as an estimate of the standard deviation of the change at 12 months, assuming it will be slightly higher than the difference seen at 1 month. Initially it was agreed that the minimum clinically worthwhile difference was 7, which is approximately half the difference between patients who improved and those who failed to improve in this series. The standardised difference was therefore 0.7, which required 75 patients randomized 2:1 for 80% power, two-sided 5% significance level. A substantial amendment in February 2012 saw the minimum clinically worthwhile difference increase to 7.5. At the IDMC on 19/09/2011 it was agreed that the P-value should be split to incorporate additional analyses of rectal bleeding score.

75 patients are needed to detect a difference of 7.5 with 80% power at the two-sided 3% significance level in the IBDQ bowel function endpoint. It is anticipated that approximately 40% patients will have grade 2-4 rectal bleeding (~30 patients). 30 patients will allow detection of an increase of 70% (from 10% in the control group to 80% in HBO group) showing a decrease in rectal bleeding grade with 80% power, at the 2% significance level.

## 1.2 Endpoints

The protocol states that the Modified Inflammatory Bowel Disease score is the first primary endpoint, the second primary endpoint is the IBDQ rectal bleeding score. Analysis will be carried out on an intention to treat basis. The average difference in change from baseline to 12 months in both trial arms will be compared using the Mann-Whitney U test, or unpaired t-test if the values are approximately normally distributed.

Changes in the Subjective descriptor LENT SOMA will be a secondary endpoint. Within each of three LENT SOMA descriptors (Subjective, Objective, Management), individual parameters are assessed on a 4-point scale. The EORTC and RTOG suggest that the descriptors can be used to develop a score for each normal tissue, by summing numerical scores of individual parameters. The aggregate Subjective parameter score will be used to reflect deterioration or improvement in the severity of late normal tissue effects, by an increase or decrease, respectively, in its aggregate score. There will be no formal statistical analysis of the other secondary endpoints but the descriptive nature of these results will be used to strengthen the interpretation of changes in the primary endpoint.

### 1.3 Randomisation

Patients were centrally randomised by telephone call to the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU). A 2:1 (HBO: Control) allocation ratio was used. Randomisation was stratified by centre and based on the random permuted blocks method (block sizes used were 9 and 12).

### 1.4 Data issues

**Data quality assurance**

The data on the Macro database was checked against paper CRFs for 100% primary endpoint data and any errors were corrected. A random selection of 20% patients was selected and a check of key fields on secondary endpoint forms completed. Key fields were also checked on the deviation and compliance forms of a random sample of 20 patients, in line with the HOT II central statistical data monitoring plan.

**Assumptions made in coding of data**

For patient reported outcomes, missing data are treated as missing. No imputation has been carried out, apart from in analyses of EORTC QLQ C30 and CR38 where EORTC guidelines[1] have been used to score each of the subscales. For clinician reported outcomes (LENTSOMA and CTCAE) where a form has been returned and a grade is missing this is assumed to be because this toxicity was not present.

### 1.5 Timelines

At the IDMC meeting held in September 2011, it was agreed that the following timelines should be adhered to;

- Questionnaires completed after 2 week assessment but before 4.5 months should be regarded as 3 month follow up
- Questionnaires completed from 4.5 to 7.49 months should be regarded as 6 month follow up
- Questionnaires completed between 7.5 and 10.49 months should be regarded as 9 month follow up
- Questionnaires completed between 10.5 and 14 months should be regarded as 12 month follow up

**Unless stated otherwise, only forms returned within the specified permissible timelines are included in the analyses**.



[1] Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

## 2 Accrual

241 patients were screened for eligibility. Of these, 58 were ineligible, no response was received from 12, 5 were treated off-trial and 1 deceased prior to being offered the trial. 81 patients declined to take part in the trial for a number of reasons including unwillingness to travel and time constraints. 84 eligible patients were entered into the trial; 55 randomised to receive hyperbaric oxygen therapy (HBO) and 29 to receive control treatment. The first patient was randomised on 14th August 2009 and the final patient was randomised on 23rd October 2012. Patients were recruited from 32 UK centres. Reasons for ineligibility and declining to take part in the study are summarised in Table 1 and accrual is detailed in Table 2 below. Figure 1 is a consort diagram showing the patients included in the intention to treat and per protocol populations for both primary endpoints.

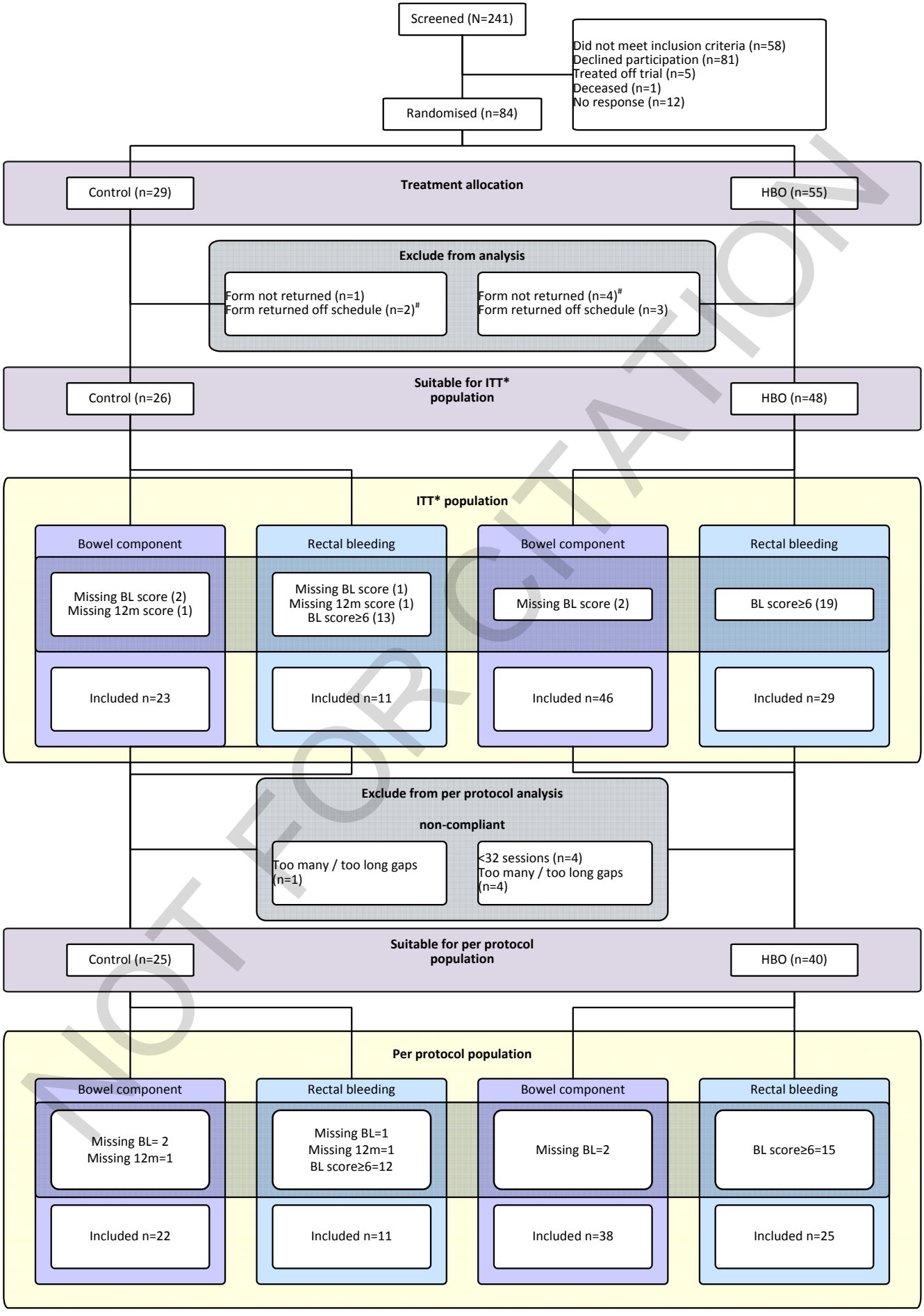
**Table 1: Summary of patients screened for eligibility for HOT II, including reasons for ineligibility and decliners**

| | n | % |
|---|---|---|
| **Consented** | **84** | **34.9%** |
| **Declined** | **81** | **33.6%** |
| Unwilling to travel | 31 | 38.3% |
| Time constraints | 23 | 28.4% |
| Feeling better | 9 | 11.1% |
| Unwilling to have sham treatment | 5 | 6.2% |
| On further treatment | 5 | 6.2% |
| No reason given | 4 | 4.9% |
| Financial constraints | 2 | 2.5% |
| Considered too risky | 2 | 2.5% |
| **Ineligible** | **58** | **24.1%** |
| RM assessment - too well | 13 | 22.4% |
| Unfit for treatment | 15 | 25.9% |
| Not Disease Free | 12 | 20.7% |
| Trial eligibility criteria not met | 11 | 19.0% |
| Recent Argon treatment | 2 | 3.4% |
| Insufficient time to complete work up | 3 | 5.2% |
| Not known | 2 | 3.4% |
| **No response** | **12** | **5.0%** |
| **Treated off trial** | **5** | **2.1%** |
| **Deceased** | **1** | **0.4%** |
| **Total** | **241** | **100.0%** |

**Table 2: Monthly and overall accrual**

| Month | Monthly accrual | Cumulative accrual |
|---|---|---|
| Aug-09 | 1 | 1 |
| Sep-09 | 1 | 2 |
| Oct-09 | 1 | 3 |
| Dec-09 | 2 | 5 |
| Feb-10 | 2 | 7 |
| Mar-10 | 1 | 8 |
| Apr-10 | 1 | 9 |
| Jun-10 | 1 | 10 |
| Sep-10 | 1 | 11 |
| Oct-10 | 1 | 12 |
| Nov-10 | 3 | 15 |
| Dec-10 | 3 | 18 |
| Jan-11 | 1 | 19 |
| Feb-11 | 1 | 20 |
| Mar-11 | 4 | 24 |
| Apr-11 | 3 | 27 |
| May-11 | 2 | 29 |
| Jun-11 | 7 | 36 |
| Jul-11 | 3 | 39 |
| Aug-11 | 3 | 42 |
| Sep-11 | 2 | 44 |
| Oct-11 | 2 | 46 |
| Dec-11 | 4 | 50 |
| Jan-12 | 1 | 51 |
| Feb-12 | 3 | 54 |
| Mar-12 | 7 | 61 |
| Apr-12 | 2 | 63 |
| May-12 | 4 | 67 |
| Jun-12 | 3 | 70 |
| Jul-12 | 3 | 73 |
| Aug-12 | 3 | 76 |
| Sep-12 | 3 | 79 |
| Oct-12 | 5 | 84 |

## Figure 1: CONSORT diagram showing patient flow through trial



*ITT Intention to treat population as defined in the SAP
#This includes 1 control patient and 2 HBO patients who received no treatment (detailed in section 6 below)

# 3 Baseline data

## 3.1 Patient characteristics

Table 3 below shows characteristics at the time of randomisation for all 84 patients randomised into HOT II according to randomised treatment group. Characteristics are generally well balanced between the two groups.

**Table 3: Baseline characteristics**

| | | Treatment | | | | | |
|---|---|---|---|---|---|---|---|
| | | Control N=29 | | HBO N=55 | | Total N=84 | |
| | | N | % | N | % | N | % |
| Age | Mean (SD) | 62.0 (11) | | 62.3 (11) | | 62.2 (11) | |
| | Median (IQR) | 63.7 (53.6, 69.9) | | 63.7 (53.9, 71.2) | | 63.7 (53.9, 71.0) | |
| | Min | 37.3 | | 34.5 | | 34.5 | |
| | Max | 79.3 | | 80.9 | | 80.9 | |
| Gender | Male | 14 | 48.3% | 23 | 41.8% | 37 | 44.0% |
| | Female | 15 | 51.7% | 32 | 58.2% | 47 | 56.0% |
| Where did the cancer start? | Prostate | 12 | 41.4% | 21 | 38.2% | 33 | 39.3% |
| | Anus | 4 | 13.8% | 4 | 7.3% | 8 | 9.5% |
| | Vagina | 3 | 10.3% | 1 | 1.8% | 4 | 4.8% |
| | Cervix | 5 | 17.2% | 17 | 30.9% | 22 | 26.2% |
| | Uterus | 3 | 10.3% | 8 | 14.5% | 11 | 13.1% |
| | Other* | 2 | 6.9% | 4 | 7.3% | 6 | 7.1% |
| Medical history | Back Pain | 3 | 10.3% | 7 | 12.7% | 10 | 11.9% |
| | Bloating | 18 | 62.1% | 30 | 54.5% | 48 | 57.1% |
| | Constipation | 5 | 17.2% | 5 | 9.1% | 10 | 11.9% |
| | Cramps/abdominal pain | 14 | 48.3% | 38 | 69.1% | 52 | 61.9% |
| | Diarrhoea | 14 | 48.3% | 30 | 54.5% | 44 | 52.4% |
| | Faecal incontinence | 19 | 65.5% | 35 | 63.6% | 54 | 64.3% |
| | Frequency | 18 | 62.1% | 38 | 69.1% | 56 | 66.7% |
| | Mucus discharge | 10 | 34.5% | 21 | 38.2% | 31 | 36.9% |
| | Nausea | 4 | 13.8% | 13 | 23.6% | 17 | 20.2% |
| | Rectal bleeding | 23 | 79.3% | 34 | 61.8% | 57 | 67.9% |
| | Rectal/perineal pain | 8 | 27.6% | 10 | 18.2% | 18 | 21.4% |
| | Steatorrhoea | 1 | 3.4% | 10 | 18.2% | 11 | 13.1% |
| | Sub-acute obstructive symptoms | 3 | 10.3% | 14 | 25.5% | 17 | 20.2% |
| | Tenesmus | 18 | 62.1% | 35 | 63.6% | 53 | 63.1% |
| | Unable to differentiate need to defecate/ pass urine | 1 | 3.4% | 2 | 3.6% | 3 | 3.6% |
| | Unable to differentiate solid/ liquid stool | 6 | 20.7% | 11 | 20.0% | 17 | 20.2% |
| | Urgency | 20 | 69.0% | 48 | 87.3% | 68 | 81.0% |
| | Weight loss | 2 | 6.9% | 10 | 18.2% | 12 | 14.3% |
| | Wind | 17 | 58.6% | 39 | 70.9% | 56 | 66.7% |
| | Other# | 6 | 20.7% | 8 | 14.5% | 14 | 16.7% |

| | | Treatment | | | | | |
|---|---|---|---|---|---|---|---|
| | | Control N=29 | | HBO N=55 | | Total N=84 | |
| | | N | % | N | % | N | % |
| Years since pelvic radiotherapy | Median (IQR) | 3.9 (2.5, 5.7) | | 3.5 (2.3, 9.7) | | 3.7 (2.4, 6.8) | |
| | Min | 1.5 | | 1.2 | | 1.2 | |
| | Max | 21.2 | | 34 | | 34 | |

*Others were anal canal (1), vulva (1) in the control group and retroperitoneum (1), pelvis (1), rectum (1) and bladder (1) in the HBO group

#Others were burning sensation between legs & perineum (1), borborygmi (1), diverticular disease; haemorrhoids (1), bleeding per rectum weekly and without warning (rectal bleeding also reported) (1), blood incontinence, urgency bleeding (rectal bleeding also reported) (1), problems controlling urine (1) in the control group; pelvic pain (1), frequency, bleeding incontinence, urgency bleeding (rectal bleeding also reported) (1), anal pain and bleeding from recurrent breakdown in anal canal (1), lymphedema - pelvic & lower abdomen (1), blood incontinence (1), passive leak - moisture (1), pads (1), soft stool, lymphedema left leg (1) in HBO group

### 3.2 Conditions at baseline

As well as collection of medical history summarised in Table 3 above, 4 instruments for measuring toxicity were used to record conditions at baseline: Modified IBDQ (patient reported), and Rectal LENTSOMA, Intestinal LENTSOMA and CTCAE (clinician reported). Conditions at baseline are summarised using LENTSOMA scores in the tables below. IBDQ and CTCAE scores at baseline are summarised in the appendix. There are no striking differences in baseline conditions between the two groups.

**Table 4: Rectal LENTSOMA scores at baseline**

| | | | Control N=29 | | HBO N=55 | | Total N=84 | |
|---|---|---|---|---|---|---|---|---|
| | | | N | % | N | % | N | % |
| Subjective | Stool frequency | Grade 0 | 5 | 17.2% | 5 | 9.1% | 10 | 11.9% |
| | | Grade 1-2 | 23 | 79.3% | 48 | 87.3% | 71 | 84.5% |
| | | Grade 3-4 | 1 | 3.4% | 2 | 3.6% | 3 | 3.6% |
| | Sphincter control | Grade 0 | 4 | 13.8% | 15 | 27.3% | 19 | 22.6% |
| | | Grade 1-2 | 16 | 55.2% | 30 | 54.5% | 46 | 54.8% |
| | | Grade 3-4 | 9 | 31.0% | 10 | 18.2% | 19 | 22.6% |
| | Pain | Grade 0 | 19 | 65.5% | 40 | 72.7% | 59 | 70.2% |
| | | Grade 1-2 | 9 | 31.0% | 12 | 21.8% | 21 | 25.0% |
| | | Grade 3-4 | 1 | 3.4% | 3 | 5.5% | 4 | 4.8% |
| | Tenesmus | Grade 0 | 2 | 6.9% | 8 | 14.5% | 10 | 11.9% |
| | | Grade 1-2 | 15 | 51.7% | 25 | 45.5% | 40 | 47.6% |
| | | Grade 3-4 | 12 | 41.4% | 22 | 40.0% | 34 | 40.5% |
| | Mucosal loss | Grade 0 | 15 | 51.7% | 35 | 63.6% | 50 | 59.5% |
| | | Grade 1-2 | 11 | 37.9% | 16 | 29.1% | 27 | 32.1% |
| | | Grade 3-4 | 3 | 10.3% | 4 | 7.3% | 7 | 8.3% |
| Objective | Bleeding | Grade 0 | 11 | 37.9% | 27 | 49.1% | 38 | 45.2% |
| | | Grade 1-2 | 9 | 31.0% | 14 | 25.5% | 23 | 27.4% |
| | | Grade 3-4 | 9 | 31.0% | 14 | 25.5% | 23 | 27.4% |
| | Stricture | Grade 0 | 29 | 100.0% | 55 | 100.0% | 84 | 100.0% |
| | Ulceration | Grade 0 | 29 | 100.0% | 55 | 100.0% | 84 | 100.0% |
| Management | Pain | Grade 0 | 24 | 82.8% | 48 | 87.3% | 72 | 85.7% |
| | | Grade 1-2 | 5 | 17.2% | 7 | 12.7% | 12 | 14.3% |
| | Tenis / frequency | Grade 0 | 17 | 58.6% | 25 | 45.5% | 42 | 50.0% |
| | | Grade 1-2 | 3 | 10.3% | 10 | 18.2% | 13 | 15.5% |
| | | Grade 3-4 | 9 | 31.0% | 20 | 36.4% | 29 | 34.5% |
| | Bleeding | Grade 0 | 24 | 82.8% | 40 | 72.7% | 64 | 76.2% |
| | | Grade 1-2 | 5 | 17.2% | 13 | 23.6% | 18 | 21.4% |
| | | Grade 3-4 | 0 | 0.0% | 2 | 3.6% | 2 | 2.4% |
| | Stricture | Grade 0 | 29 | 100.0% | 55 | 100.0% | 84 | 100.0% |
| | Ulceration | Grade 0 | 29 | 100.0% | 54 | 98.2% | 83 | 98.8% |
| | | Grade 1-2 | 0 | 0.0% | 1 | 1.8% | 1 | 1.2% |
| | Sphincter control | Grade 0 | 12 | 41.4% | 29 | 52.7% | 41 | 48.8% |
| | | Grade 1-2 | 4 | 13.8% | 11 | 20.0% | 15 | 17.9% |
| | | Grade 3-4 | 13 | 44.8% | 15 | 27.3% | 28 | 33.3% |

**Table 5: Intestinal LENTSOMA scores at baseline**

| | | | Control N=29 | | HBO N=55 | | Total N=84 | |
|---|---|---|---|---|---|---|---|---|
| | | | N | % | N | % | N | % |
| Subjective | Stool frequency | Grade 0 | 4 | 13.8% | 5 | 9.1% | 9 | 10.7% |
| | | Grade 1-2 | 24 | 82.8% | 48 | 87.3% | 72 | 85.7% |
| | | Grade 3-4 | 1 | 3.4% | 2 | 3.6% | 3 | 3.6% |
| | Stool consistency | Grade 0 | 21 | 72.4% | 32 | 58.2% | 53 | 63.1% |
| | | Grade 1-2 | 8 | 27.6% | 23 | 41.8% | 31 | 36.9% |
| | Pain | Grade 0 | 16 | 55.2% | 18 | 32.7% | 34 | 40.5% |
| | | Grade 1-2 | 10 | 34.5% | 24 | 43.6% | 34 | 40.5% |
| | | Grade 3-4 | 3 | 10.3% | 13 | 23.6% | 16 | 19.0% |
| | Constipation | Grade 0 | 28 | 96.6% | 53 | 96.4% | 81 | 96.4% |
| | | Grade 1-2 | 1 | 3.4% | 2 | 3.6% | 3 | 3.6% |
| Objective | Melena | Grade 0 | 24 | 82.8% | 48 | 87.3% | 72 | 85.7% |
| | | Grade 1-2 | 4 | 13.8% | 7 | 12.7% | 11 | 13.1% |
| | | Grade 3-4 | 1 | 3.4% | 0 | 0.0% | 1 | 1.2% |
| | Weight loss from RT | Grade 0 | 28 | 96.6% | 53 | 96.4% | 81 | 96.4% |
| | | Grade 1-2 | 1 | 3.4% | 1 | 1.8% | 2 | 2.4% |
| | | Grade 3-4 | 0 | 0.0% | 1 | 1.8% | 1 | 1.2% |
| | Stricture | Grade 0 | 29 | 100.0% | 54 | 98.2% | 83 | 98.8% |
| | | Grade 1-2 | 0 | 0.0% | 1 | 1.8% | 1 | 1.2% |
| | Ulceration | Grade 0 | 29 | 100.0% | 55 | 100.0% | 84 | 100.0% |
| Management | Pain | Grade 0 | 22 | 75.9% | 40 | 72.7% | 62 | 73.8% |
| | | Grade 1-2 | 6 | 20.7% | 13 | 23.6% | 19 | 22.6% |
| | | Grade 3-4 | 1 | 3.4% | 2 | 3.6% | 3 | 3.6% |
| | Stool consistency / frequency | Grade 0 | 9 | 31.0% | 14 | 25.5% | 23 | 27.4% |
| | | Grade 1-2 | 19 | 65.5% | 39 | 70.9% | 58 | 69.0% |
| | | Grade 3-4 | 1 | 3.4% | 2 | 3.6% | 3 | 3.6% |
| | Bleeding | Grade 0 | 28 | 96.6% | 53 | 96.4% | 81 | 96.4% |
| | | Grade 1-2 | 1 | 3.4% | 2 | 3.6% | 3 | 3.6% |
| | Stricture | Grade 0 | 29 | 100.0% | 55 | 100.0% | 84 | 100.0% |
| | Ulceration | Grade 0 | 29 | 100.0% | 55 | 100.0% | 84 | 100.0% |

## 4 Treatment compliance

The protocol dictates that each participant should receive a total of 40 pressure exposures (five days per week for eight weeks). Where three or fewer sessions were missed during the course of treatment, the protocol permitted additional sessions to be performed at the end of the 8 week trial period up a total of 40 sessions.

**Table 6: Number of sessions attended by each patient**

| Number of sessions attended | Control | | HBO | | Total | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| 0 | 1 | 3.4% | 2 | 3.6% | 3 | 3.6% |
| 2 | 0 | 0.0% | 1 | 1.8% | 1 | 1.2% |
| 4 | 0 | 0.0% | 1 | 1.8% | 1 | 1.2% |
| 11 | 0 | 0.0% | 1 | 1.8% | 1 | 1.2% |
| 18 | 0 | 0.0% | 1 | 1.8% | 1 | 1.2% |
| 31 | 0 | 0.0% | 1 | 1.8% | 1 | 1.2% |
| 38 | 1 | 3.4% | 0 | 0.0% | 1 | 1.2% |
| 40 | 27 | 93.1% | 48 | 87.3% | 75 | 89.3% |
| Total | 29 | 100.0% | 55 | 100.0% | 84 | 100.0% |

### 4.1 Deviations and reasons for non-compliance

Other than deviations from the treatment schedule, there were 8 reported deviations from the study protocol; 3 patients were found to be ineligible after entering the study, 1 patient withdrew consent, 1 patient was lost to follow up and there were 3 “other” deviations (see table 7 below).

**Table 7: Types of deviations (excluding treatment non-compliance)**

| | Treatment | | |
|---|---|---|---|
| Type of deviation | Control | HBO | Total |
| Ineligible | 1 | 2 | 3 |
| Withdrew consent | 0 | 1 | 1 |
| Lost to follow up | 0 | 1 | 1 |
| Other | 1 | 2 | 3 |
| Total | 2 | 6 | 8 |

Deviations from the protocol mandated treatment schedule were not well reported on the deviation forms. In order to define the per protocol population, at the end of the study centres were asked to provide further details of missed treatments, including the exact dates treatments were missed, for patients whose compliance with planned treatment could not be determined from their treatment compliance and deviation forms. Protocol violations that were reported on deviation forms are included in tables 8 and 9 below.

The per protocol population is described in the SAP as the population that contains all patients registered into the main study who are considered evaluable. Patients are considered evaluable if they

received a minimum of 32 treatment sessions within a 10 week period, excluding patients who received fewer than 3 treatments per week for 2 or more weeks or patients who missed five consecutive treatments. Reasons for exclusion from the per protocol analysis population are given in Table 10.

**Table 8: Protocol violations in patients included in per protocol analysis**

| Arm | Deviation | N patients |
|---|---|---|
| Control | Missed 1 or more treatment sessions | 7 |
| Hyperbaric oxygen | Missed 1 or more treatment sessions | 7 |
| | One session ended early | 2 |

**Table 9: Protocol violations in patients excluded from per protocol analysis**

| Arm | Deviation | N patients |
|---|---|---|
| Control | Treatment gap of more than 5 days | 1 |
| Hyperbaric oxygen | Treatment gap of more than 5 days | 5 |
| | Treatment stopped early | 2 |
| | Missed 1 or more treatment sessions | 1 |
| | One session ended early | 1 |
| | One session not delivered according to protocol | 1 |

**Table 10: Reasons for exclusion from per protocol analysis**

| Arm | Reason for exclusion | N patients |
|---|---|---|
| Control | Gap >5 days | 2 |
| | No treatment received | 1 |
| HBO | Gap >5 days | 5 |
| | No treatment received | 2 |
| | Received <3 treatments for 2 weeks | 1 |
| | Received <32 treatments | 5 |

## 4.2 CRF returns

The IBDQ questionnaire was requested at baseline, 2 weeks and 3, 6, 9 and 12 months, while Rectal and intestinal LENT SOMA forms were collected at baseline, 2 weeks and 12 months. Quality of life Questionnaires were requested at baseline, 3, 6, 9 and 12 months.

The IDMC agreed that only forms completed within the correct timelines should be included in both the intention to treat and per protocol analyses. The timelines that were laid out by the IDMC are as follows:

- Questionnaires completed after 2 week assessment but before 4.5 months should be treated as 3 month follow up;
- Questionnaires completed from 4.5 to 7.49 months should be regarded as 6 month follow up;
- Questionnaires completed between 7.5 and 10.49 months should be regarded as 9 month follow up, and;
- Questionnaires completed between 10.5 and 14 months should be regarded as 12 month follow up

If multiple questionnaires fit within the permissible timeframe for a particular visit, the questionnaire with the date closest to the scheduled assessment date was used for that visit.

Table 11 below shows the number of forms returned at each time point, and the number of forms returned within the IDMC-specified time frames.

**Table 11: Forms returned overall and in the correct time frame**

| | Baseline | 2 week | 3 month | 6 month | 9 month | 12 month |
|---|---|---|---|---|---|---|
| IBDQ forms returned | 84 | 75 | 79 | 78 | 78 | 79 |
| IBDQ forms returned* | 84 | 75 | 68 | 76 | 74 | 74 |
| Rectal LENTSOMA | 84 | 78 | - | - | - | 79 |
| Rectal LENTSOMA* | 84 | 78 | - | - | - | 72 |
| Intestinal LENTSOMA | 84 | 78 | - | - | - | 79 |
| Intestinal LENTSOMA* | 84 | 78 | - | - | - | 72 |
| CTCAE | 83 | 78 | - | - | - | 79 |
| CTCAE* | 83 | 78 | - | - | - | 72 |
| QLQ C30 | 84 | - | 77 | 78 | 78 | 79 |
| QLQ C30* | 84 | - | 65 | 76 | 74 | 74 |
| QLQ CR38 | 84 | - | 77 | 78 | 78 | 79 |
| QLQ CR38* | 84 | - | 65 | 76 | 74 | 74 |

*Includes only forms returned within the pre-specified permissible timeframe

### 4.3 On treatment toxicities

On-treatment toxicities were reported on the treatment compliance CRF, details were requested relating to 12 pre-specified toxicities. 81 patients received at least 1 treatment session; 41 of these were reported to have experienced 1 or more on-treatment toxicity. The tables below show on treatment toxicities and SAEs reported by allocated treatment.

**Table 12: On treatment toxicities**

| | Control (N=28) | | HBO (N=53) | | Total (N=81) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Eye refractive change / myopia | 3 | 10.7% | 16 | 30.2% | 19 | 23.5% |
| Cataract development de novo | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Accelerated maturation of cataract | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Increased fatigue or tiredness | 3 | 10.7% | 2 | 3.8% | 5 | 6.2% |
| Ear pain / barotrauma | 6 | 21.4% | 15 | 28.3% | 21 | 25.9% |
| Sinus pain | 2 | 7.1% | 2 | 3.8% | 4 | 4.9% |
| Dental pain / damage | 2 | 7.1% | 2 | 3.8% | 4 | 4.9% |
| Seizure | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Peripheral numbness and tingling | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Claustrophobia | 0 | 0.0% | 3 | 5.7% | 3 | 3.7% |
| Decompression illness | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Pulmonary barotraumas | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| Other* | 3 | 10.7% | 10 | 18.9% | 13 | 16.0% |

*No coding of other toxicities has been performed

**Table 13: SAEs in HOT II patients**

| | Classification | N patients |
|---|---|---|
| Control | SAE (hospitalisation) | 1 |
| | SAE (life threatening) | 1 |
| | SAE (disability) | 1 |
| HBO | SAE (hospitalisation) | 7 |
| | SAE (important medical event) | 1 |

## 5 Primary analyses

As stated in the protocol, to make some allowance for multiple testing, for the bowel function component of the primary analyses P-values of <0.03 will be deemed statistically significant. For the rectal bleeding score, P-values of <0.02 will be deemed statistically significant.

### Modified IBDQ questionnaire

The IBDQ questionnaire consists of 32 questions, responses are graded from 1-7 and the maximum overall score is 224. A high score denotes better function. 10 of the individual questions can be summed to generate a bowel function component score;

- Q1 Had your bowel open?
- Q5 Had loose bowel movements?
- Q9 Been troubled by pain in your bottom?
- Q13 Cramp in tummy or bottom?
- Q17 Passed a large amount of gas?
- Q20 Been troubled by bloating?
- Q22 Had a problem with bleeding from your bottom?
- Q24 Felt like you need to have your bowel open but nothing happens?
- Q26 Been troubled by accidental soiling?
- Q29 Felt disgusted about your bowel problems?

The bowel function component score is used to address the first of the primary endpoints and has a possible range of 10-70 (10 denoting worst possible bowel function, 70 denoting best possible bowel function).

The second primary endpoint is addressed using rectal bleeding score, which consists of only 1 question with a range of 1-7;

- Q22 Had a problem with bleeding from your bottom?

For all IBDQ endpoints, a positive change from baseline indicates an improvement in condition. Raw IBDQ bowel and rectal bleeding scores are provided in the appendix.

### 5.1.1 Bowel function component of the Modified Inflammatory Bowel Disease questionnaire

The median difference in change of the bowel function component from baseline to 12 months in both trial arms is compared using the Mann Whitney U test. Analysis is by intention to treat and includes all data returned within the specified timeframes.

| **Primary endpoint 1: Bowel function component of the modified IBDQ** | Control (n=23) | HBO (n=46) | Total (n=69) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +4 (-6, 9) | +3.5 (-3, 11) | +4 (-3, 10) |
| Mann-Whitney test U Score | 0.67 | | |
| P-value | 0.50 | | |

### 5.1.2 Rectal bleeding score of the Modified Inflammatory Bowel Disease questionnaire

The median difference in change of the rectal bleeding score from baseline to 12 months in both trial arms is compared using the Mann Whitney U test. Analysis is by intention to treat and includes all data returned within the specified timeframes. This analysis is performed only in patients who reported rectal bleeding on the baseline questionnaire ("some increase in frequency" or worse on the IBDQ scale).

| **Primary endpoint 2: rectal bleeding score from the modified IBDQ** | Control (n=11) | HBO (n=29) | Total (n=40) |
|---|---|---|---|
| Median change (from baseline to 12m) | +1 (1, 2) | +3 (1, 3) | +2 (1, 3) |
| Mann-Whitney test U Score | 1.69 | | |
| P-value | 0.09 | | |

### 5.2 Sensitivity analyses of primary endpoints

Analysis of the primary endpoints was repeated including all data returned at the time point it was returned for, irrespective of whether the date of completion complied with the specified permissible timelines.

### 5.2.1 Bowel function component of the Modified Inflammatory Bowel Disease questionnaire

| **Primary endpoint 1: Bowel function component of the modified IBDQ** | Control (n=25) | HBO (n=48) | Total (n=73) |
|---|---|---|---|
| Median change (from baseline to 12m) | +3 (-7, 8) | +2.5 (-5, 10.5) | +3 (-7, 10) |
| Mann-Whitney test U Score | 0.71 | | |
| P-value | 0.48 | | |

### 5.2.2 Rectal bleeding score of the Modified Inflammatory Bowel Disease questionnaire including patients who reported rectal bleeding at baseline ("some increase in frequency" or worse on the IBDQ scale)

| **Primary endpoint 2: rectal bleeding score from the modified IBDQ** | Control (n=13) | HBO (n=30) | Total (n=43) |
|---|---|---|---|
| Median change (from baseline to 12m) | +1 (0, 2) | +3 (1, 4) | +2 (0, 3) |
| Mann-Whitney test U Score | 2.06 | | |
| P-value | 0.04 | | |

## 5.3 Per protocol analysis of the primary endpoint

The SAP states that analysis of the primary endpoints should be repeated in the per protocol population, to determine whether close adherence to the protocol affects the effectiveness of treatment. The results of the analyses in the per protocol population are shown below:

| **Primary endpoint 1: Bowel function component of the modified IBDQ** | Control (n=22) | HBO (n=38) | Total (n=60) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +3.5 (-6, 9) | +4 (-2, 11) | +4 (-2.5, 10.5) |
| Mann-Whitney test U Score | 0.94 | | |
| P-value | 0.35 | | |

| **Primary endpoint 2: rectal bleeding score from the modified IBDQ** | Control (n=11) | HBO (n=25) | Total (n=36) |
|---|---|---|---|
| Median change (from baseline to 12m) | +1 (1, 2) | +3 (0, 3) | +2 (0.5, 3) |
| Mann-Whitney test U Score | 1.44 | | |
| P-value | 0.15 | | |

# 6 Secondary endpoints

## 6.1 Physician assessment of rectal dysfunction using LENT SOMA scales of radiation injury

Within each of three LENT SOMA descriptors (subjective, objective and management) individual parameters are assessed on a 4 point scale (with a higher score denoting worse function). The EORTC and RTOG suggest that descriptors can be used to develop a score for each normal tissue, by summing numerical scores of individual parameters. An increase in score reflects deterioration and a decrease in score represents an improvement in severity of late normal tissue effects. Sections 6.1.1 and 6.1.2 summarise the proportion of patients reported to have suffered grade 3-4 LENT SOMA toxicities at each time point for each of the 3 subscales and overall, split by treatment group.

Tabulations of all LENT SOMA grades for each assessment at each time point by treatment are shown in the appendix.

The Mann-Whitney U test was used to test for a difference in aggregate subjective parameter score from baseline to 12 months in the two treatment groups.

### 6.1.1 RECTAL LENT SOMA

**Table 14: The proportion of items graded as marked or severe (grade 3 or 4)**

| | | Control | | HBO | | Total | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| Baseline | | N=29 | | N=55 | | N=84 | |
| Subjective | Grade 0-2 | 12 | 41.4% | 27 | 49.1% | 39 | 46.4% |
| | Grade 3-4 | 17 | 58.6% | 28 | 50.9% | 45 | 53.6% |
| Objective | Grade 0-2 | 20 | 69.0% | 41 | 74.5% | 61 | 72.6% |
| | Grade 3-4 | 9 | 31.0% | 14 | 25.5% | 23 | 27.4% |
| Management | Grade 0-2 | 12 | 41.4% | 27 | 49.1% | 39 | 46.4% |
| | Grade 3-4 | 17 | 58.6% | 28 | 50.9% | 45 | 53.6% |
| Overall | Grade 0-2 | 3 | 10.3% | 10 | 18.2% | 13 | 15.5% |
| | Grade 3-4 | 26 | 89.7% | 45 | 81.8% | 71 | 84.5% |
| 2 weeks | | N=28 | | N=50 | | N=78 | |
| Subjective | Grade 0-2 | 20 | 71.4% | 30 | 60.0% | 50 | 64.1% |
| | Grade 3-4 | 8 | 28.6% | 20 | 40.0% | 28 | 35.9% |
| Objective | Grade 0-2 | 19 | 67.9% | 43 | 86.0% | 62 | 79.5% |
| | Grade 3-4 | 6 | 21.4% | 6 | 12.0% | 12 | 15.4% |
| | Missing | 3 | 10.7% | 1 | 2.0% | 4 | 5.1% |
| Management | Grade 0-2 | 14 | 50.0% | 25 | 50.0% | 39 | 50.0% |
| | Grade 3-4 | 14 | 50.0% | 25 | 50.0% | 39 | 50.0% |
| Overall | Grade 0-2 | 8 | 28.6% | 18 | 36.0% | 26 | 33.3% |
| | Grade 3-4 | 20 | 71.4% | 32 | 64.0% | 52 | 66.7% |
| 12 months | | N=26 | | N=46 | | N=72 | |
| Subjective | Grade 0-2 | 17 | 65.4% | 24 | 52.2% | 41 | 56.9% |
| | Grade 3-4 | 9 | 34.6% | 22 | 47.8% | 31 | 43.1% |
| Objective | Grade 0-2 | 24 | 92.3% | 41 | 89.1% | 65 | 90.3% |
| | Grade 3-4 | 2 | 7.7% | 4 | 8.7% | 6 | 8.3% |
| | Missing | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |
| Management | Grade 0-2 | 13 | 50.0% | 26 | 56.5% | 39 | 54.2% |
| | Grade 3-4 | 13 | 50.0% | 20 | 43.5% | 33 | 45.8% |
| Overall | Grade 0-2 | 9 | 34.6% | 16 | 34.8% | 25 | 34.7% |
| | Grade 3-4 | 17 | 65.4% | 30 | 65.2% | 47 | 65.3% |

Mann-Whitney U test of aggregate subjective parameter score

| **Secondary endpoint: aggregate subjective parameter score** | Control (n=26) | HBO (n=46) | Total (n=72) |
|---|---|---|---|
| Median change (from baseline to 12m) | -1.5 (-4, 0) | -1 (-2, 1) | -1 (-3, 0.5) |
| Mann-Whitney test U Score | 1.56 | | |
| P-value | 0.12 | | |

### 6.1.2 INTESTINAL LENT SOMA

**Table 15: The proportion of items graded as marked or severe (grade 3 or 4)**

| | | Control | | HBO | | Total | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| Baseline | | N=29 | | N=55 | | N=84 | |
| Subjective | Grade 0-2 | 25 | 86.2% | 41 | 74.5% | 66 | 78.6% |
| | Grade 3-4 | 4 | 13.8% | 14 | 25.5% | 18 | 21.4% |
| Objective | Grade 0-2 | 28 | 96.6% | 54 | 98.2% | 82 | 97.6% |
| | Grade 3-4 | 1 | 3.4% | 1 | 1.8% | 2 | 2.4% |
| Management | Grade 0-2 | 27 | 93.1% | 51 | 92.7% | 78 | 92.9% |
| | Grade 3-4 | 2 | 6.9% | 4 | 7.3% | 6 | 7.1% |
| Overall | Grade 0-2 | 23 | 79.3% | 39 | 70.9% | 62 | 73.8% |
| | Grade 3-4 | 6 | 20.7% | 16 | 29.1% | 22 | 26.2% |
| 2 weeks | | N=28 | | N=50 | | N=78 | |
| Subjective | Grade 0-2 | 25 | 89.3% | 44 | 88.0% | 69 | 88.5% |
| | Grade 3-4 | 3 | 10.7% | 6 | 12.0% | 9 | 11.5% |
| Objective | Grade 0-2 | 25 | 89.3% | 49 | 98.0% | 74 | 94.9% |
| | Grade 3-4 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | Missing | 3 | 10.7% | 1 | 2.0% | 4 | 5.1% |
| Management | Grade 0-2 | 25 | 89.3% | 48 | 96.0% | 73 | 93.6% |
| | Grade 3-4 | 1 | 3.6% | 2 | 4.0% | 3 | 3.8% |
| | Missing | 2 | 7.1% | 0 | 0.0% | 2 | 2.6% |
| Overall | Grade 0-2 | 24 | 85.7% | 43 | 86.0% | 67 | 85.9% |
| | Grade 3-4 | 4 | 14.3% | 7 | 14.0% | 11 | 14.1% |
| 12 months | | N=26 | | N=46 | | N=72 | |
| Subjective | Grade 0-2 | 22 | 84.6% | 40 | 87.0% | 62 | 86.1% |
| | Grade 3-4 | 4 | 15.4% | 6 | 13.0% | 10 | 13.9% |
| Objective | Grade 0-2 | 26 | 100.0% | 45 | 97.8% | 71 | 98.6% |
| | Grade 3-4 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| | Missing | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |
| Management | Grade 0-2 | 25 | 96.2% | 44 | 95.7% | 69 | 95.8% |
| | Grade 3-4 | 1 | 3.8% | 2 | 4.3% | 3 | 4.2% |
| Overall | Grade 0-2 | 22 | 84.6% | 40 | 87.0% | 62 | 86.1% |
| | Grade 3-4 | 4 | 15.4% | 6 | 13.0% | 10 | 13.9% |

Mann-Whitney U test of aggregate subjective parameter score

| **Secondary endpoint: aggregate subjective parameter score** | Control (n=26) | HBO (n=46) | Total (n=72) |
|---|---|---|---|
| Median change (from baseline to 12m) | 0 (-1, 1) | 0 (-2, 0) | 0 (-2, 0) |
| Mann-Whitney test U Score | -1.30 | | |
| P-value | 0.20 | | |

### 6.2 Sensitivity analyses of secondary endpoints

As stated in the SAP, a sensitivity analysis was performed including all data returned. The Mann Whitney U test for a difference in aggregate subjective parameter score was performed on all data returned at the time point it was returned for, irrespective of whether the date of completion complied with the specified timelines. Results were similar to the analysis in the ITT population and are shown below.

Physician assessment of rectal dysfunction of radiation injury (RECTAL LENT SOMA)

| **Secondary endpoint: aggregate subjective parameter score** | Control (n=28) | HBO (n=51) | Total (n=79) |
|---|---|---|---|
| Median change (from baseline to 12m) | -1 (-3.5, 0.5) | 0 (-1, 2) | -1 (-2, 1) |
| Mann-Whitney test U Score | 1.62 | | |
| P-value | 0.11 | | |

Physician assessment of rectal dysfunction of radiation injury (INTESTINAL LENT SOMA)

| **Secondary endpoint: aggregate subjective parameter score** | Control (n=28) | HBO (n=51) | Total (n=79) |
|---|---|---|---|
| Median change (from baseline to 12m) | 0 (-1, 0.5) | 0 (-2, 0) | 0 (-2, 0) |
| Mann-Whitney test U Score | -1.41 | | |
| P-value | 0.16 | | |

## 7 Common Terminology Criteria for Adverse Events (CTCAE)

Modified CTCAE was used to assess adverse events at baseline, 2 weeks and 12 months. Table & Figure 2 show the maximum CTC grade reported at each time point for each treatment group. Table 17 and figure 3 show the CTC grades reported for rectal bleeding reported at each time point. Figure 4 shows CTC grades reported for each other CTC toxicity at each time point, split by treatment group. Tables for all other toxicities can be found in the appendix.

**Table 16: Maximum CTCAE toxicities at each time point**

| | Control | | HBO | | Total | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Baseline | N=29 | | N=54 | | N=83 | |
| 0 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| 1 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| 2 | 22 | 75.9% | 40 | 74.1% | 62 | 74.7% |
| 3 | 7 | 24.1% | 13 | 24.1% | 20 | 24.1% |
| 4 | 0 | 0.0% | 1 | 1.9% | 1 | 1.2% |
| 2 weeks | N=28 | | N=50 | | N=78 | |
| 0 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| 1 | 7 | 25.0% | 12 | 24.0% | 19 | 24.4% |
| 2 | 19 | 67.9% | 30 | 60.0% | 49 | 62.8% |
| 3 | 2 | 7.1% | 8 | 16.0% | 10 | 12.8% |
| 4 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |
| 12 months | N=26 | | N=46 | | N=72 | |
| 0 | 1 | 3.8% | 1 | 2.2% | 2 | 2.8% |
| 1 | 6 | 23.1% | 6 | 13.0% | 12 | 16.7% |
| 2 | 14 | 53.8% | 32 | 69.6% | 46 | 63.9% |
| 3 | 5 | 19.2% | 7 | 15.2% | 12 | 16.7% |
| 4 | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% |

**Figure 2: Maximum CTCAE toxicities at each time point**

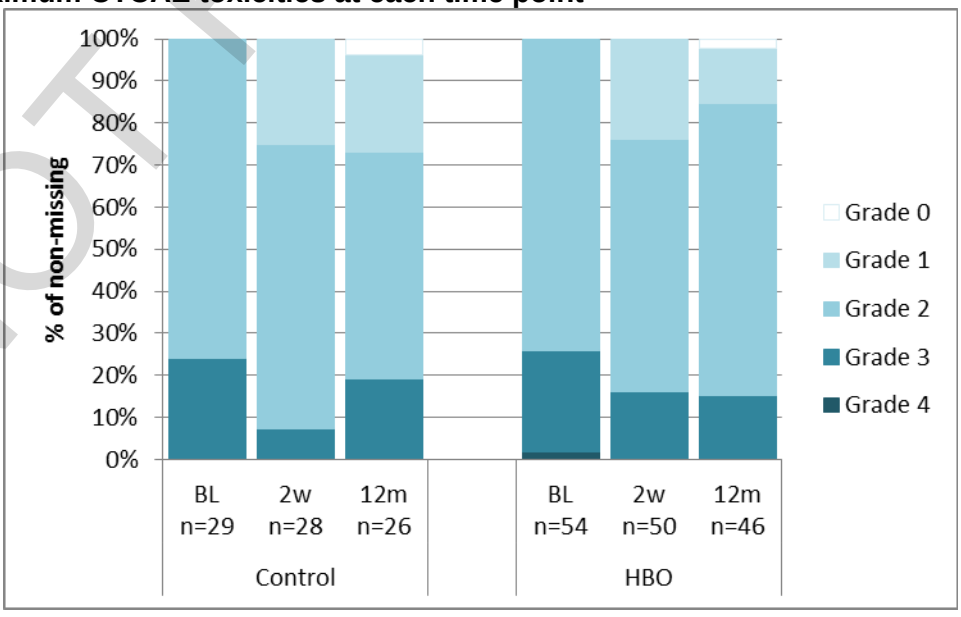


**Table 17: Rectal bleeding grade at each time point**

| | Control | | HBO | | Total | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Baseline | N=29 | | N=54 | | N=83 | |
| 0 | 10 | 35.7% | 27 | 50.0% | 37 | 44.6% |
| 1 | 7 | 25.0% | 6 | 11.1% | 13 | 15.7% |
| 2 | 11 | 39.3% | 16 | 29.6% | 27 | 32.5% |
| 3 | 1 | 3.6% | 5 | 9.3% | 6 | 7.2% |
| 2 weeks | N=28 | | N=50 | | N=78 | |
| 0 | 12 | 42.9% | 23 | 46.0% | 35 | 44.9% |
| 1 | 11 | 39.3% | 17 | 34.0% | 28 | 35.9% |
| 2 | 5 | 17.9% | 8 | 16.0% | 13 | 16.7% |
| 3 | 0 | 0.0% | 2 | 4.0% | 2 | 2.6% |
| 12 months | N=26 | | N=46 | | N=72 | |
| 0 | 11 | 42.3% | 25 | 54.3% | 36 | 50.0% |
| 1 | 14 | 53.8% | 14 | 30.4% | 27 | 37.5% |
| 2 | 1 | 3.8% | 6 | 13.0% | 8 | 11.1% |
| 3 | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |

**Figure 3: Rectal bleeding grade at each time point**

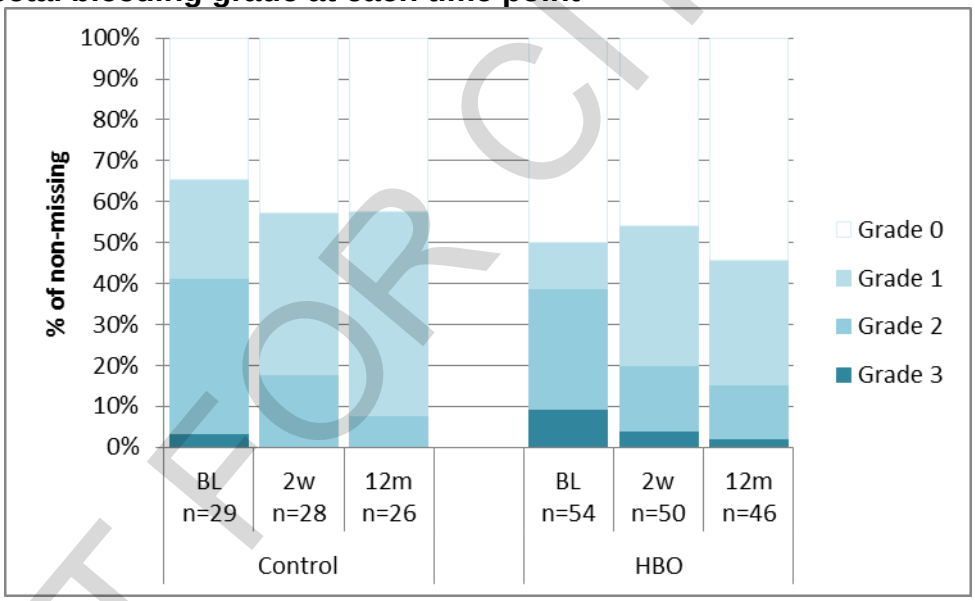
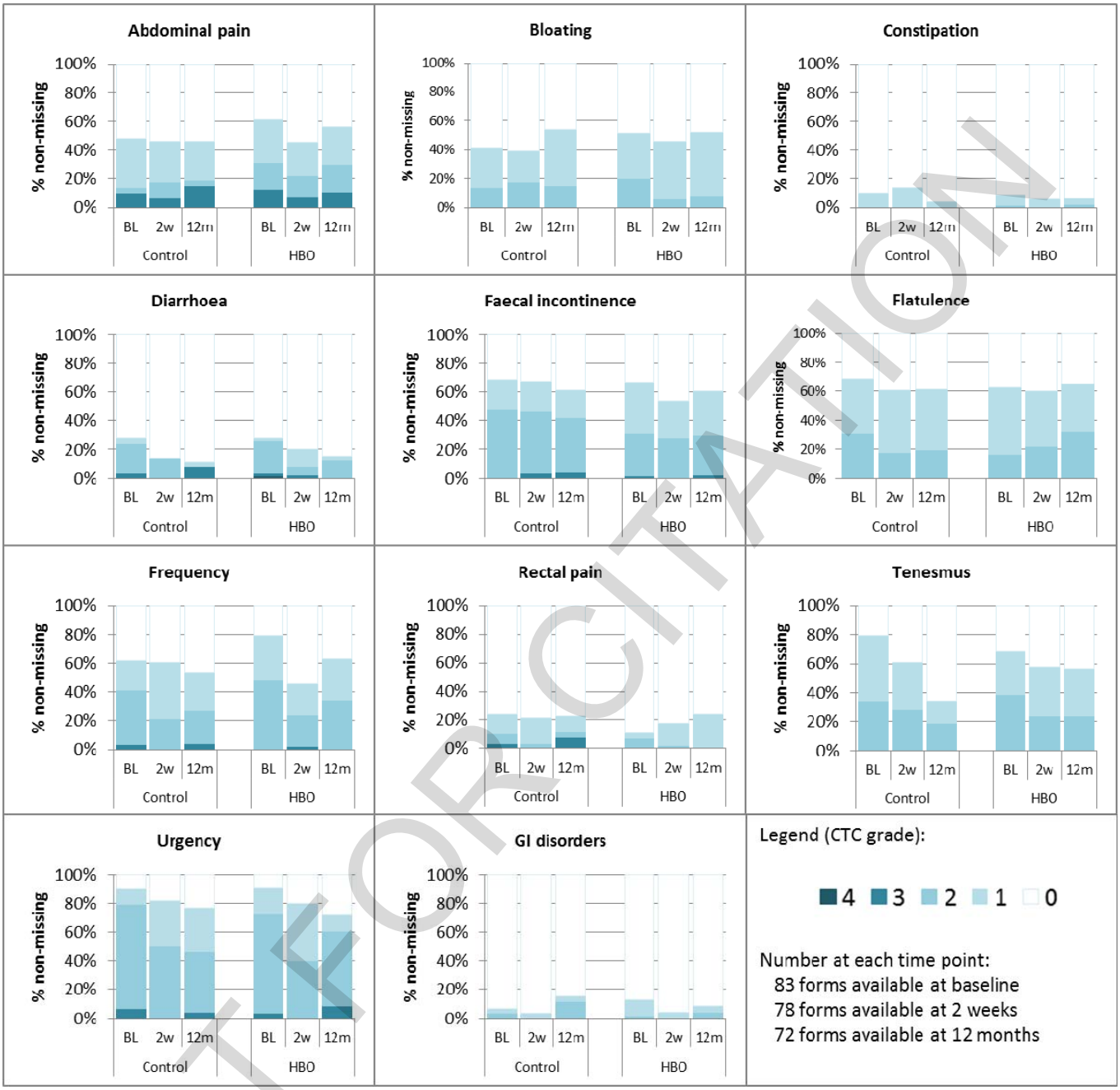


**Figure 4: CTC grades reported for each CTC toxicity at each time point, by treatment group**



## 8 EORTC QLQ-C30 & CR38

Standard scoring procedures, as described in the EORTC QLQ-C30 manual were used to describe changes in QoL domains using EORTC QLQ-C30 and CR38.

### 8.1 EORTC QLQ-C30

The EORTC questionnaire consists of 30 questions, scored on a 4-point scale (1-4). Scores from individual items are combined and transformed to make subscales with scores ranging from 0 to 100.

For the 6 function scores (physical function, role function, emotional function, cognitive function, social function and global health status) a high score represents high function (good).

For the 9 symptom scores (fatigue, nausea & vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) a high score represents high symptomatology (bad).

#### Cross sectional analysis

The plots in figures 5a-i below show median, IQR and range for EORTC QLQ-C30 scales at each time point by treatment group and include patients in the ITT population who returned forms within the correct timeframe (as specified in section 4.2). All observations available at a given time point are included. Boxplots are shown for scales with more than 1 item only (i.e. not dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties).

Scores at each time point are tabulated in tables 18a-d below.

**Figure 5a: Physical function**

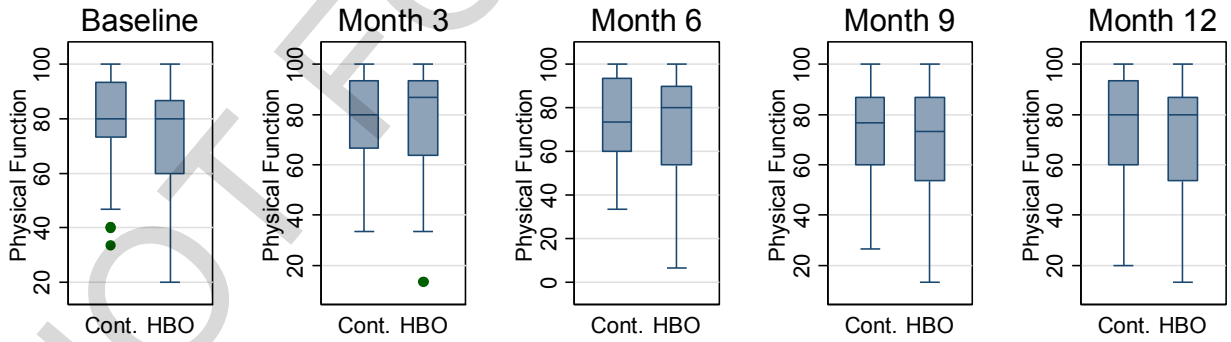


**Figure 5b: Role function**

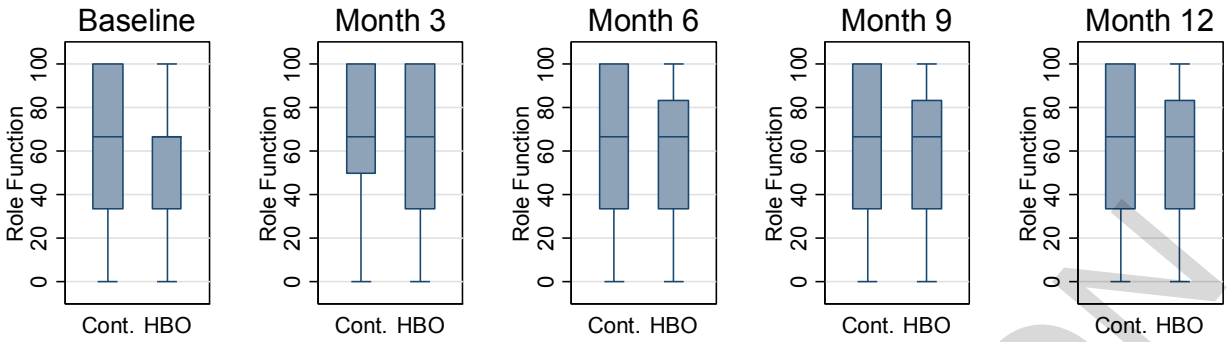



**Figure 5c: Emotional function**

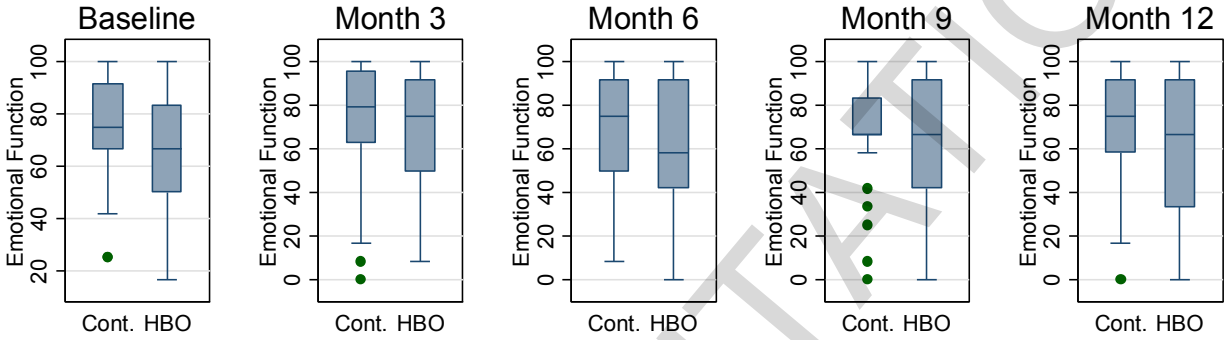



**Figure 5d: Cognitive function**

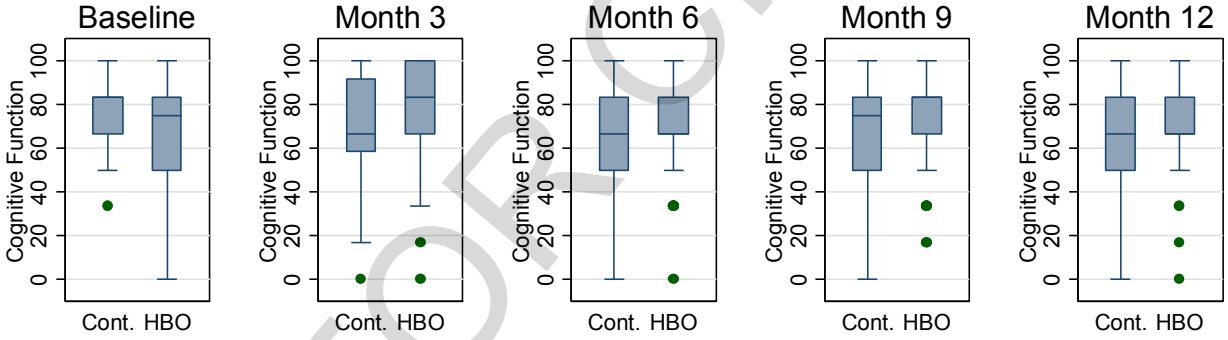



**Figure 5e: Social function**

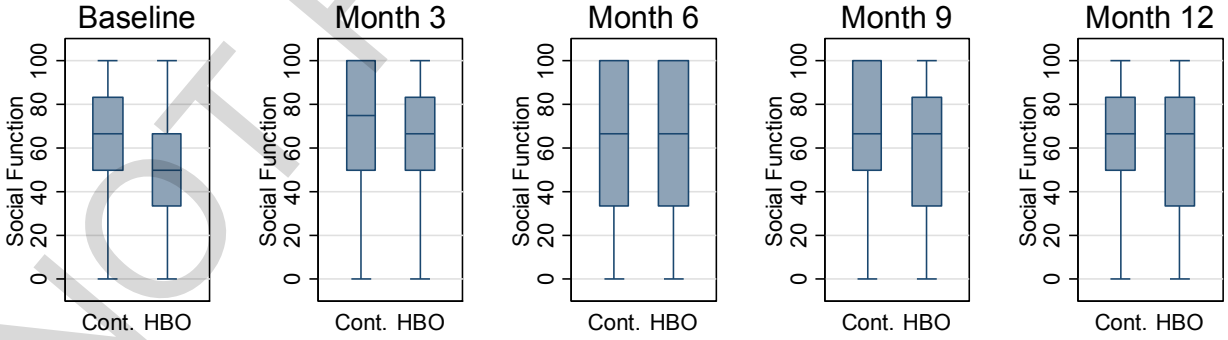


**Figure 5f: Global health status**

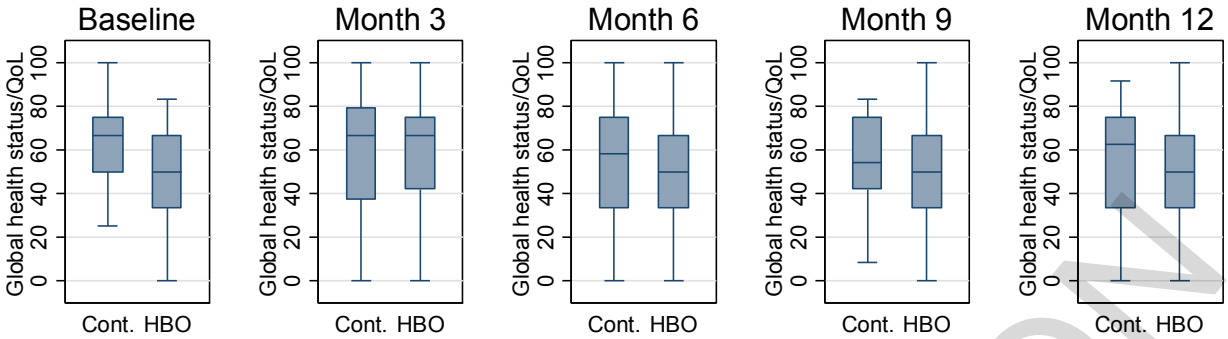



**Figure 5g: Fatigue**

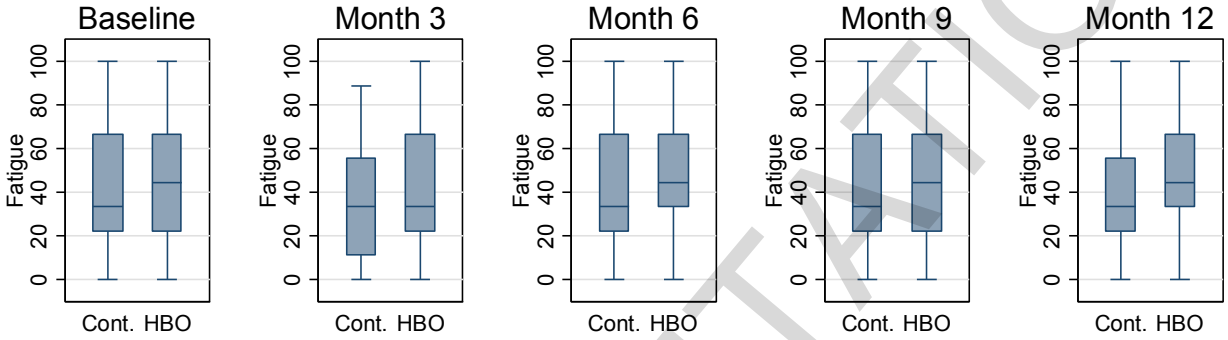



**Figure 5h: Nausea & vomiting**

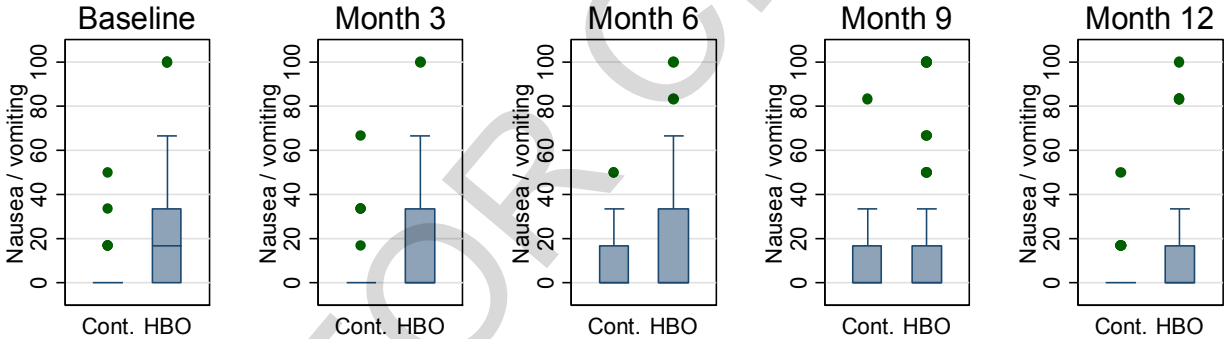



**Figure 5i: Pain**

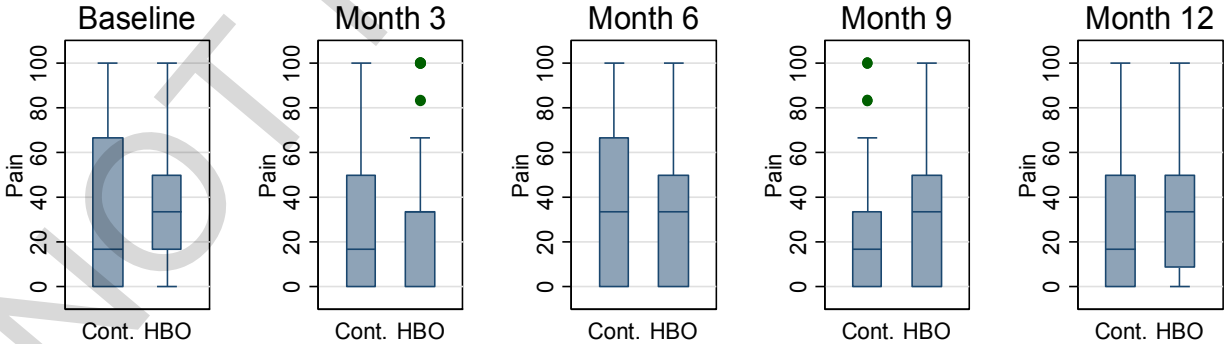


**Table18a: Baseline EORTC QLQ C30 scores by treatment group**

| | Control | | | | HBO | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Median | Lower quartile | Upper quartile | N | Median | Lower quartile | Upper quartile |
| Global health status | 29 | 66.67 | 50 | 75 | 55 | 50 | 33.33 | 66.67 |
| Physical function | 28 | 80 | 73.33 | 93.33 | 53 | 80 | 60 | 86.67 |
| Role function | 29 | 66.67 | 33.33 | 100 | 54 | 66.67 | 33.33 | 66.67 |
| Emotional function | 29 | 75 | 66.67 | 91.67 | 55 | 66.67 | 50 | 83.33 |
| Cognitive function | 29 | 83.33 | 66.67 | 83.33 | 54 | 75 | 50 | 83.33 |
| Social function | 29 | 66.67 | 50 | 83.33 | 55 | 50 | 33.33 | 66.67 |
| Fatigue | 29 | 33.33 | 22.22 | 66.67 | 55 | 44.44 | 22.22 | 66.67 |
| Nausea / vomiting | 29 | 0 | 0 | 0 | 55 | 16.67 | 0 | 33.33 |
| Pain | 29 | 16.67 | 0 | 66.67 | 55 | 33.33 | 16.67 | 50 |
| Dyspnoea | 29 | 0 | 0 | 33.33 | 55 | 0 | 0 | 33.33 |
| Insomnia | 29 | 33.33 | 0 | 66.67 | 55 | 33.33 | 33.33 | 66.67 |
| Appetite loss | 29 | 0 | 0 | 33.33 | 54 | 0 | 0 | 33.33 |
| Constipation | 29 | 0 | 0 | 33.33 | 55 | 0 | 0 | 33.33 |
| Diarrhoea | 29 | 33.33 | 0 | 66.67 | 55 | 33.33 | 0 | 66.67 |
| Financial problems | 29 | 0 | 0 | 33.33 | 55 | 0 | 0 | 33.33 |

**Table 18b: 3 months EORTC QLQ C30 scores by treatment group**

| | Control | | | | HBO | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Median | Lower quartile | Upper quartile | N | Median | Lower quartile | Upper quartile |
| Global health status | 24 | 66.67 | 37.5 | 79.17 | 41 | 66.67 | 41.67 | 75 |
| Physical function | 24 | 80 | 66.67 | 93.33 | 40 | 86.67 | 63.33 | 93.33 |
| Role function | 23 | 66.67 | 50 | 100 | 41 | 66.67 | 33.33 | 100 |
| Emotional function | 24 | 79.17 | 62.5 | 95.83 | 41 | 75 | 50 | 91.67 |
| Cognitive function | 24 | 66.67 | 58.33 | 91.67 | 41 | 83.33 | 66.67 | 100 |
| Social function | 24 | 75 | 50 | 100 | 41 | 66.67 | 50 | 83.33 |
| Fatigue | 24 | 33.33 | 11.11 | 55.56 | 41 | 33.33 | 22.22 | 66.67 |
| Nausea / vomiting | 24 | 0 | 0 | 0 | 41 | 0 | 0 | 33.33 |
| Pain | 24 | 16.67 | 0 | 50 | 41 | 33.33 | 0 | 33.33 |
| Dyspnoea | 24 | 0 | 0 | 33.33 | 41 | 0 | 0 | 33.33 |
| Insomnia | 24 | 33.33 | 0 | 66.67 | 41 | 33.33 | 33.33 | 66.67 |
| Appetite loss | 24 | 0 | 0 | 33.33 | 41 | 0 | 0 | 33.33 |
| Constipation | 24 | 0 | 0 | 33.33 | 41 | 0 | 0 | 33.33 |
| Diarrhoea | 24 | 33.33 | 0 | 33.33 | 41 | 33.33 | 0 | 33.33 |
| Financial problems | 24 | 0 | 0 | 50 | 41 | 0 | 0 | 33.33 |

**Table 18c: 6 months EORTC QLQ C30 scores by treatment group**

| | Control | | | | HBO | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Median | Lower quartile | Upper quartile | N | Median | Lower quartile | Upper quartile |
| Global health status | 27 | 58.33 | 33.33 | 75 | 49 | 50 | 33.33 | 66.67 |
| Physical function | 27 | 73.33 | 60 | 93.33 | 48 | 80 | 53.33 | 90 |
| Role function | 27 | 66.67 | 33.33 | 100 | 49 | 66.67 | 33.33 | 83.33 |
| Emotional function | 27 | 75 | 50 | 91.67 | 49 | 58.33 | 41.67 | 91.67 |
| Cognitive function | 27 | 66.67 | 50 | 83.33 | 49 | 66.67 | 66.67 | 83.33 |
| Social function | 26 | 66.67 | 33.33 | 100 | 49 | 66.67 | 33.33 | 100 |
| Fatigue | 27 | 33.33 | 22.22 | 66.67 | 49 | 44.44 | 33.33 | 66.67 |
| Nausea / vomiting | 27 | 0 | 0 | 16.67 | 49 | 0 | 0 | 33.33 |
| Pain | 27 | 33.33 | 0 | 66.67 | 49 | 33.33 | 0 | 50 |
| Dyspnoea | 27 | 0 | 0 | 33.33 | 48 | 0 | 0 | 33.33 |
| Insomnia | 27 | 33.33 | 0 | 66.67 | 49 | 33.33 | 33.33 | 66.67 |
| Appetite loss | 27 | 0 | 0 | 33.33 | 49 | 33.33 | 0 | 33.33 |
| Constipation | 27 | 0 | 0 | 33.33 | 49 | 0 | 0 | 33.33 |
| Diarrhoea | 27 | 33.33 | 0 | 33.33 | 49 | 33.33 | 33.33 | 66.67 |
| Financial problems | 27 | 0 | 0 | 66.67 | 49 | 0 | 0 | 33.33 |

**Table 18d: 9 months EORTC QLQ C30 scores by treatment group**

| | Control | | | | HBO | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Median | Lower quartile | Upper quartile | N | Median | Lower quartile | Upper quartile |
| Global health status | 26 | 54.17 | 41.67 | 75 | 47 | 50 | 33.33 | 66.67 |
| Physical function | 26 | 76.67 | 60 | 86.67 | 47 | 73.33 | 53.33 | 86.67 |
| Role function | 26 | 66.67 | 33.33 | 100 | 47 | 66.67 | 33.33 | 83.33 |
| Emotional function | 26 | 66.67 | 66.67 | 83.33 | 47 | 66.67 | 41.67 | 91.67 |
| Cognitive function | 26 | 75 | 50 | 83.33 | 47 | 83.33 | 66.67 | 83.33 |
| Social function | 26 | 66.67 | 50 | 100 | 47 | 66.67 | 33.33 | 83.33 |
| Fatigue | 26 | 33.33 | 22.22 | 66.67 | 47 | 44.44 | 22.22 | 66.67 |
| Nausea / vomiting | 26 | 0 | 0 | 16.67 | 47 | 0 | 0 | 16.67 |
| Pain | 26 | 16.67 | 0 | 33.33 | 47 | 33.33 | 0 | 50 |
| Dyspnoea | 26 | 0 | 0 | 33.33 | 47 | 33.33 | 0 | 33.33 |
| Insomnia | 26 | 33.33 | 0 | 66.67 | 47 | 33.33 | 0 | 66.67 |
| Appetite loss | 25 | 0 | 0 | 33.33 | 47 | 33.33 | 0 | 33.33 |
| Constipation | 26 | 33.33 | 0 | 33.33 | 47 | 0 | 0 | 33.33 |
| Diarrhoea | 26 | 33.33 | 0 | 66.67 | 47 | 33.33 | 0 | 66.67 |
| Financial problems | 26 | 0 | 0 | 66.67 | 47 | 0 | 0 | 33.33 |

**Table 18d: 12 months EORTC QLQ C30 scores by treatment group**

| | Control | | | | HBO | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Median | Lower quartile | Upper quartile | N | Median | Lower quartile | Upper quartile |
| Global health status | 26 | 62.5 | 33.33 | 75 | 48 | 50 | 33.33 | 66.67 |
| Physical function | 26 | 80 | 60 | 93.33 | 48 | 80 | 53.33 | 86.67 |
| Role function | 26 | 66.67 | 33.33 | 100 | 48 | 66.67 | 33.33 | 83.33 |
| Emotional function | 26 | 75 | 58.33 | 91.67 | 48 | 66.67 | 33.33 | 91.67 |
| Cognitive function | 26 | 66.67 | 50 | 83.33 | 48 | 66.67 | 66.67 | 83.33 |
| Social function | 26 | 66.67 | 50 | 83.33 | 48 | 66.67 | 33.33 | 83.33 |
| Fatigue | 26 | 33.33 | 22.22 | 55.56 | 48 | 44.44 | 33.33 | 66.67 |
| Nausea / vomiting | 26 | 0 | 0 | 0 | 48 | 0 | 0 | 16.67 |
| Pain | 26 | 16.67 | 0 | 50 | 48 | 33.33 | 8.33 | 50 |
| Dyspnoea | 26 | 0 | 0 | 33.33 | 48 | 0 | 0 | 33.33 |
| Insomnia | 26 | 33.33 | 0 | 66.67 | 48 | 33.33 | 0 | 66.67 |
| Appetite loss | 26 | 0 | 0 | 33.33 | 48 | 0 | 0 | 33.33 |
| Constipation | 26 | 16.67 | 0 | 33.33 | 48 | 0 | 0 | 33.33 |
| Diarrhoea | 26 | 33.33 | 0 | 66.67 | 48 | 33.33 | 0 | 66.67 |
| Financial problems | 26 | 0 | 0 | 33.33 | 48 | 0 | 0 | 33.33 |

## 8.2 CR38

EORTC CR38 is a supplementary questionnaire which consists of 38 questions, scored in the same way as EORTC C30. There are 4 function scales (body image, sexual function, sexual enjoyment and future perspective) and 8 symptom scales (micturition problems, gastrointestinal problems, chemotherapy side-effects (excluded), defecation problems, stoma-related problems (excluded), male sexual problems, female sexual problems and weight loss). Boxplots given for scales with more than 1 item (i.e. not sexual enjoyment, future perspective or weight loss). Figures 6a-g show boxplots of each of the scales at each time point, by treatment group. Scores for each treatment group are tabulated in tables 19a-e below.

**Figure 6a: Female sexual problems**

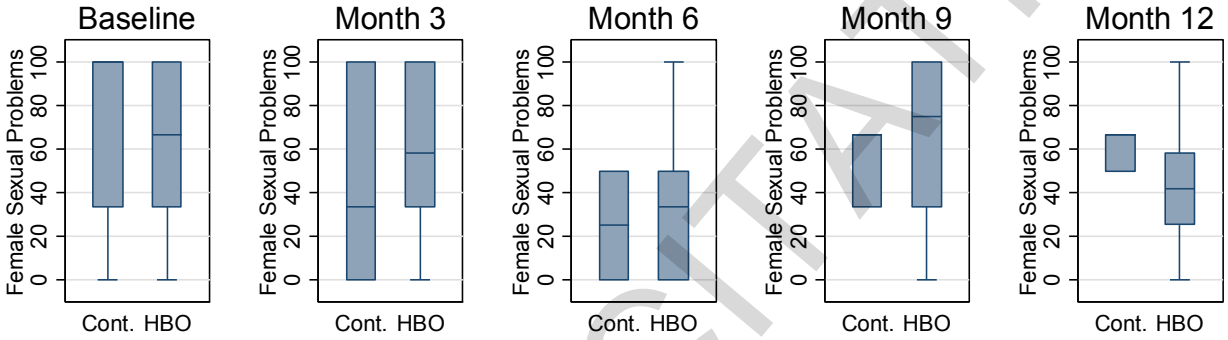



**Figure 6b: Body image**

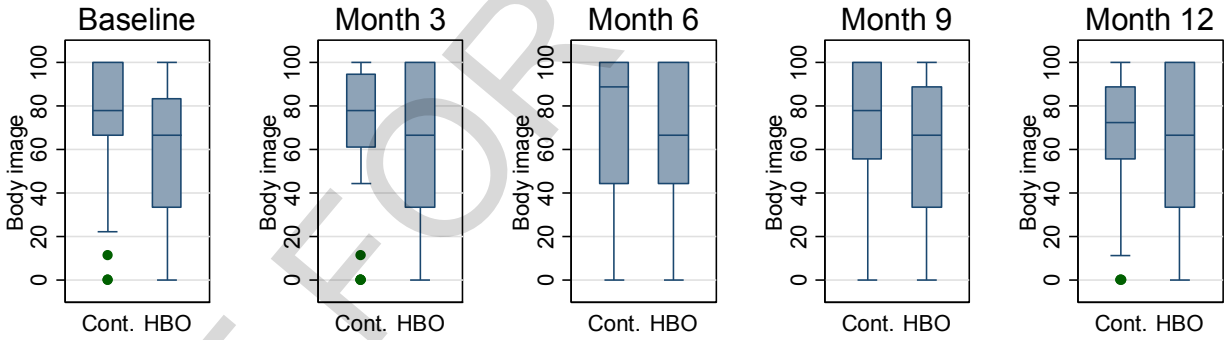



**Figure 6c: Defecation symptoms**

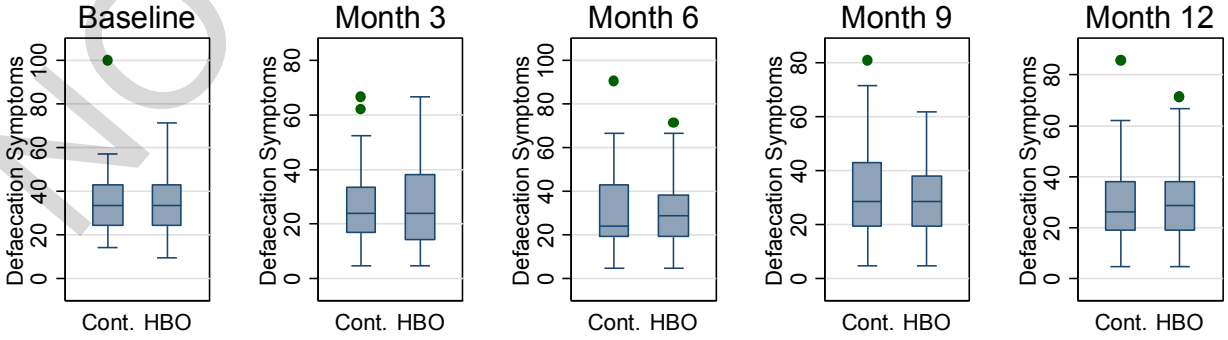


**Figure 6d: Gastrointestinal symptoms**

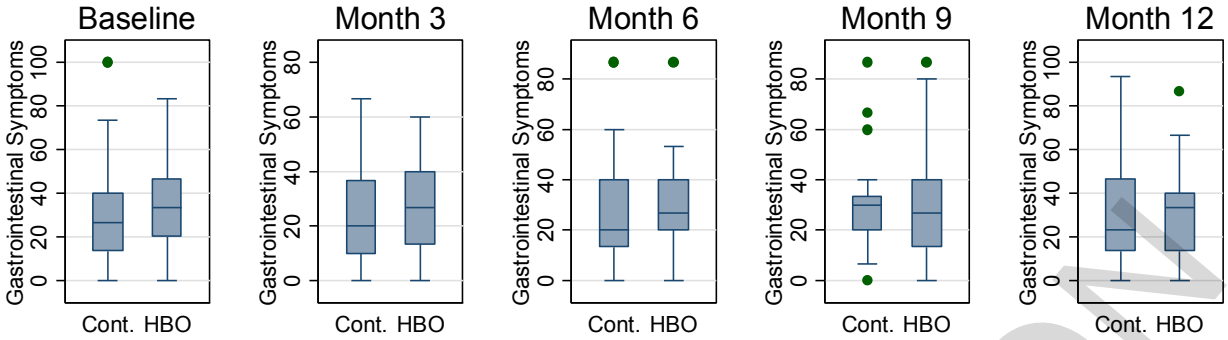



**Figure 6e: Micturition problems**

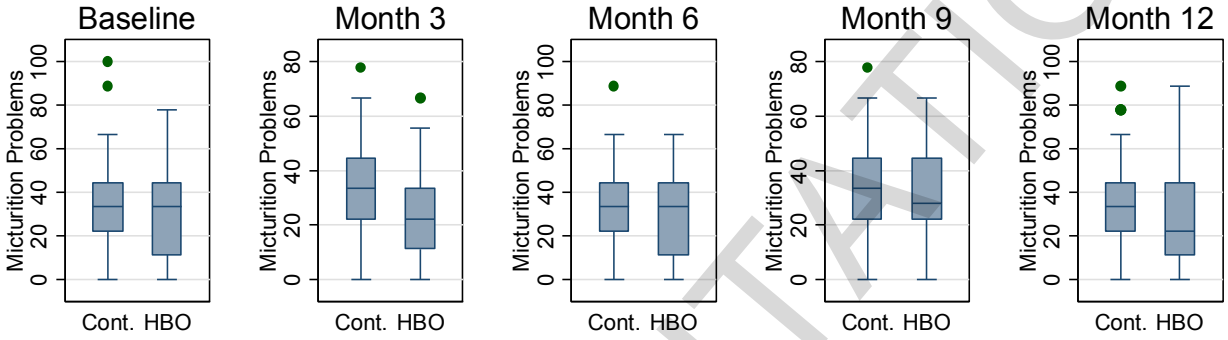



**Figure 6f: Male sexual problems**

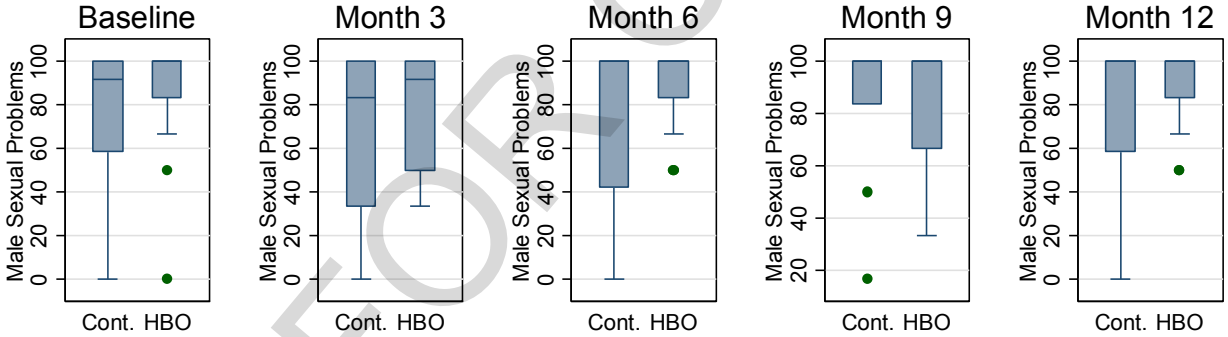



**Figure 6g: Sexual function**

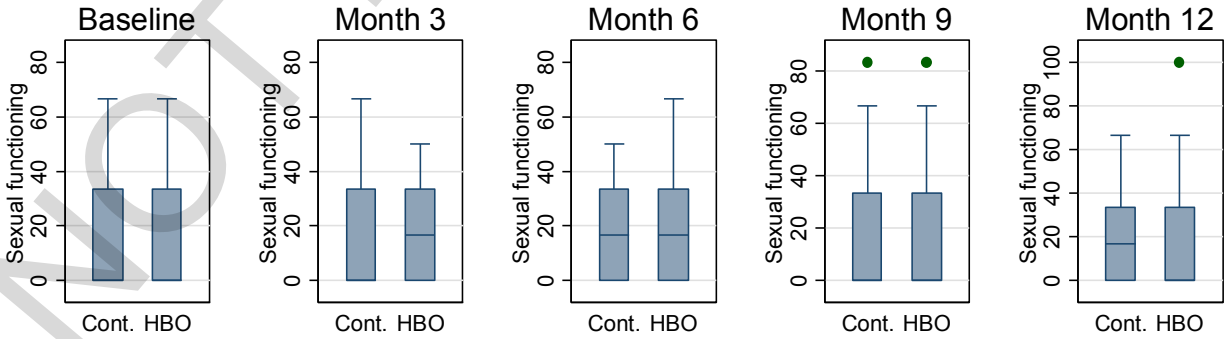


**Table 19a: Baseline EORTC QLQ CR38 scores by treatment group**

| | Control | | | | HBO | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Median | Lower quartile | Upper quartile | N | Median | Lower quartile | Upper quartile |
| Body image | 29 | 77.78 | 66.67 | 100 | 54 | 66.67 | 33.33 | 83.33 |
| Sexual function | 29 | 0 | 0 | 33.33 | 52 | 0 | 0 | 33.33 |
| Sexual enjoyment | 8 | 33.33 | 33.33 | 66.67 | 15 | 33.33 | 33.33 | 66.67 |
| Future perspective | 29 | 66.67 | 33.33 | 66.67 | 55 | 33.33 | 0 | 66.67 |
| Micturition problems | 28 | 33.33 | 22.22 | 44.44 | 55 | 33.33 | 11.11 | 44.44 |
| GI problems | 29 | 26.67 | 13.33 | 40 | 55 | 33.33 | 20 | 46.67 |
| Chemotherapy symptoms | 29 | 16.67 | 11.11 | 22.22 | 55 | 22.22 | 11.11 | 33.33 |
| Defecation symptoms | 29 | 33.33 | 23.81 | 42.86 | 55 | 33.33 | 23.81 | 42.86 |
| Male sexual problems | 12 | 91.67 | 58.33 | 100 | 20 | 100 | 83.33 | 100 |
| Female sexual problems | 5 | 100 | 33.33 | 100 | 9 | 66.67 | 33.33 | 100 |
| Weight loss | 29 | 0 | 0 | 33.33 | 55 | 0 | 0 | 33.33 |

**Table 19b: 3 months EORTC QLQ CR38 scores by treatment group**

| | Control | | | | HBO | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Median | Lower quartile | Upper quartile | N | Median | Lower quartile | Upper quartile |
| Body image | 24 | 77.78 | 61.11 | 94.44 | 41 | 66.67 | 33.33 | 100 |
| Sexual function | 24 | 0 | 0 | 33.33 | 39 | 16.67 | 0 | 33.33 |
| Sexual enjoyment | 7 | 33.33 | 33.33 | 33.33 | 14 | 33.33 | 0 | 33.33 |
| Future perspective | 24 | 66.67 | 66.67 | 83.33 | 41 | 66.67 | 33.33 | 100 |
| Micturition problems | 23 | 33.33 | 22.22 | 44.44 | 40 | 22.22 | 11.11 | 33.33 |
| GI problems | 24 | 20 | 10 | 36.67 | 41 | 26.67 | 13.33 | 40 |
| Chemotherapy symptoms | 24 | 11.11 | 5.56 | 27.78 | 41 | 11.11 | 0 | 22.22 |
| Defecation symptoms | 24 | 23.81 | 16.67 | 33.33 | 39 | 23.81 | 14.29 | 38.1 |
| Male sexual problems | 13 | 83.33 | 33.33 | 100 | 14 | 91.67 | 50 | 100 |
| Female sexual problems | 3 | 33.33 | 0 | 100 | 6 | 58.33 | 33.33 | 100 |
| Weight loss | 24 | 0 | 0 | 0 | 41 | 0 | 0 | 0 |

**Table 19c: 6 months EORTC QLQ CR38 scores by treatment group**

| | Control | | | | HBO | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Median | Lower quartile | Upper quartile | N | Median | Lower quartile | Upper quartile |
| Body image | 27 | 88.89 | 44.44 | 100 | 49 | 66.67 | 44.44 | 100 |
| Sexual function | 25 | 16.67 | 0 | 33.33 | 45 | 16.67 | 0 | 33.33 |
| Sexual enjoyment | 4 | 66.67 | 50 | 66.67 | 13 | 33.33 | 33.33 | 66.67 |
| Future perspective | 27 | 66.67 | 33.33 | 66.67 | 49 | 66.67 | 33.33 | 66.67 |
| Micturition problems | 26 | 33.33 | 22.22 | 44.44 | 48 | 33.33 | 11.11 | 44.44 |
| GI problems | 27 | 20 | 13.33 | 40 | 49 | 26.67 | 20 | 40 |
| Chemotherapy symptoms | 27 | 11.11 | 11.11 | 22.22 | 49 | 11.11 | 11.11 | 22.22 |
| Defecation symptoms | 27 | 23.81 | 19.05 | 42.86 | 49 | 28.57 | 19.05 | 38.1 |
| Male sexual problems | 12 | 100 | 41.67 | 100 | 18 | 100 | 83.33 | 100 |
| Female sexual problems | 2 | 25 | 0 | 50 | 7 | 33.33 | 0 | 50 |
| Weight loss | 26 | 0 | 0 | 0 | 49 | 0 | 0 | 33.33 |

**Table 19d: 9 months EORTC QLQ CR38 scores by treatment group**

| | Control | | | | HBO | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Median | Lower quartile | Upper quartile | N | Median | Lower quartile | Upper quartile |
| Body image | 26 | 77.78 | 55.56 | 100 | 47 | 66.67 | 33.33 | 88.89 |
| Sexual function | 25 | 0 | 0 | 33.33 | 44 | 0 | 0 | 33.33 |
| Sexual enjoyment | 6 | 50 | 33.33 | 66.67 | 12 | 33.33 | 33.33 | 66.67 |
| Future perspective | 26 | 66.67 | 33.33 | 66.67 | 47 | 66.67 | 33.33 | 66.67 |
| Micturition problems | 25 | 33.33 | 22.22 | 44.44 | 46 | 27.78 | 22.22 | 44.44 |
| GI problems | 26 | 30 | 20 | 33.33 | 47 | 26.67 | 13.33 | 40 |
| Chemotherapy symptoms | 26 | 11.11 | 11.11 | 22.22 | 47 | 11.11 | 11.11 | 33.33 |
| Defecation symptoms | 26 | 28.57 | 19.05 | 42.86 | 47 | 28.57 | 19.05 | 38.1 |
| Male sexual problems | 11 | 100 | 83.33 | 100 | 18 | 100 | 66.67 | 100 |
| Female sexual problems | 3 | 66.67 | 33.33 | 66.67 | 6 | 75 | 33.33 | 100 |
| Weight loss | 26 | 0 | 0 | 0 | 47 | 0 | 0 | 33.33 |

**Table 19e: 12 months EORTC QLQ CR38 scores by treatment group**

| | Control | | | | HBO | | | |
|---|---|---|---|---|---|---|---|---|
| | N | Median | Lower quartile | Upper quartile | N | Median | Lower quartile | Upper quartile |
| Body image | 26 | 72.22 | 55.56 | 88.89 | 48 | 66.67 | 33.33 | 100 |
| Sexual function | 25 | 16.67 | 0 | 33.33 | 48 | 0 | 0 | 33.33 |
| Sexual enjoyment | 9 | 33.33 | 33.33 | 66.67 | 16 | 33.33 | 33.33 | 66.67 |
| Future perspective | 26 | 66.67 | 33.33 | 66.67 | 48 | 50 | 33.33 | 66.67 |
| Micturition problems | 25 | 33.33 | 22.22 | 44.44 | 46 | 22.22 | 11.11 | 44.44 |
| GI problems | 26 | 23.33 | 13.33 | 46.67 | 48 | 33.33 | 13.33 | 40 |
| Chemotherapy symptoms | 26 | 11.11 | 0 | 33.33 | 48 | 11.11 | 0 | 33.33 |
| Defecation symptoms | 26 | 26.19 | 19.05 | 38.1 | 48 | 28.57 | 19.05 | 38.1 |
| Male sexual problems | 12 | 100 | 58.33 | 100 | 16 | 100 | 83.33 | 100 |
| Female sexual problems | 3 | 66.67 | 50 | 66.67 | 8 | 41.67 | 25 | 58.33 |
| Weight loss | 26 | 0 | 0 | 0 | 48 | 0 | 0 | 33.33 |

**Analysis of EORTC over time**

Figures 7a-o and 8a-h show mean change from baseline at each time point for each of the EORTC QLQ C30 and CR38 subscales. Patients are included for each time point at which they completed a questionnaire so the number of patients included at each time point may not be equal.

Tables 20a-d and 21a-d show number of patients in each group and mean change from baseline with corresponding 99% CI, split by treatment group. P-values shown come from ANCOVA model adjusted for baseline score.

**Figure 7a: Global health status by treatment**

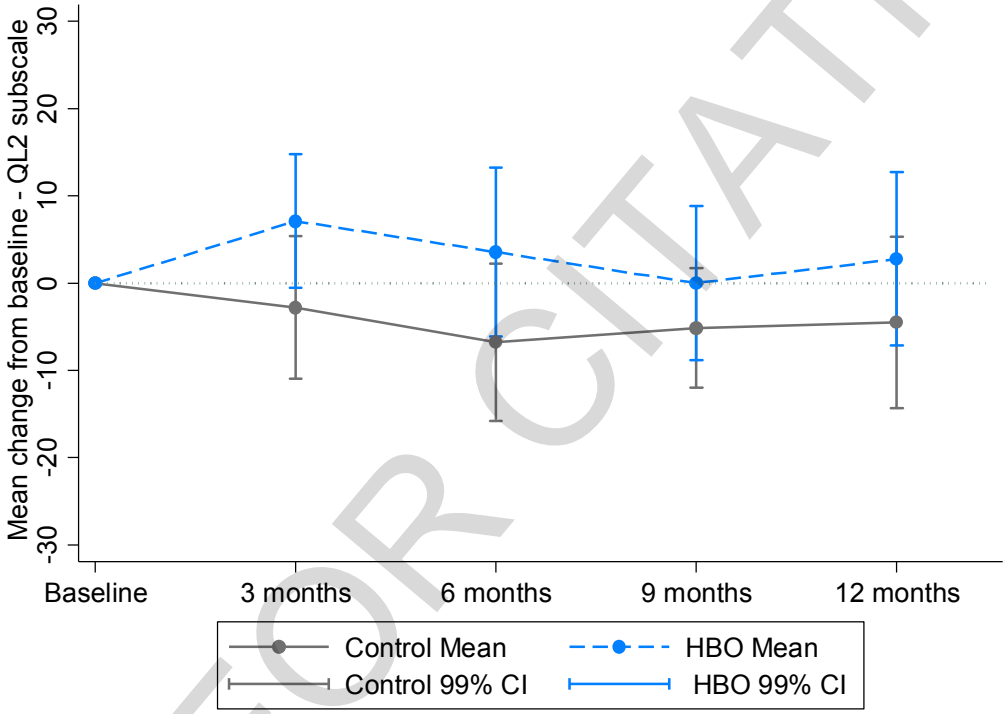


**Figure 7b: Physical function by treatment**

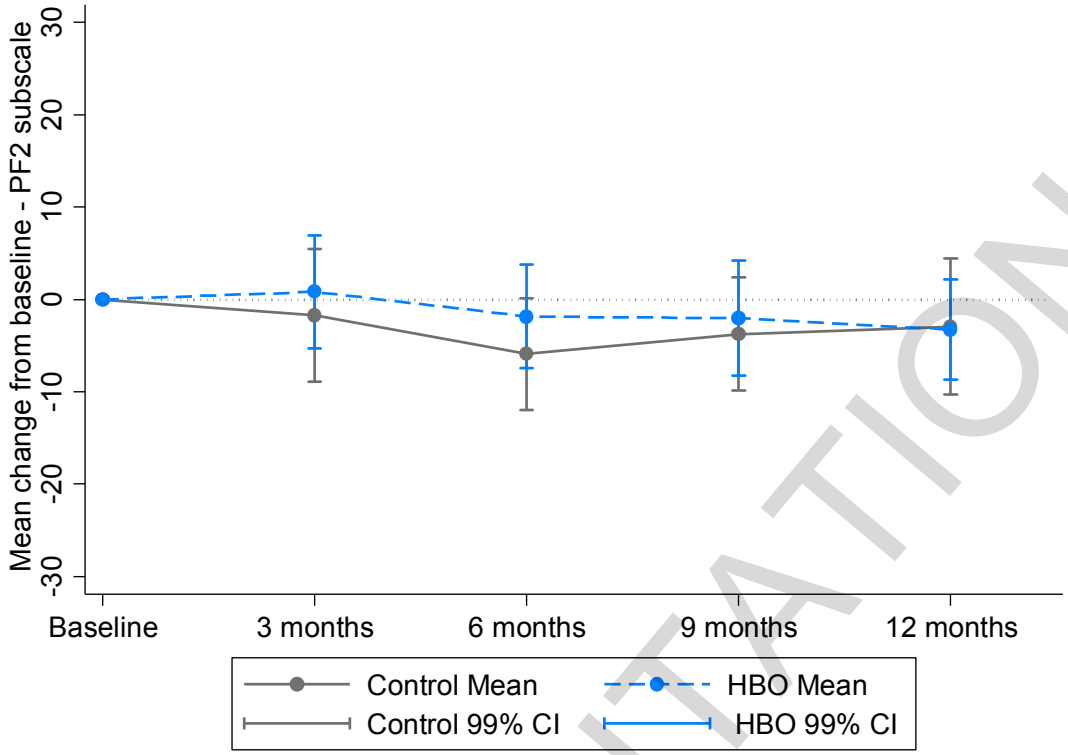



**Figure 7c: Role function by treatment**

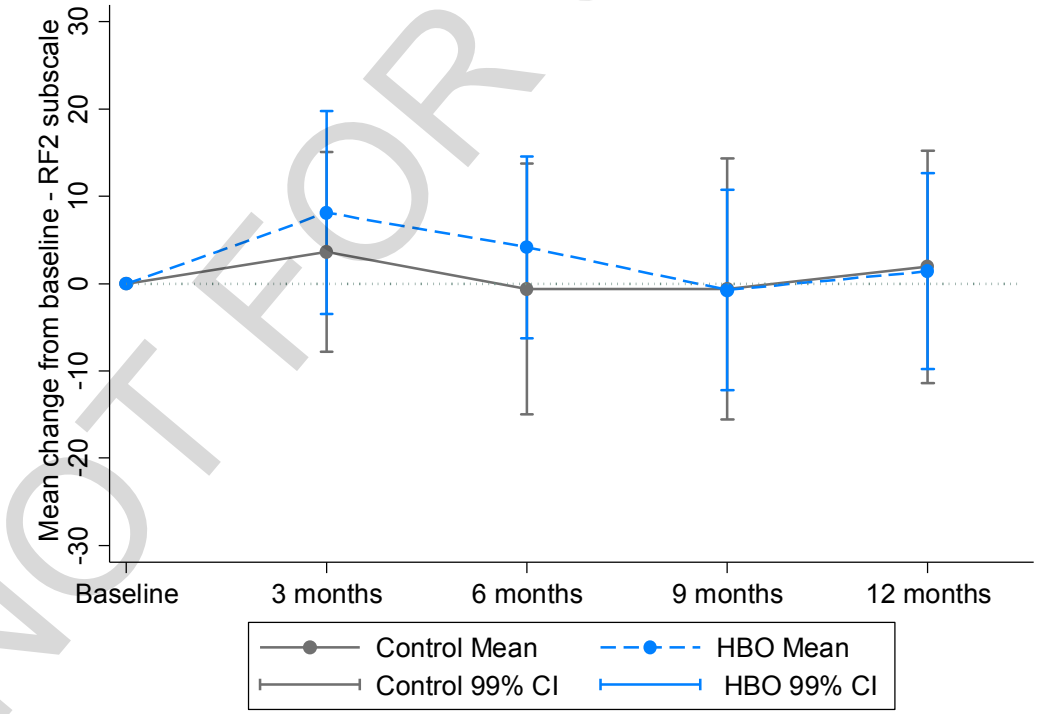


**Figure 7d: Emotional function by treatment**

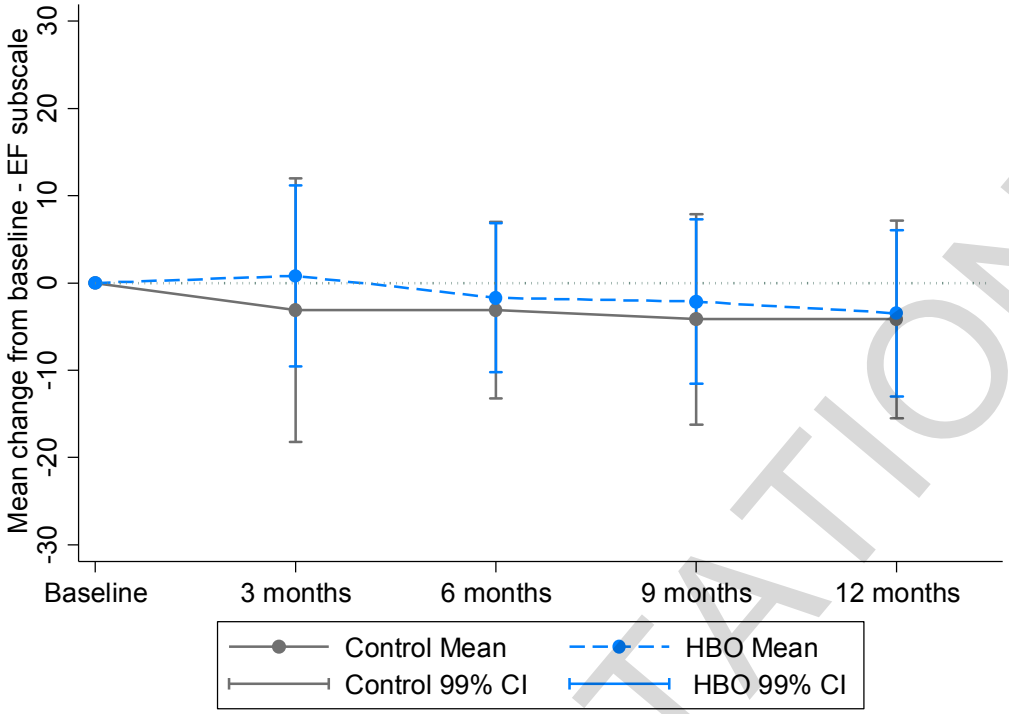



**Figure 7e: Cognitive function by treatment**

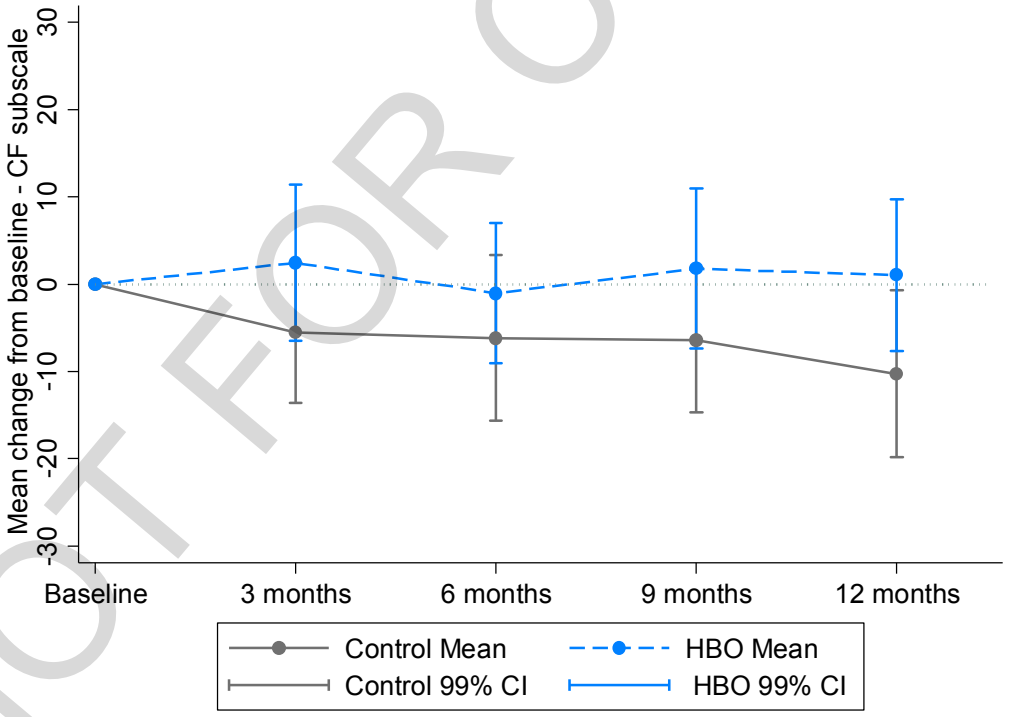


**Figure 7f: Social function by treatment**

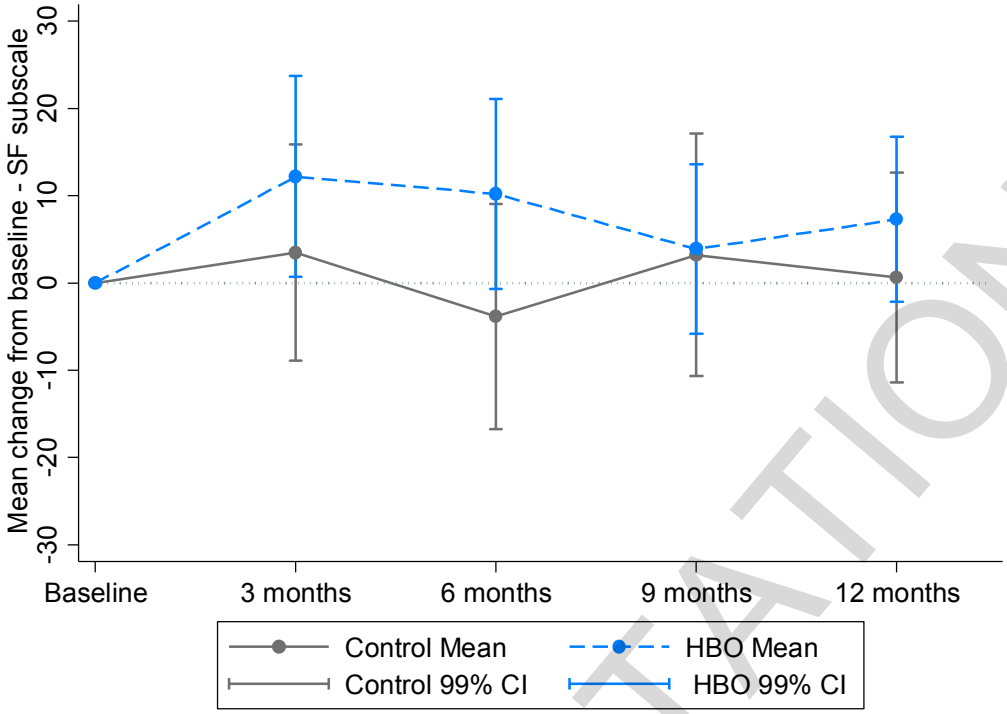



**Figure 7g: Fatigue by treatment**

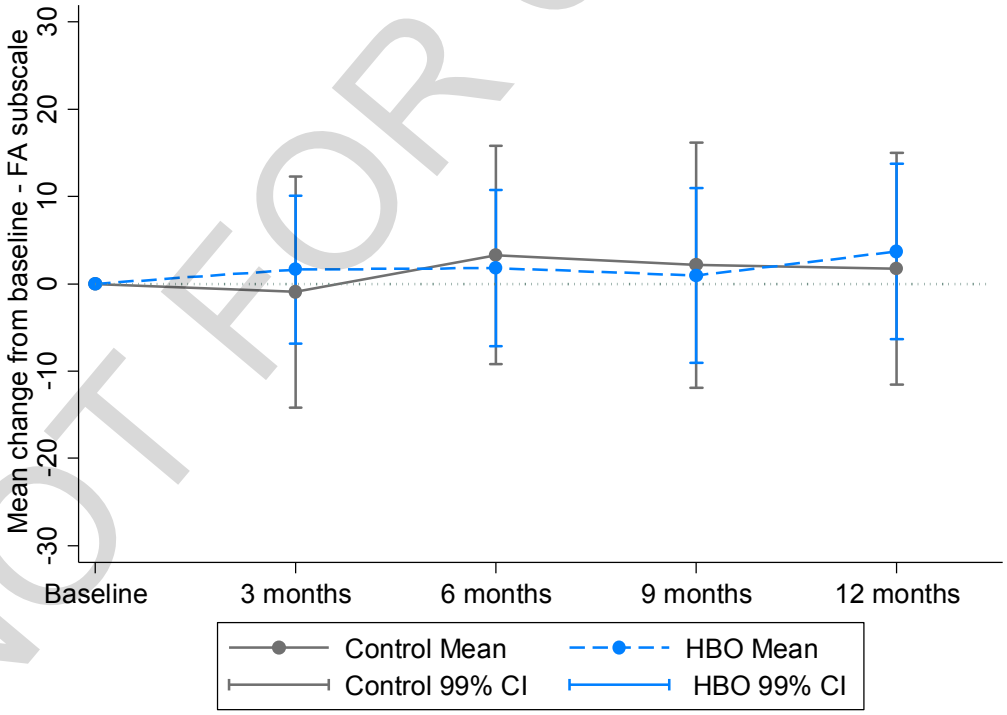


**Figure 7h: Nausea & vomiting by treatment**

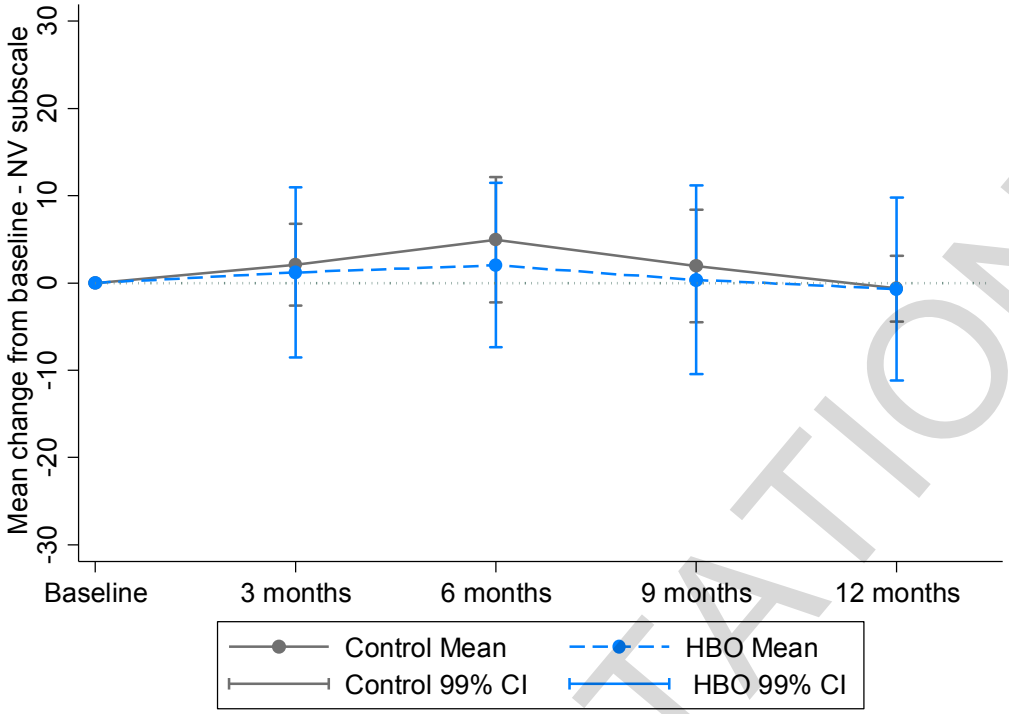



**Figure 7i: Pain by treatment**

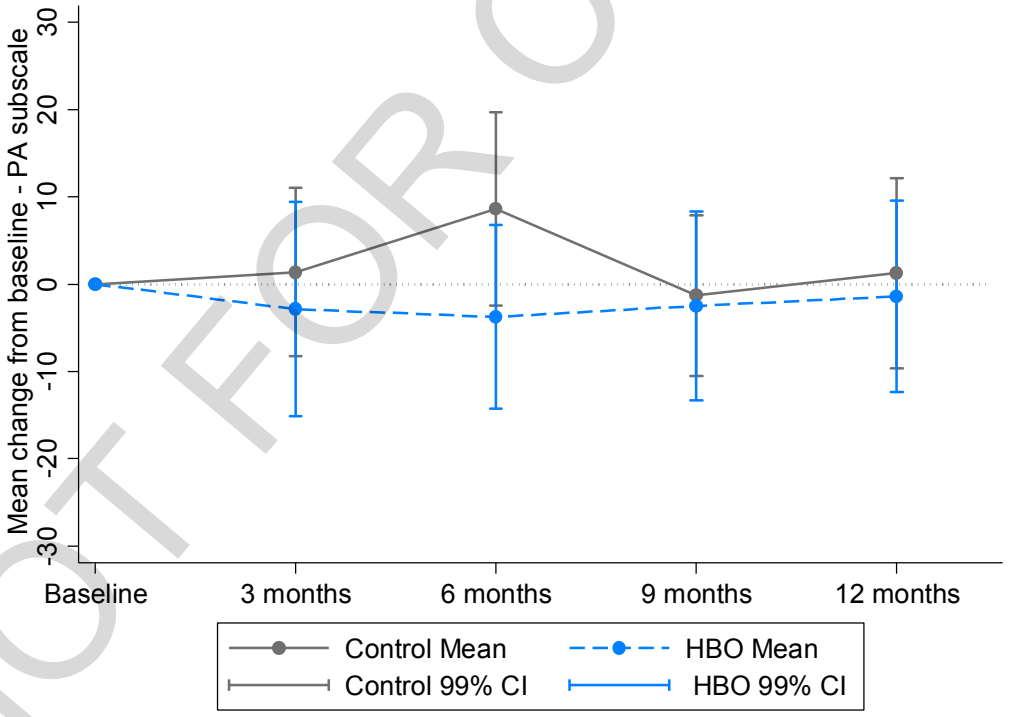


**Figure 7j: Dyspnoea by treatment**

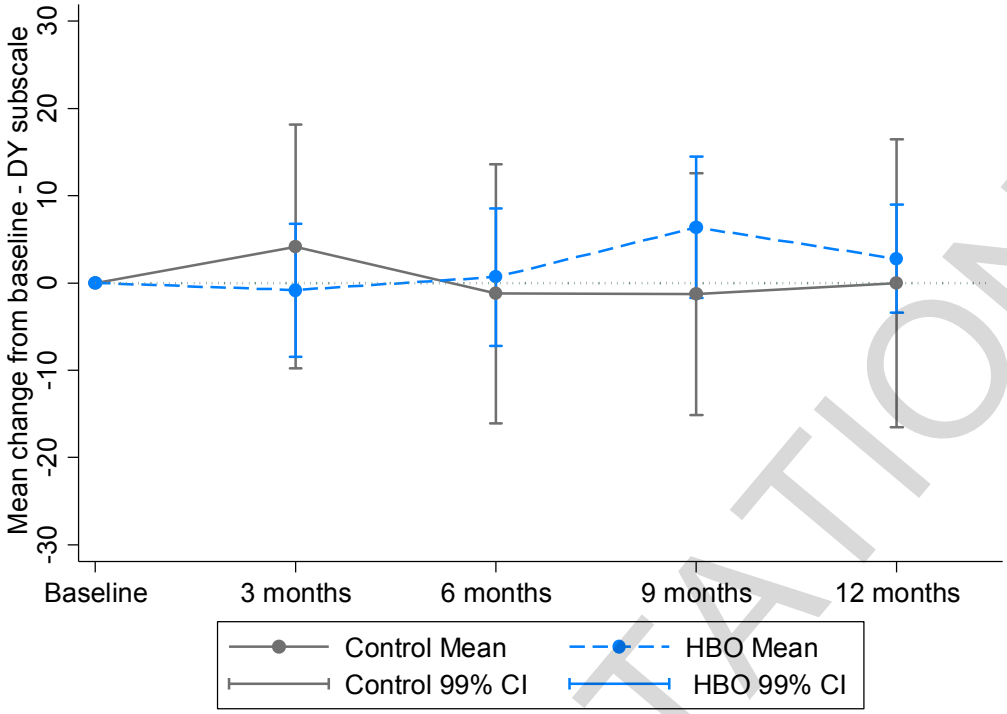



**Figure 7k: Insomnia by treatment**

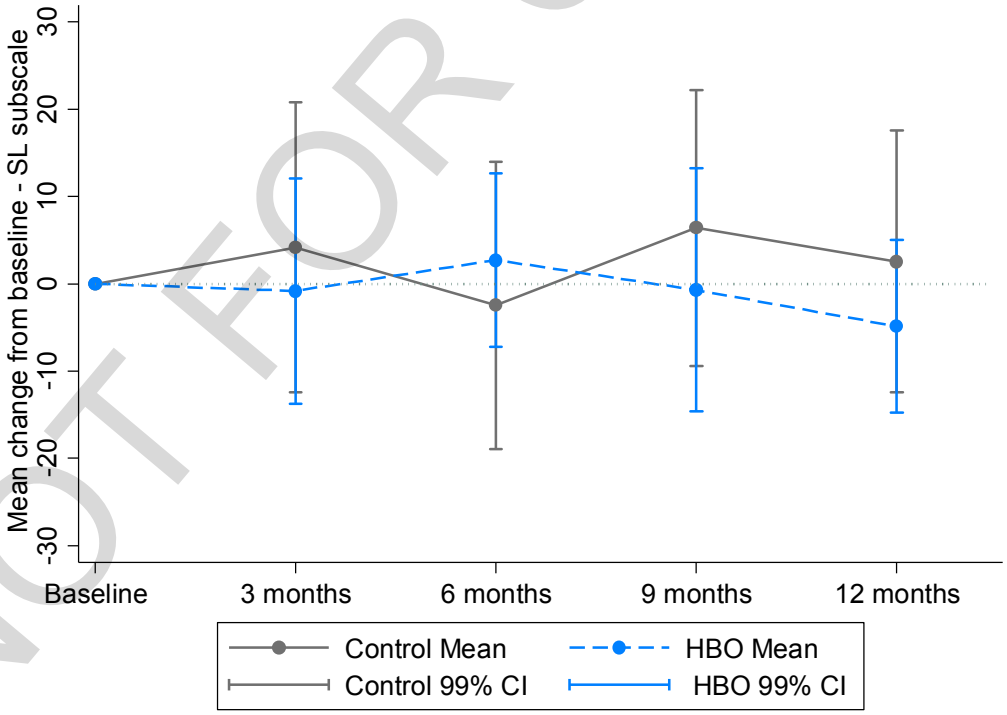


**Figure 7l: Appetite loss by treatment**

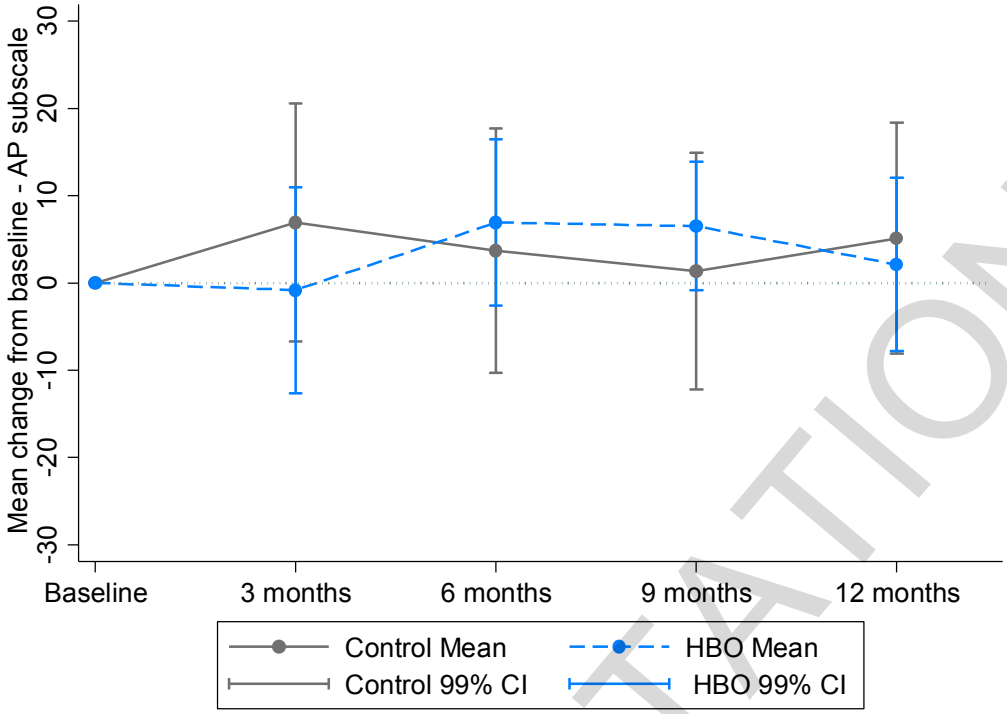



**Figure 7m: Constipation by treatment**

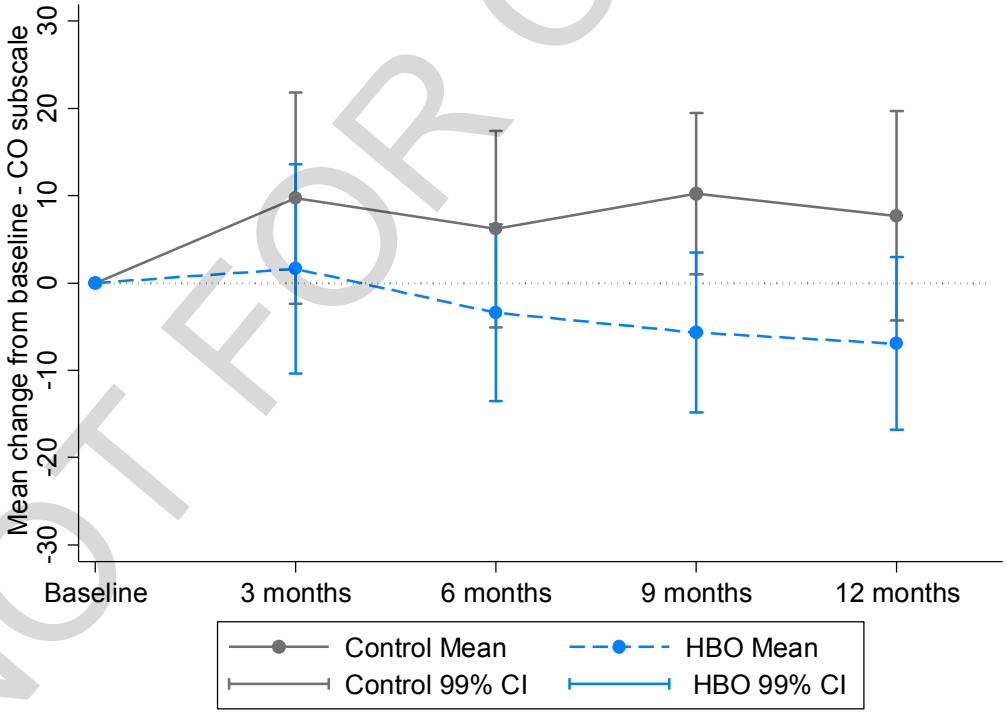


**Figure 7n: Diarrhoea by treatment**

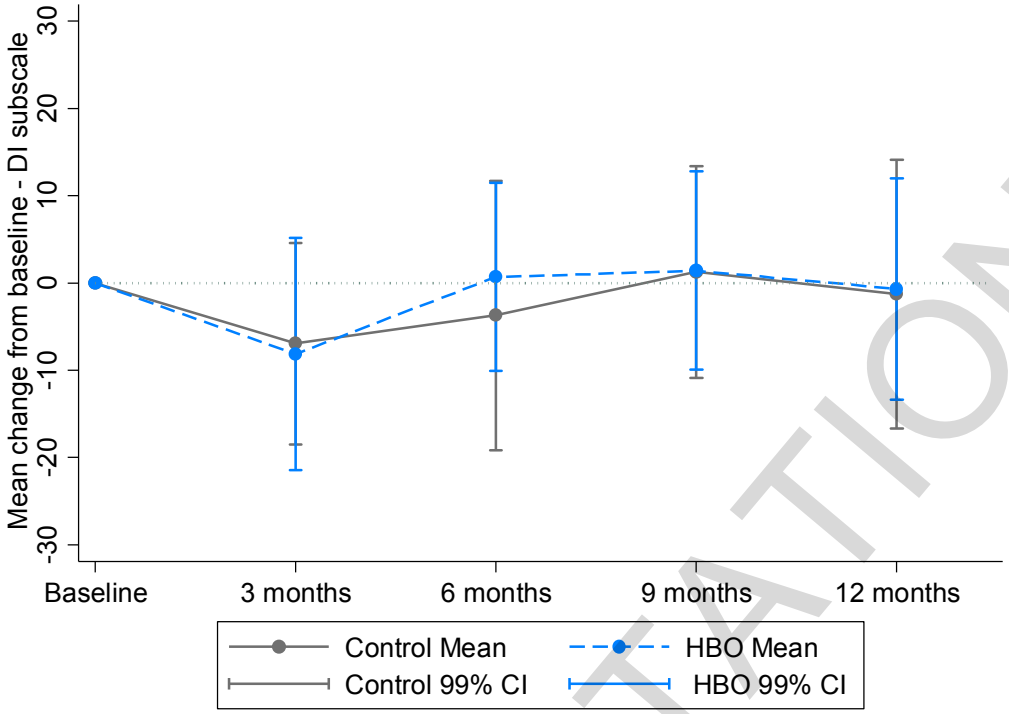



**Figure 7o: Financial problems by treatment**

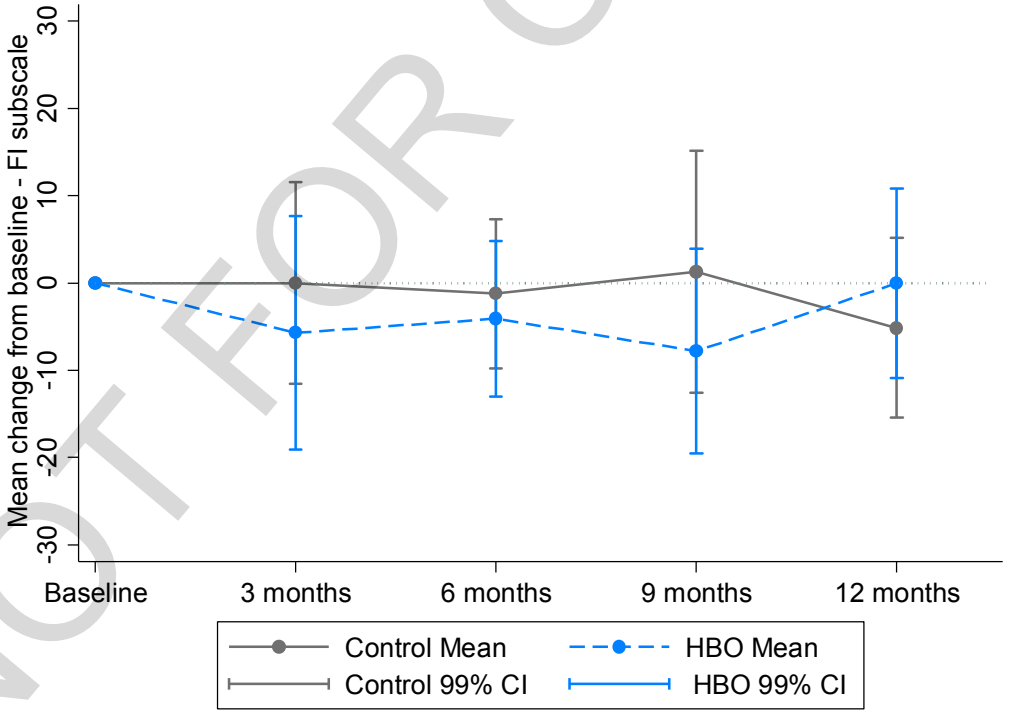


**Table 20a: Change from baseline to month 3 by treatment**

| | Control | | | HBO | | | Control v. HBO | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean change from BL | 99% CI | n | Mean change from BL | 99% CI | Difference (Control-HBO) | 99% CI |
| Global health status | 24 | -2.8 | -11.6 - 6.1 | 41 | 7.1 | -0.9 - 15.2 | -9.9 | -22.1 - 2.3 |
| Physical function | 23 | -1.7 | -9.6 - 6.1 | 40 | 0.8 | -5.6 - 7.3 | -2.6 | -12.6 - 7.5 |
| Role function | 23 | 3.6 | -8.9 - 16.1 | 41 | 8.1 | -4.1 - 20.3 | -4.5 | -22.8 - 13.8 |
| Emotional function | 24 | -3.1 | -19.6 - 13.3 | 41 | 0.8 | -10.1 - 11.7 | -3.9 | -22.3 - 14.4 |
| Cognitive function | 24 | -5.6 | -14.3 - 3.2 | 41 | 2.4 | -6.9 - 11.8 | -8.0 | -21.6 - 5.6 |
| Social function | 24 | 3.5 | -10.0 - 17.0 | 41 | 12.2 | 0.1 - 24.3 | -8.7 | -27.1 - 9.6 |
| Fatigue | 24 | -0.9 | -15.3 - 13.5 | 41 | 1.6 | -7.3 - 10.5 | -2.6 | -18.0 - 12.9 |
| Nausea / vomiting | 24 | 2.1 | -3.0 - 7.2 | 41 | 1.2 | -9.0 - 11.5 | 0.9 | -12.8 - 14.6 |
| Pain | 24 | 1.4 | -9.1 - 11.9 | 41 | -2.8 | -15.7 - 10.0 | 4.2 | -14.0 - 22.5 |
| Dyspnoea | 24 | 4.2 | -11.1 - 19.4 | 41 | -0.8 | -8.8 - 7.2 | 5.0 | -10.1 - 20.0 |
| Insomnia | 24 | 4.2 | -13.9 - 22.3 | 41 | -0.8 | -14.3 - 12.7 | 5.0 | -16.8 - 26.7 |
| Appetite loss | 24 | 6.9 | -7.9 - 21.8 | 41 | -0.8 | -13.2 - 11.6 | 7.8 | -11.5 - 27.0 |
| Constipation | 24 | 9.7 | -3.5 - 22.9 | 41 | 1.6 | -10.9 - 14.2 | 8.1 | -10.7 - 26.9 |
| Diarrhoea | 24 | -6.9 | -19.5 - 5.6 | 41 | -8.1 | -22.1 - 5.9 | 1.2 | -19.0 - 21.4 |
| Financial problems | 24 | 0.0 | -12.6 - 12.6 | 41 | -5.7 | -19.7 - 8.4 | 5.7 | -14.5 - 25.9 |

**Table 20b: Change from baseline to month 6 by treatment**

| | Control | | | HBO | | | Control v. HBO | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean change from BL | 99% CI | n | Mean change from BL | 99% CI | Difference (Control-HBO) | 99% CI |
| Global health status | 27 | -6.8 | -16.5 - 2.9 | 49 | 3.6 | -6.5 - 13.7 | -10.4 | -25.4 - 4.7 |
| Physical function | 26 | -5.9 | -12.4 - 0.6 | 47 | -1.8 | -7.7 - 4.0 | -4.1 | -13.1 - 5.0 |
| Role function | 27 | -0.6 | -16.1 - 14.9 | 48 | 4.2 | -6.7 - 15.0 | -4.8 | -22.9 - 13.3 |
| Emotional function | 27 | -3.1 | -14.0 - 7.8 | 49 | -1.7 | -10.6 - 7.2 | -1.4 | -15.5 - 12.7 |
| Cognitive function | 27 | -6.2 | -16.4 - 4.1 | 49 | -1.0 | -9.4 - 7.4 | -5.2 | -18.4 - 8.1 |
| Social function | 26 | -3.8 | -17.8 - 10.1 | 49 | 10.2 | -1.1 - 21.6 | -14.1 | -32.2 - 4.1 |
| Fatigue | 27 | 3.3 | -10.2 - 16.8 | 49 | 1.8 | -7.5 - 11.1 | 1.5 | -14.1 - 17.1 |
| Nausea / vomiting | 27 | 4.9 | -2.8 - 12.7 | 49 | 2.0 | -7.8 - 11.9 | 2.9 | -11.3 - 17.1 |
| Pain | 27 | 8.6 | -3.3 - 20.6 | 49 | -3.7 | -14.7 - 7.2 | 12.4 | -4.4 - 29.2 |
| Dyspnoea | 27 | -1.2 | -17.2 - 14.8 | 48 | 0.7 | -7.5 - 8.9 | -1.9 | -17.6 - 13.8 |
| Insomnia | 27 | -2.5 | -20.2 - 15.3 | 49 | 2.7 | -7.7 - 13.1 | -5.2 | -23.8 - 13.4 |
| Appetite loss | 27 | 3.7 | -11.4 - 18.8 | 48 | 6.9 | -3.0 - 16.9 | -3.2 | -20.2 - 13.7 |
| Constipation | 27 | 6.2 | -6.0 - 18.3 | 49 | -3.4 | -13.9 - 7.1 | 9.6 | -6.8 - 26.0 |
| Diarrhoea | 27 | -3.7 | -20.3 - 12.9 | 49 | 0.7 | -10.5 - 11.9 | -4.4 | -23.3 - 14.6 |
| Financial problems | 27 | -1.2 | -10.5 - 8.0 | 49 | -4.1 | -13.3 - 5.2 | 2.8 | -11.1 - 16.8 |

**Table 20c: Change from baseline to month 9 by treatment**

| | Control | | | HBO | | | Control v. HBO | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean change from BL | 99% CI | n | Mean change from BL | 99% CI | Difference (Control-HBO) | 99% CI |
| Global health status | 26 | -5.1 | -12.5 - 2.3 | 47 | 0.0 | -9.2 - 9.2 | -5.1 | -18.4 - 8.2 |
| Physical function | 25 | -3.7 | -10.4 - 2.9 | 46 | -2.0 | -8.5 - 4.5 | -1.7 | -11.6 - 8.1 |
| Role function | 26 | -0.6 | -16.8 - 15.6 | 46 | -0.7 | -12.7 - 11.3 | 0.1 | -19.4 - 19.6 |
| Emotional function | 26 | -4.2 | -17.2 - 8.9 | 47 | -2.1 | -12.0 - 7.7 | -2.0 | -18.0 - 13.9 |
| Cognitive function | 26 | -6.4 | -15.4 - 2.5 | 47 | 1.8 | -7.8 - 11.3 | -8.2 | -22.4 - 6.0 |
| Social function | 26 | 3.2 | -11.8 - 18.2 | 47 | 3.9 | -6.2 - 14.0 | -0.7 | -17.8 - 16.4 |
| Fatigue | 26 | 2.1 | -13.0 - 17.3 | 47 | 0.9 | -9.5 - 11.4 | 1.2 | -16.3 - 18.7 |
| Nausea / vomiting | 26 | 1.9 | -5.1 - 8.9 | 47 | 0.4 | -10.9 - 11.6 | 1.6 | -14.2 - 17.3 |
| Pain | 26 | -1.3 | -11.2 - 8.7 | 47 | -2.5 | -13.8 - 8.8 | 1.2 | -15.4 - 17.8 |
| Dyspnoea | 26 | -1.3 | -16.3 - 13.7 | 47 | 6.4 | -2.1 - 14.8 | -7.7 | -23.1 - 7.7 |
| Insomnia | 26 | 6.4 | -10.7 - 23.5 | 47 | -0.7 | -15.2 - 13.8 | 7.1 | -15.6 - 29.9 |
| Appetite loss | 25 | 1.3 | -13.4 - 16.1 | 46 | 6.5 | -1.2 - 14.2 | -5.2 | -19.7 - 9.3 |
| Constipation | 26 | 10.3 | 0.3 - 20.3 | 47 | -5.7 | -15.2 - 3.9 | 15.9 | 1.4 - 30.4 |
| Diarrhoea | 26 | 1.3 | -11.8 - 14.4 | 47 | 1.4 | -10.4 - 13.3 | -0.1 | -18.4 - 18.1 |
| Financial problems | 26 | 1.3 | -13.7 - 16.3 | 47 | -7.8 | -20.0 - 4.4 | 9.1 | -10.3 - 28.5 |

**Table 20d: Change from baseline to month 12 by treatment**

| | Control | | | HBO | | | Control v. HBO | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean change from BL | 99% CI | n | Mean change from BL | 99% CI | Difference (Control-HBO) | 99% CI |
| Global health status | 26 | -4.5 | -15.1 - 6.2 | 48 | 2.8 | -7.6 - 13.1 | -7.3 | -23.0 - 8.5 |
| Physical function | 25 | -2.9 | -10.9 - 5.1 | 47 | -3.3 | -8.9 - 2.4 | 0.3 | -9.1 - 9.7 |
| Role function | 26 | 1.9 | -12.5 - 16.3 | 47 | 1.4 | -10.3 - 13.1 | 0.5 | -18.1 - 19.1 |
| Emotional function | 26 | -4.2 | -16.4 - 8.1 | 48 | -3.5 | -13.4 - 6.5 | -0.7 | -16.5 - 15.1 |
| Cognitive function | 26 | -10.3 | -20.6 - 0.1 | 48 | 1.0 | -8.0 - 10.1 | -11.3 | -25.4 - 2.8 |
| Social function | 26 | 0.6 | -12.4 - 13.6 | 48 | 7.3 | -2.6 - 17.2 | -6.7 | -22.7 - 9.4 |
| Fatigue | 26 | 1.7 | -12.6 - 16.1 | 48 | 3.7 | -6.8 - 14.2 | -2.0 | -19.2 - 15.3 |
| Nausea / vomiting | 26 | -0.6 | -4.7 - 3.4 | 48 | -0.7 | -11.6 - 10.2 | 0.1 | -14.9 - 15.0 |
| Pain | 26 | 1.3 | -10.5 - 13.1 | 48 | -1.4 | -12.8 - 10.1 | 2.7 | -14.8 - 20.1 |
| Dyspnoea | 26 | 0.0 | -17.9 - 17.9 | 48 | 2.8 | -3.7 - 9.2 | -2.8 | -17.9 - 12.3 |
| Insomnia | 26 | 2.6 | -13.7 - 18.8 | 48 | -4.9 | -15.2 - 5.5 | 7.4 | -10.4 - 25.3 |
| Appetite loss | 26 | 5.1 | -9.2 - 19.4 | 47 | 2.1 | -8.2 - 12.5 | 3.0 | -14.0 - 20.0 |
| Constipation | 26 | 7.7 | -5.3 - 20.6 | 48 | -6.9 | -17.2 - 3.4 | 14.6 | -1.9 - 31.1 |
| Diarrhoea | 26 | -1.3 | -18.0 - 15.4 | 48 | -0.7 | -13.9 - 12.5 | -0.6 | -21.8 - 20.6 |
| Financial problems | 26 | -5.1 | -16.3 - 6.0 | 48 | 0.0 | -11.3 - 11.3 | -5.1 | -22.2 - 11.9 |

**Figure 8a: Body image by treatment**

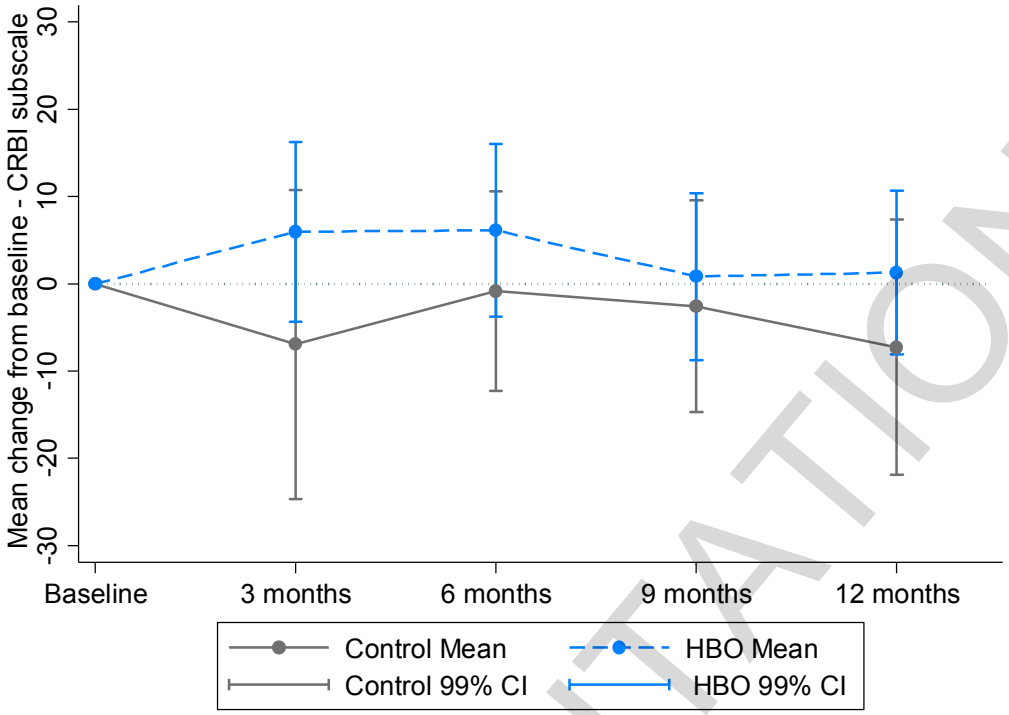



**Figure 8b: Sexual function by treatment**

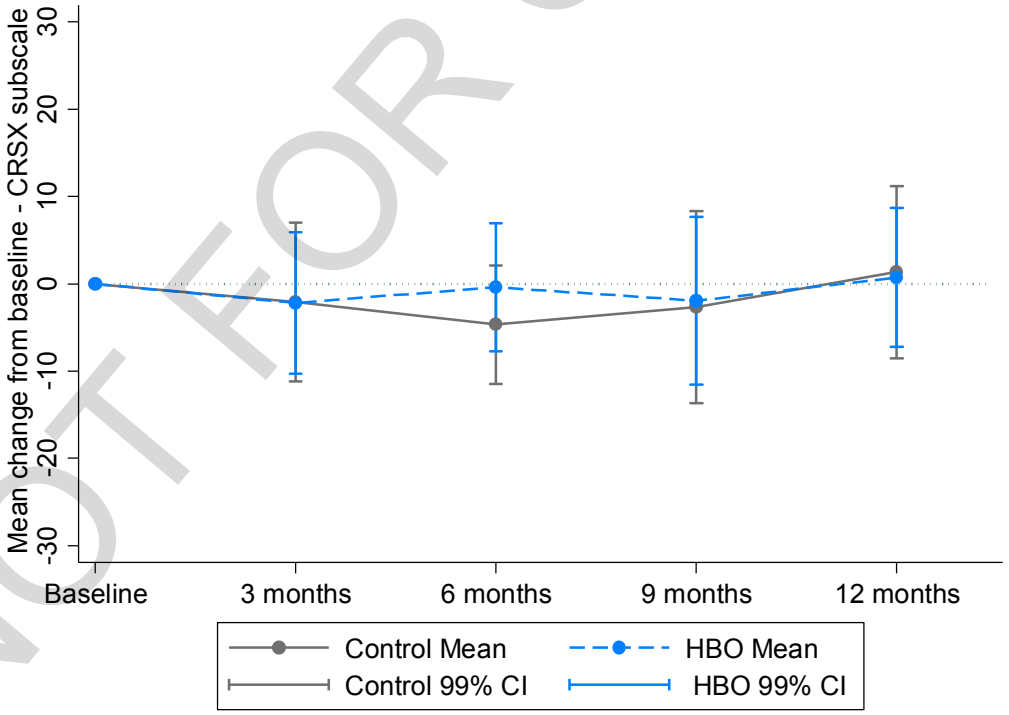


**Figure 8c: Sexual enjoyment by treatment**

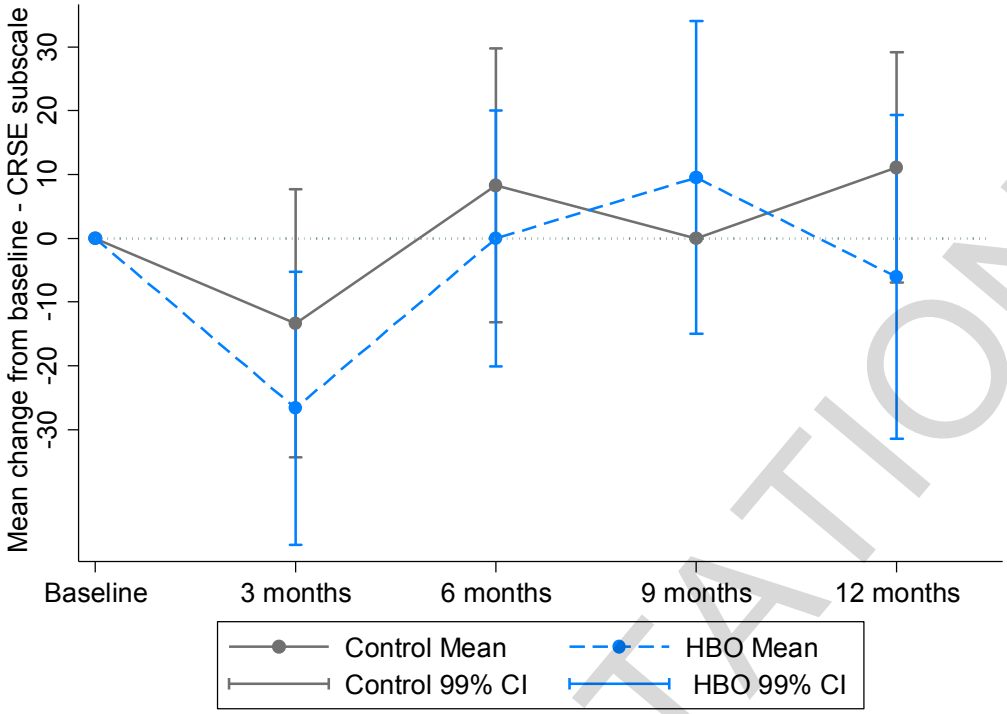



**Figure 8d: Future perspective by treatment**

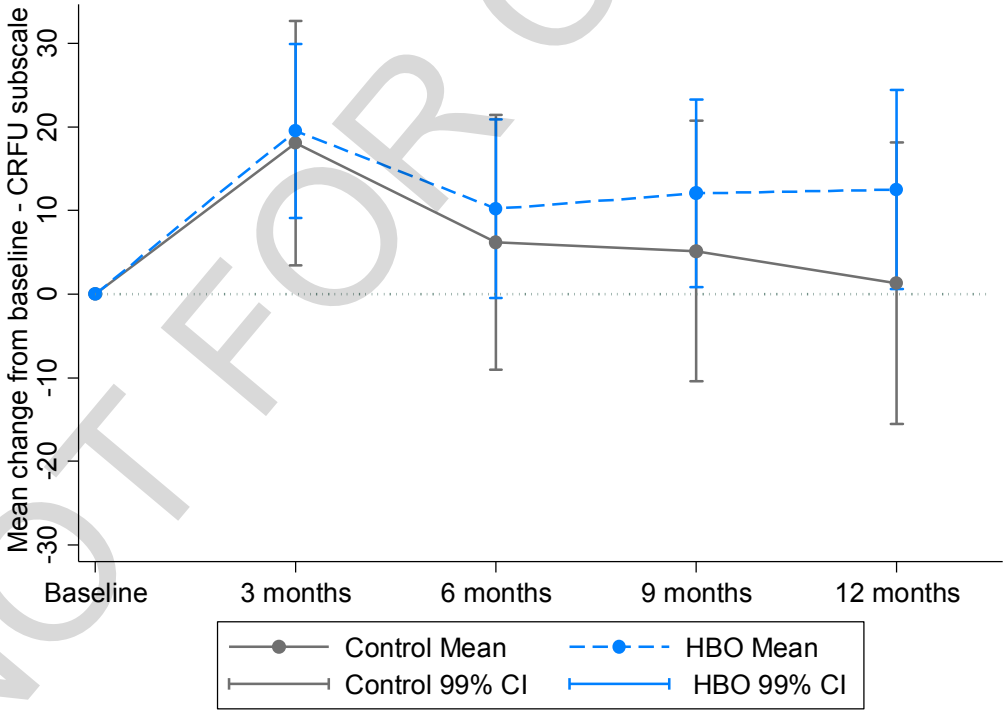


**Figure 8e: Micturition problems by treatment**

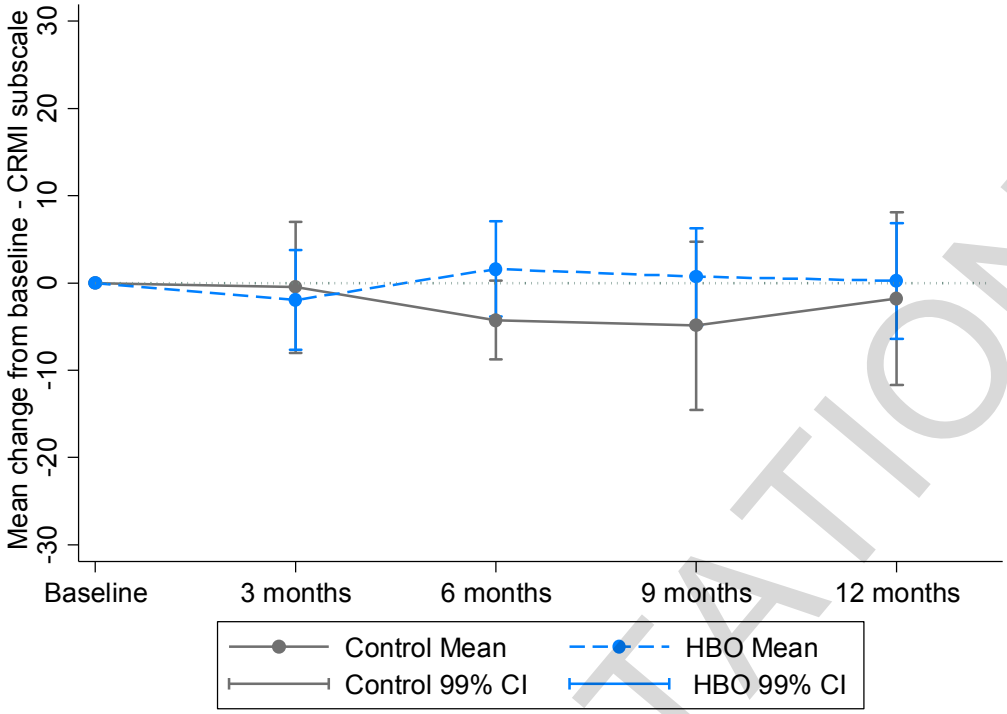



**Figure 8f: GI problems by treatment**

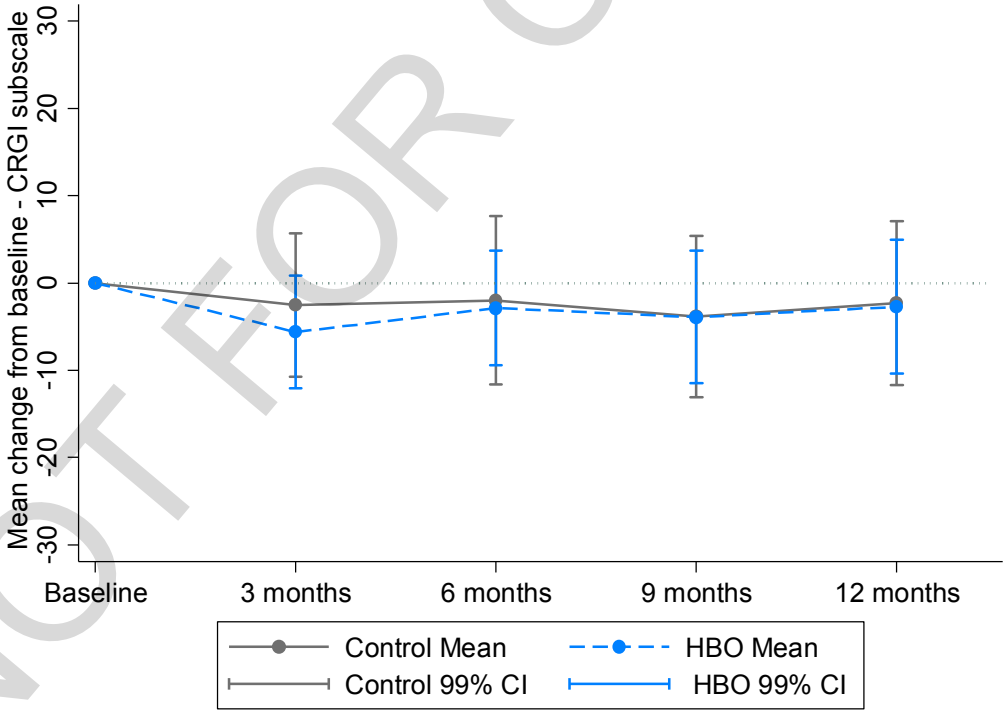


**Figure 8g: Chemotherapy symptoms by treatment**

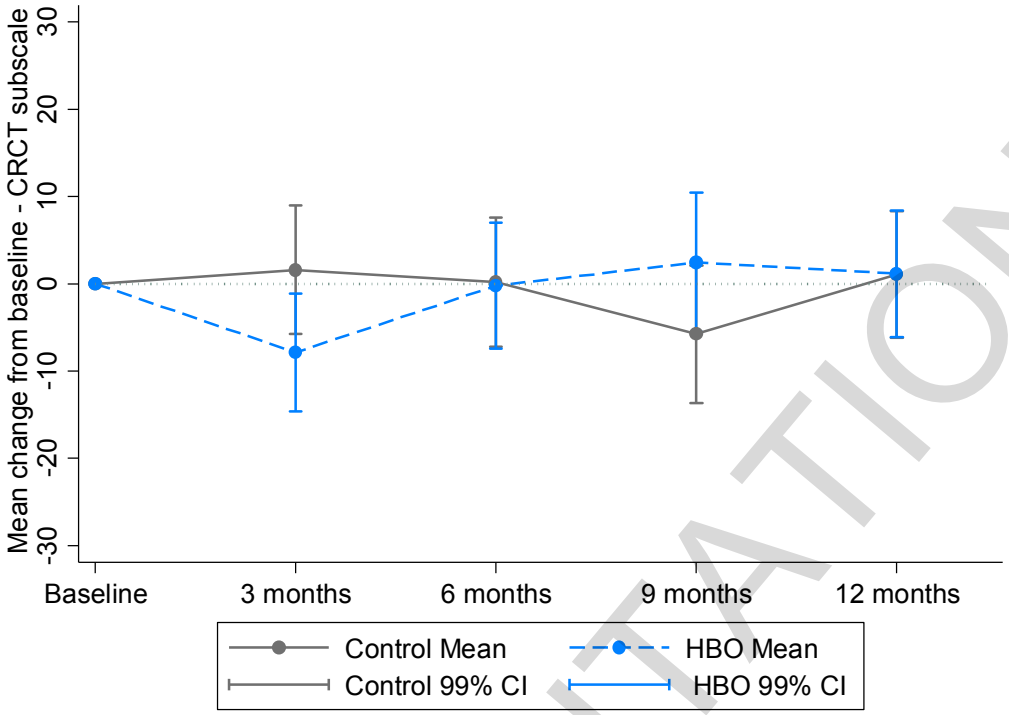
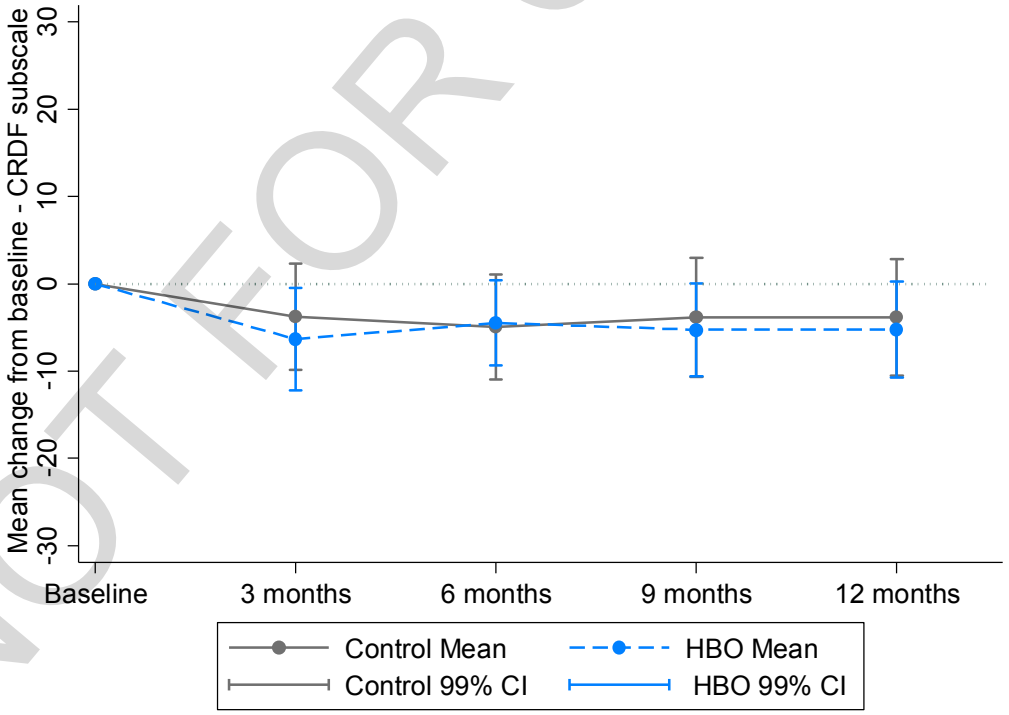



**Figure 8h: Defecation symptoms by treatment**




Not enough data were available to produce plots for male and female sexual problems, weight loss or stoma questions.

**Table 21a: Change from baseline to month 3 by treatment**

| | Control | | | HBO | | | Control v. HBO | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean change from BL | 99% CI | n | Mean change from BL | 99% CI | Difference (Control-HBO) | 99% CI |
| Body image | 24 | -6.9 | -26.3 - 12.4 | 40 | 6.0 | -4.8 - 16.8 | -12.9 | -32.6 - 6.8 |
| Sexual function | 24 | -2.1 | -12.0 - 7.8 | 38 | -2.2 | -10.8 - 6.4 | 0.1 | -12.8 - 13.0 |
| Sexual enjoyment | 5 | -13.3 | -50.9 - 24.3 | 10 | -26.7 | -53.7 - 0.4 | 13.3 | -26.4 - 53.1 |
| Future perspective | 24 | 18.1 | 2.1 - 34.0 | 41 | 19.5 | 8.6 - 30.4 | -1.5 | -19.6 - 16.7 |
| Micturition problems | 23 | -0.5 | -8.7 - 7.7 | 40 | -1.9 | -7.9 - 4.0 | 1.5 | -8.3 - 11.2 |
| GI problems | 24 | -2.5 | -11.4 - 6.4 | 41 | -5.6 | -12.4 - 1.2 | 3.1 | -7.7 - 13.9 |
| Chemotherapy symptoms | 24 | 1.6 | -6.4 - 9.7 | 41 | -7.9 | -14.9 - -0.8 | 9.5 | -1.3 - 20.3 |
| Defecation symptoms | 24 | -3.8 | -10.4 - 2.9 | 39 | -6.3 | -12.5 - -0.1 | 2.6 | -6.6 - 11.8 |
| Male sexual problems | 11 | -12.1 | -49.2 - 25.0 | 13 | -15.4 | -35.7 - 5.0 | 3.3 | -33.2 - 39.8 |
| Female sexual problems | 3 | 0.0 | 0.0 - 0.0 | 6 | -2.8 | -14.0 - 8.4 | 2.8 | -11.5 - 17.0 |
| Weight loss | 24 | -8.3 | -22.4 - 5.7 | 41 | 0.0 | -11.4 - 11.4 | -8.3 | -26.1 - 9.5 |

**Table 21b: Change from baseline to month 6 by treatment**

| | Control | | | HBO | | | Control v. HBO | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean change from BL | 99% CI | n | Mean change from BL | 99% CI | Difference (Control-HBO) | 99% CI |
| Body image | 27 | -0.8 | -13.1 - 11.5 | 48 | 6.1 | -4.2 - 16.5 | -7.0 | -23.1 - 9.2 |
| Sexual function | 25 | -4.7 | -12.0 - 2.7 | 44 | -0.4 | -8.0 - 7.3 | -4.3 | -15.6 - 7.0 |
| Sexual enjoyment | 4 | 8.3 | -40.3 - 57.0 | 11 | 0.0 | -24.7 - 24.7 | 8.3 | -33.9 - 50.6 |
| Future perspective | 27 | 6.2 | -10.3 - 22.6 | 49 | 10.2 | -0.9 - 21.3 | -4.0 | -22.8 - 14.7 |
| Micturition problems | 26 | -4.3 | -9.2 - 0.6 | 48 | 1.6 | -4.1 - 7.3 | -5.9 | -14.3 - 2.5 |
| GI problems | 27 | -2.0 | -12.4 - 8.4 | 49 | -2.9 | -9.7 - 4.0 | 0.9 | -10.8 - 12.5 |
| Chemotherapy symptoms | 27 | 0.2 | -7.8 - 8.2 | 49 | -0.2 | -7.7 - 7.3 | 0.4 | -11.0 - 11.9 |
| Defecation symptoms | 27 | -4.9 | -11.4 - 1.6 | 49 | -4.5 | -9.5 - 0.6 | -0.5 | -8.6 - 7.7 |
| Male sexual problems | 10 | -8.3 | -51.2 - 34.6 | 17 | -2.0 | -16.3 - 12.4 | -6.4 | -39.5 - 26.8 |
| Female sexual problems | 2 | -41.7 | -3755.0 - 3671.6 | 5 | -16.7 | -51.0 - 17.7 | -25.0 | -159.2 - 109.2 |
| Weight loss | 26 | -5.1 | -18.5 - 8.2 | 49 | -1.4 | -12.4 - 9.7 | -3.8 | -21.3 - 13.8 |

**Table 21c: Change from baseline to month 6 by treatment**

| | Control | | | HBO | | | Control v. HBO | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean change from BL | 99% CI | n | Mean change from BL | 99% CI | Difference (Control-HBO) | 99% CI |
| Body image | 26 | -2.6 | -15.7 - 10.6 | 46 | 0.8 | -9.1 - 10.8 | -3.4 | -19.5 - 12.7 |
| Sexual function | 25 | -2.7 | -14.6 - 9.3 | 43 | -1.9 | -12.0 - 8.1 | -0.7 | -16.3 - 14.9 |
| Sexual enjoyment | 3 | 0.0 | 0.0 - 0.0 | 7 | 9.5 | -25.8 - 44.8 | -9.5 | -60.1 - 41.0 |
| Future perspective | 26 | 5.1 | -11.7 - 22.0 | 47 | 12.1 | 0.4 - 23.8 | -6.9 | -26.5 - 12.6 |
| Micturition problems | 25 | -4.9 | -15.4 - 5.6 | 46 | 0.7 | -5.1 - 6.6 | -5.6 | -16.3 - 5.1 |
| GI problems | 26 | -3.8 | -13.8 - 6.2 | 47 | -3.9 | -11.8 - 4.0 | 0.1 | -12.6 - 12.7 |
| Chemotherapy symptoms | 26 | -5.8 | -14.3 - 2.8 | 47 | 2.5 | -5.8 - 10.8 | -8.3 | -20.8 - 4.3 |
| Defecation symptoms | 26 | -3.8 | -11.2 - 3.5 | 47 | -5.3 | -10.8 - 0.3 | 1.4 | -7.6 - 10.4 |
| Male sexual problems | 9 | 3.7 | -36.7 - 44.1 | 17 | -8.8 | -23.4 - 5.7 | 12.5 | -18.3 - 43.4 |
| Female sexual problems | 2 | 0.0 | -2121.9 - 2121.9 | 4 | 0.0 | 0.0 - 0.0 | 0.0 | -94.0 - 94.0 |
| Weight loss | 26 | -3.8 | -14.6 - 6.9 | 47 | 2.1 | -8.9 - 13.2 | -6.0 | -22.5 - 10.5 |

**Table 21d: Change from baseline to month 12 by treatment**

| | Control | | | HBO | | | Control v. HBO | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean change from BL | 99% CI | n | Mean change from BL | 99% CI | Difference (Control-HBO) | 99% CI |
| Body image | 26 | -7.3 | -23.1 - 8.6 | 47 | 1.3 | -8.5 - 11.1 | -8.6 | -25.7 - 8.5 |
| Sexual function | 25 | 1.3 | -9.4 - 12.1 | 45 | 0.7 | -7.6 - 9.1 | 0.6 | -12.8 - 13.9 |
| Sexual enjoyment | 6 | 11.1 | -17.2 - 39.4 | 11 | -6.1 | -37.3 - 25.2 | 17.2 | -25.5 - 59.8 |
| Future perspective | 26 | 1.3 | -16.9 - 19.5 | 48 | 12.5 | 0.1 - 24.9 | -11.2 | -32.1 - 9.7 |
| Micturition problems | 25 | -1.8 | -12.5 - 8.9 | 46 | 0.2 | -6.7 - 7.2 | -2.0 | -13.9 - 9.9 |
| GI problems | 26 | -2.3 | -12.5 - 7.8 | 48 | -2.7 | -10.7 - 5.2 | 0.4 | -12.4 - 13.2 |
| Chemotherapy symptoms | 26 | 1.1 | -6.8 - 8.9 | 48 | 1.2 | -6.4 - 8.7 | -0.1 | -11.6 - 11.4 |
| Defecation symptoms | 26 | -3.8 | -11.1 - 3.4 | 48 | -5.2 | -11.0 - 0.5 | 1.4 | -7.8 - 10.6 |
| Male sexual problems | 10 | -6.7 | -53.9 - 40.6 | 15 | 1.1 | -19.7 - 21.9 | -7.8 | -48.7 - 33.1 |
| Female sexual problems | 3 | 16.7 | -236.0 - 269.3 | 5 | -20.0 | -76.4 - 36.4 | 36.7 | -55.1 - 128.4 |
| Weight loss | 26 | -3.8 | -18.7 - 11.0 | 48 | 0.0 | -10.3 - 10.3 | -3.8 | -21.1 - 13.4 |

# 9 IBDQ exploratory endpoints

## 9.1 Time since radiotherapy (ITT population)

Time since radiotherapy varied widely in both the control and HBO group and it was suggested that patients whose radiotherapy was completed more recently may see a greater improvement in symptoms than those whose radiotherapy was completed more than 5 years prior to HBO treatment. A comparison of treatment effect was made between patients treated with radiotherapy 1-5 years prior to trial entry and patients who received radiotherapy more than 5 years prior to trial entry. There was no significant difference in treatment effect between the two groups in patients who radiotherapy 1-5 years prior to trial entry or in patients who received radiotherapy >5 years prior to trial entry for either of the primary endpoints.

| **Endpoint 1: Bowel function component of the modified IBDQ** | Radiotherapy completed 1-5 years prior to trial entry | | | Radiotherapy completed >5 years prior to trial entry | | |
|---|---|---|---|---|---|---|
| | Control (n=15) | HBO (n=28) | Total (n=43) | Control (n=8) | HBO (n=15) | Total (n=23) |
| Median (IQR) change from baseline to 12m | +8 (1, 11) | +4 (1, 9) | +4 (1, 11) | -5 (-12.5, 5) | +1 (-12, 10) | -2 (-12, 9) |
| Mann-Whitney test U Score | 0.59 | | | 0.45 | | |
| P-value | 0.56 | | | 0.65 | | |

| **Endpoint 2: Rectal bleeding question of the modified IBDQ** | Radiotherapy completed 1-5 years prior to trial entry | | | Radiotherapy completed >5 years prior to trial entry | | |
|---|---|---|---|---|---|---|
| | Control (n=9) | HBO (n=20) | Total (n=29) | Control (n=2) | HBO (n=6) | Total (n=8) |
| Median (IQR) change from baseline to 12m | +1 (1, 2) | +3 (0.5, 4) | +2 (1, 3) | +1.5 (1, 2) | +2 (0, 3) | +2 (0.5, 2.5) |
| Mann-Whitney test U Score | 1.57 | | | 0.34 | | |
| P-value | 0.12 | | | 0.73 | | |

## 9.2 Primary endpoints at 2 weeks, and 3, 6 and 9 months post treatment (ITT population)

The TMG suggested that it would be possible to see a transient benefit from HBO therapy that may disappear by 12 months of follow up. IBDQ scores were collected at 2 weeks, 3, 6, and 9 months. The change from baseline was calculated and a Mann Whitney U test used to compare change from baseline in the two treatment groups at each of the time points. There was no statistically significant evidence of benefit at any of the time points.

Bowel function endpoint at 2 weeks:

| **Endpoint 1: Bowel function component of the modified IBDQ** | Control (n=22) | HBO (n=42) | Total (n=64) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +5.5 (-2, 8) | +5 (-1, 13) | +5 (-1.5, 12) |
| Mann-Whitney test U Score | 0.93 | | |
| P-value | 0.35 | | |

Rectal bleeding endpoint at 2 weeks:

| **Endpoint 2: Rectal bleeding question of the modified IBDQ** | Control (n=12) | HBO (n=27) | Total (n=39) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +1 (0, 3) | +1 (0, 4) | +1 (0, 4) |
| Mann-Whitney test U Score | 0.25 | | |
| P-value | 0.81 | | |

Bowel function endpoint at 3 months:

| **Endpoint 1: Bowel function component of the modified IBDQ** | Control (n=22) | HBO (n=41) | Total (n=63) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +7.5 (0, 12) | +4 (0, 10) | +5 (0, 11) |
| Mann-Whitney test U Score | -0.76 | | |
| P-value | 0.45 | | |

Rectal bleeding endpoint at 3 months:

| **Endpoint 2: Rectal bleeding question of the modified IBDQ** | Control (n=11) | HBO (n=28) | Total (n=39) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +2 (1, 4) | +2 (1, 3.5) | +2 (1, 4) |
| Mann-Whitney test U Score | 0.18 | | |
| P-value | 0.86 | | |

Bowel function endpoint at 6 months:

| **Endpoint 1: Bowel function component of the modified IBDQ** | Control (n=25) | HBO (n=46) | Total (n=71) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +4 (-1, 8) | +3 (-5, 12) | +3 (-3, 10) |
| Mann-Whitney test U Score | 0.34 | | |
| P-value | 0.73 | | |

Rectal bleeding endpoint at 6 months:

| **Endpoint 2: Rectal bleeding question of the modified IBDQ** | Control (n=12) | HBO (n=29) | Total (n=41) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +1 (-0.5, 2) | +2 (0, 4) | +2 (0, 3) |
| Mann-Whitney test U Score | 1.71 | | |
| P-value | 0.09 | | |

Bowel function endpoint at 9 months:

| **Endpoint 1: Bowel function component of the modified IBDQ** | Control (n=25) | HBO (n=44) | Total (n=69) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +3 (-3, 6) | +3.5 (-3, 11) | +3 (-3, 11) |
| Mann-Whitney test U Score | 0.41 | | |
| P-value | 0.68 | | |

Rectal bleeding endpoint at 9 months:

| **Endpoint 2: Rectal bleeding question of the modified IBDQ** | Control (n=13) | HBO (n=29) | Total (n=42) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +2 (-1, 3) | +2 (1, 3) | +2 (0, 3) |
| Mann-Whitney test U Score | 0.66 | | |
| P-value | 0.51 | | |

## 9.3 Hood vs. mask

The protocol does not specify whether a mask or hood should be used to deliver therapy to patients in HOT II. Some centres uses hoods and some masks. The TMG suggested that, as in many instances the masks cannot deliver 100% oxygen and it is often variable, it may be of interest to look at response in the subgroup of patients who received treatment by hood only.

The method of administration was the same for all patients treated at a given centre. Table 22 below demonstrates the methods used by individual centres.

**Table 22: Methods of delivery of treatment by centre**

| Unit | Method of delivery | Number of patients in analysis |
|---|---|---|
| Cardiff | Monochamber* | 7 |
| Chichester | Hood | 13 |
| Hull | Hood | 5 |
| Great Yarmouth | Hood | 2 |
| Whipps Cross | Hood | 7 |
| St John's Wood | Mask | 19 |
| Plymouth | Monochamber* | 5 |
| Poole | Hood | 4 |
| Rugby | Mask | 4 |
| Wirral | Mask | 3 |

*Monochamber included as hood as the two methods are equivalent

At the request of members of the TMG, the primary analysis was repeated in the subgroup of patients whose treatment was delivered by hood or monochamber, and the subgroup of patients whose treatment was delivered using a mask. These analyses were suggested after preliminary review of the results and are purely exploratory.

| **Bowel function in patients treated with a hood or monochamber** | Control (n=14) | HBO (n=29) | Total (n=43) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +4 (1, 9) | +2 (-7, 11) | +3 (-3, 11) |
| Mann-Whitney test U Score | -0.31 | | |
| P-value | 0.76 | | |

| **Bowel function in patients treated with a mask** | Control (n=9) | HBO (n=17) | Total (n=26) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +1 (-8, 4) | +8 (1, 13) | +4 (-6, 10) |
| Mann-Whitney test U Score | 1.59 | | |
| P-value | 0.11 | | |

| **Rectal bleeding in patients treated with a hood or monochamber** | Control (n=7) | HBO (n=16) | Total (n=23) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +1 (0, 2) | +3 (2.5, 4.5) | +3 (1, 3) |
| Mann-Whitney test U Score | 2.9 | | |
| P-value | 0.004 | | |

| **Rectal bleeding in patients treated with a mask** | Control (n=4) | HBO (n=13) | Total (n=17) |
|---|---|---|---|
| Median (IQR) change from baseline to 12m | +1 (1, 2.5) | +1 (0, 3) | +1 (0, 3) |
| Mann-Whitney test U Score | -0.63 | | |
| P-value | 0.53 | | |

### 9.4 Difference in proportion of patients showing an improvement in IBDQ

The proportion of participants showing any improvement in rectal bleeding IBDQ score was calculated in members of the ITT population who had rectal bleeding at the start. This included patients with an IBDQ rectal bleeding score ≤6 at baseline. A two sample test of proportions was used to test for difference in proportions between the two groups:

10/15 (66.7%; 95% CI* (38.4%, 88.2%)) control and 26/35 (74.3%; 95% CI* (56.7%, 87.5%)) HBO patients saw an improvement in rectal bleeding. Difference of 7.6% (95% CI (-20.3%, 35.5%)) 2 sided P-value 0.58.

## 10 LENT SOMA Exploratory (SAP 8.5.4)

The proportion of patients showing an improvement in rectal bleeding on the LENTSOMA scales was also compared between the two treatment groups. Rectal bleeding appears in the objective and management parameters of the rectal LENT SOMA questionnaire, and the objective parameter of the intestinal LENT SOMA questionnaire; the three questions were treated independently of one another. Patients included in the ITT population with reported rectal bleeding at baseline (LENT SOMA grade 1 or worse) were included in the analysis. A two sample test of proportions was used.

**Rectal LENT SOMA: Objective**

12/16 (75.0% 95% CI* (47.6%, 92.7%)) patients in the control arm and 14/23 (60.9% 95% CI* (38.5%, 80.3%)) patients in the HBO arm saw an improvement in LENTSOMA objective rectal bleeding score. Difference of -14.1% (95% CI (-43.3%, 15.0%)) 2 sided P-value 0.36.

**Rectal LENT SOMA: Management**

5/5 (100.0%; 97.5% CI*# (47.8%, 100.0%)) patients in the control arm and 4/13 (30.8%; 95% CI* (9.1%, 61.4%)) patients in the HBO arm saw an improvement in LENT SOMA management rectal bleeding score. Difference of -69.2% (95% CI (-94.3%, -44.1%)) 2 sided P-value 0.01.

**Intestinal LENT SOMA: Objective**

There are not enough data to perform this test; 2 patients with intestinal (management) rectal bleeding score>0 at baseline in the HBO arm and 1 patient in the control arm.

*Exact binomial probabilities used to calculate 95% CIs #one sided 97.5% CI presented as symmetric 2 sided 95% CI crosses 1.

## 11 Other exploratory analyses

Unless stated otherwise, all analyses in this section were performed in the ITT population.

### 11. 1 Proportion of patients with improvement in rectal bleeding score

The proportion of patients showing an improvement in rectal bleeding score was compared between the two treatment groups using a two sample test of proportions as an exploratory analysis. The following analyses were not specified apriori and should therefore be interpreted as purely exploratory.

All patients included in the ITT population for whom any rectal bleeding was present at baseline (according to each of the scales separately) are included in the analyses below.

The tests were performed for CTCAE rectal bleeding and EORTC QLQ-CR38 question 59 ("Have you had blood with your stools?").

**CTC grade**

17 control and 22 HBO patients were available for analysis. 12 (70.6%; 95% CI 48.9%, 92.2%) patients showed an improvement in CTC rectal bleeding score in the control group compared with 13 (59.1%; 95% CI 38.5%, 79.6%) in the HBO group; change of -11.4, two-sided P=0.46.

**EORTC-CR38 Q59: Have you had blood with your stools?**

18 control and 29 HBO patients were available for analysis. 8 (44.4%; 21.5% to 67.4%) patients showed an improvement in question score in the control group compared with 17 (58.6%; 40.7% to 76.5%) in the HBO group; change of +14.2%, two-sided P=0.34.

### 11.2 Comparison of Rectal LENTSOMA total score from baseline to 2 weeks

The change in rectal LENT SOMA score from baseline to 2 weeks was compared between the two groups.

| **Change in rectal LENT SOMA total score from baseline to 2 weeks** | Control (n=28) | HBO (n=50) | Total (n=78) |
|---|---|---|---|
| Median (IQR) change from baseline to 2 weeks | -2 (-3, 0) | -2 (-3, 1) | -2 (-3, 0) |
| Mann-Whitney test U Score | 0.35 | | |
| P-value | 0.72 | | |

## 12 Deviations from the SAP

The HOT II SAP was adhered to as closely as possible. The hood versus mask analyses were performed post-hoc, at the request of members of the TMG. Prior to the completion of analysis it became apparent that it would not be possible to perform a comparison of photos of rectal mucosa (secondary endpoint v) because the photographs were not of adequate quality. This was agreed with members of the TMG.

# APPENDIX 1
# IBDQ raw scores

## 1.1.1 IBDQ raw bowel scores (grouped) at baseline and 12 months in all ITT patients

| | Control | HBO | Total |
|---|---|---|---|
| Baseline | n=27 | n=53 | n=79 |
| Score 11-20 | 2 | 1 | 3 |
| Score 21-30 | 2 | 5 | 7 |
| Score 31-40 | 2 | 5 | 7 |
| Score 41-50 | 6 | 24 | 30 |
| Score 51-60 | 11 | 13 | 24 |
| Score 61-70 | 4 | 4 | 8 |
| Median (IQR) | 51 (43, 59) | 48 (41.5, 51) | 48 (42, 55) |
| 12 months | n=25 | n=48 | n=73 |
| Score 11-20 | 0 | 1 | 1 |
| Score 21-30 | 3 | 6 | 9 |
| Score 31-40 | 3 | 6 | 9 |
| Score 41-50 | 5 | 12 | 17 |
| Score 51-60 | 8 | 10 | 18 |
| Score 61-70 | 6 | 13 | 19 |
| Median (IQR) | 54 (46, 59) | 50 (37.5, 61.5) | 52 (40, 61) |

## 1.1.2 IBDQ raw bowel scores (grouped) at baseline and 12 months in patients included in the primary endpoint

| | Control | HBO | Total |
|---|---|---|---|
| | n=23 | n=46 | n=69 |
| Baseline | | | |
| Score 11-20 | 2 | 1 | 3 |
| Score 21-30 | 1 | 4 | 5 |
| Score 31-40 | 1 | 4 | 5 |
| Score 41-50 | 6 | 20 | 26 |
| Score 51-60 | 10 | 13 | 23 |
| Score 61-70 | 3 | 4 | 7 |
| Median (IQR) | 51 (44, 59) | 48 (42, 52) | 48 (43, 55) |
| 12 months | | | |
| Score 11-20 | 0 | 1 | 1 |
| Score 21-30 | 3 | 6 | 9 |
| Score 31-40 | 3 | 6 | 9 |
| Score 41-50 | 5 | 10 | 15 |
| Score 51-60 | 8 | 10 | 18 |
| Score 61-70 | 4 | 13 | 17 |
| Median (IQR) | 53 (40, 59) | 51 (36, 62) | 52 (39, 60) |
| Change from baseline at 12 months | | | |
| Median (IQR) | 4 (-6, 9) | 3.5 (-3, 11) | 4 (-3, 10) |

### 1.2.1 IBDQ raw rectal bleeding scores at baseline and 12 months in all ITT patients

| | Control | HBO | Total |
|---|---|---|---|
| Baseline | n=28 | n=55 | n=83 |
| Score=1 | 3 | 8 | 11 |
| Score=2 | 3 | 6 | 9 |
| Score=3 | 4 | 8 | 12 |
| Score=4 | 3 | 6 | 9 |
| Score=5 | 1 | 5 | 6 |
| Score=6 | 5 | 7 | 12 |
| Score=7 | 9 | 15 | 24 |
| Median (IQR) | 5.5 (3, 7) | 4 (2, 7) | 5 (3, 7) |
| 12 months | n=25 | n=48 | n=73 |
| Score=1 | 1 | 4 | 5 |
| Score=2 | 2 | 1 | 3 |
| Score=3 | 4 | 3 | 7 |
| Score=4 | 3 | 2 | 5 |
| Score=5 | 2 | 4 | 6 |
| Score=6 | 4 | 12 | 16 |
| Score=7 | 9 | 22 | 31 |
| Median (IQR) | 6 (3, 7) | 6 (5, 7) | 6 (4, 7) |

### 1.2.2 IBDQ raw rectal bleeding scores at baseline and 12 months in patients included in the primary endpoint

| | Control | HBO | Total |
|---|---|---|---|
| | n=11 | n=29 | n=40 |
| Baseline | | | |
| Score=1 | 2 | 7 | 9 |
| Score=2 | 3 | 4 | 7 |
| Score=3 | 3 | 8 | 11 |
| Score=4 | 2 | 5 | 7 |
| Score=5 | 1 | 5 | 6 |
| Score=6 | 0 | 0 | 0 |
| Score=7 | 0 | 0 | 0 |
| Median (IQR) | 3 (2, 4) | 3 (2, 4) | 3 (2, 4) |
| 12 months | | | |
| Score=1 | 1 | 4 | 5 |
| Score=2 | 2 | 1 | 3 |
| Score=3 | 2 | 3 | 5 |
| Score=4 | 2 | 2 | 4 |
| Score=5 | 1 | 2 | 3 |
| Score=6 | 2 | 8 | 10 |
| Score=7 | 1 | 9 | 10 |
| Median (IQR) | 4 (2, 6) | 6 (3, 7) | 5.5 (3, 6.5) |
| Change from baseline at 12 months | | | |
| Median (IQR) | 1 (1, 2) | 3 (1, 3) | 2 (1, 3) |

## Appendix 2 LENTSOMA – Rectum

A2.1: Number of patients with grade 0-4 rectal LENT SOMA by toxicity at baseline

| | | | Control N=29 | | HBO N=55 | | Total N=84 | |
|---|---|---|---|---|---|---|---|---|
| | | | N | % | N | % | N | % |
| Subjective | Stool frequency | 0 | 5 | 17.2% | 5 | 9.4% | 10 | 11.9% |
| | | 1 | 17 | 58.6% | 26 | 49.1% | 43 | 51.2% |
| | | 2 | 6 | 20.7% | 22 | 41.5% | 28 | 33.3% |
| | | 3 | 1 | 3.4% | 2 | 3.8% | 3 | 3.6% |
| | Sphincter control | 0 | 4 | 13.8% | 15 | 28.3% | 19 | 22.6% |
| | | 1 | 8 | 27.6% | 14 | 26.4% | 22 | 26.2% |
| | | 2 | 8 | 27.6% | 16 | 30.2% | 24 | 28.6% |
| | | 3 | 9 | 31.0% | 10 | 18.9% | 19 | 22.6% |
| | Pain | 0 | 19 | 65.5% | 40 | 75.5% | 59 | 70.2% |
| | | 1 | 6 | 20.7% | 4 | 7.5% | 10 | 11.9% |
| | | 2 | 3 | 10.3% | 8 | 15.1% | 11 | 13.1% |
| | | 3 | 1 | 3.4% | 3 | 5.7% | 4 | 4.8% |
| | Tenesmus | 0 | 2 | 6.9% | 8 | 15.1% | 10 | 11.9% |
| | | 1 | 4 | 13.8% | 6 | 11.3% | 10 | 11.9% |
| | | 2 | 11 | 37.9% | 19 | 35.8% | 30 | 35.7% |
| | | 3 | 12 | 41.4% | 22 | 41.5% | 34 | 40.5% |
| | Mucosal loss | 0 | 15 | 51.7% | 35 | 66.0% | 50 | 59.5% |
| | | 1 | 6 | 20.7% | 9 | 17.0% | 15 | 17.9% |
| | | 2 | 5 | 17.2% | 7 | 13.2% | 12 | 14.3% |
| | | 3 | 3 | 10.3% | 4 | 7.5% | 7 | 8.3% |
| Objective | Bleeding | 0 | 11 | 37.9% | 27 | 50.9% | 38 | 45.2% |
| | | 1 | 5 | 17.2% | 6 | 11.3% | 11 | 13.1% |
| | | 2 | 4 | 13.8% | 8 | 15.1% | 12 | 14.3% |
| | | 3 | 9 | 31.0% | 14 | 26.4% | 23 | 27.4% |
| | Stricture | 0 | 29 | 100.0% | 22 | 41.5% | 84 | 100.0% |
| | Ulceration | 0 | 29 | 100.0% | 55 | 103.8% | 84 | 100.0% |
| Management | Pain | 0 | 24 | 82.8% | 48 | 90.6% | 72 | 85.7% |
| | | 1 | 2 | 6.9% | 6 | 11.3% | 8 | 9.5% |
| | | 2 | 3 | 10.3% | 1 | 1.9% | 4 | 4.8% |
| | Tenis / frequency | 0 | 17 | 58.6% | 25 | 47.2% | 42 | 50.0% |
| | | 1 | 0 | 0.0% | 4 | 7.5% | 4 | 4.8% |
| | | 2 | 3 | 10.3% | 6 | 11.3% | 9 | 10.7% |
| | | 3 | 9 | 31.0% | 20 | 37.7% | 29 | 34.5% |
| | Bleeding | 0 | 24 | 82.8% | 40 | 75.5% | 64 | 76.2% |
| | | 1 | 4 | 13.8% | 11 | 20.8% | 15 | 17.9% |
| | | 2 | 1 | 3.4% | 2 | 3.8% | 3 | 3.6% |
| | | 3 | 0 | 0.0% | 2 | 3.8% | 2 | 2.4% |
| | Stricture | 0 | 29 | 100.0% | 55 | 103.8% | 84 | 100.0% |
| | Ulceration | 0 | 29 | 100.0% | 54 | 101.9% | 83 | 98.8% |
| | | 1 | 0 | 0.0% | 1 | 1.9% | 1 | 1.2% |
| | Sphincter control | 0 | 12 | 41.4% | 29 | 54.7% | 41 | 48.8% |
| | | 1 | 1 | 3.4% | 6 | 11.3% | 7 | 8.3% |
| | | 2 | 3 | 10.3% | 5 | 9.4% | 8 | 9.5% |
| | | 3 | 13 | 44.8% | 15 | 28.3% | 28 | 33.3% |

A2.2: Number of patients with grade 0-4 rectal LENT SOMA by toxicity at 2 weeks

| | | | Control N=28 | | HBO N=50 | | Total N=78 | |
|---|---|---|---|---|---|---|---|---|
| | | | N | % | N | % | N | % |
| Subjective | Stool frequency | 0 | 7 | 25.0% | 13 | 26.0% | 20 | 25.6% |
| | | 1 | 17 | 60.7% | 26 | 52.0% | 43 | 55.1% |
| | | 2 | 4 | 14.3% | 9 | 18.0% | 13 | 16.7% |
| | | 3 | 0 | 0.0% | 2 | 4.0% | 2 | 2.6% |
| | Sphincter control | 0 | 9 | 32.1% | 25 | 50.0% | 34 | 43.6% |
| | | 1 | 4 | 14.3% | 9 | 18.0% | 13 | 16.7% |
| | | 2 | 9 | 32.1% | 11 | 22.0% | 20 | 25.6% |
| | | 3 | 6 | 21.4% | 5 | 10.0% | 11 | 14.1% |
| | Pain | 0 | 20 | 71.4% | 37 | 74.0% | 57 | 73.1% |
| | | 1 | 5 | 17.9% | 6 | 12.0% | 11 | 14.1% |
| | | 2 | 3 | 10.7% | 6 | 12.0% | 9 | 11.5% |
| | | 3 | 0 | 0.0% | 1 | 2.0% | 1 | 1.3% |
| | Tenesmus | 0 | 8 | 28.6% | 14 | 28.0% | 22 | 28.2% |
| | | 1 | 8 | 28.6% | 11 | 22.0% | 19 | 24.4% |
| | | 2 | 8 | 28.6% | 15 | 30.0% | 23 | 29.5% |
| | | 3 | 4 | 14.3% | 10 | 20.0% | 14 | 17.9% |
| | Mucosal loss | 0 | 17 | 60.7% | 32 | 64.0% | 49 | 62.8% |
| | | 1 | 3 | 10.7% | 9 | 18.0% | 12 | 15.4% |
| | | 2 | 5 | 17.9% | 2 | 4.0% | 7 | 9.0% |
| | | 3 | 3 | 10.7% | 7 | 14.0% | 10 | 12.8% |
| Objective | Bleeding | 0 | 11 | 39.3% | 24 | 48.0% | 35 | 44.9% |
| | | 1 | 8 | 28.6% | 9 | 18.0% | 17 | 21.8% |
| | | 2 | 3 | 10.7% | 11 | 22.0% | 14 | 17.9% |
| | | 3 | 6 | 21.4% | 6 | 12.0% | 12 | 15.4% |
| | Stricture | 0 | 25 | 89.3% | 49 | 98.0% | 74 | 94.9% |
| | | Missing | 3 | 10.7% | 1 | 2.0% | 4 | 5.1% |
| | Ulceration | 0 | 25 | 89.3% | 49 | 98.0% | 74 | 94.9% |
| | | Missing | 3 | 10.7% | 1 | 2.0% | 4 | 5.1% |
| Management | Pain | 0 | 24 | 85.7% | 45 | 90.0% | 69 | 88.5% |
| | | 1 | 2 | 7.1% | 4 | 8.0% | 6 | 7.7% |
| | | 2 | 2 | 7.1% | 1 | 2.0% | 3 | 3.8% |
| | Tenis / frequency | 0 | 20 | 71.4% | 21 | 42.0% | 41 | 52.6% |
| | | 1 | 1 | 3.6% | 5 | 10.0% | 6 | 7.7% |
| | | 2 | 0 | 0.0% | 5 | 10.0% | 5 | 6.4% |
| | | 3 | 7 | 25.0% | 19 | 38.0% | 26 | 33.3% |
| | Bleeding | 0 | 21 | 75.0% | 35 | 70.0% | 56 | 71.8% |
| | | 1 | 7 | 25.0% | 13 | 26.0% | 20 | 25.6% |
| | | 2 | 0 | 0.0% | 1 | 2.0% | 1 | 1.3% |
| | | 3 | 0 | 0.0% | 1 | 2.0% | 1 | 1.3% |
| | Stricture | 0 | 27 | 96.4% | 50 | 100.0% | 77 | 98.7% |
| | | 1 | 1 | 3.6% | 0 | 0.0% | 1 | 1.3% |
| | Ulceration | 0 | 28 | 100.0% | 50 | 100.0% | 78 | 100.0% |
| | Sphincter control | 0 | 15 | 53.6% | 30 | 60.0% | 45 | 57.7% |
| | | 1 | 1 | 3.6% | 4 | 8.0% | 5 | 6.4% |
| | | 2 | 1 | 3.6% | 2 | 4.0% | 3 | 3.8% |
| | | 3 | 11 | 39.3% | 14 | 28.0% | 25 | 32.1% |

A2.3: Number of patients with grade 0-4 rectal LENT SOMA by toxicity at 12 months

| | | | Control N=26 | | HBO N=46 | | Total N=72 | |
|---|---|---|---|---|---|---|---|---|
| | | | N | % | N | % | N | % |
| Subjective | Stool frequency | 0 | 7 | 26.9% | 8 | 17.4% | 15 | 20.8% |
| | | 1 | 12 | 46.2% | 25 | 54.3% | 37 | 51.4% |
| | | 2 | 5 | 19.2% | 11 | 23.9% | 16 | 22.2% |
| | | 3 | 2 | 7.7% | 2 | 4.3% | 4 | 5.6% |
| | Sphincter control | 0 | 10 | 38.5% | 17 | 37.0% | 27 | 37.5% |
| | | 1 | 6 | 23.1% | 9 | 19.6% | 15 | 20.8% |
| | | 2 | 7 | 26.9% | 12 | 26.1% | 19 | 26.4% |
| | | 3 | 3 | 11.5% | 8 | 17.4% | 11 | 15.3% |
| | Pain | 0 | 19 | 73.1% | 30 | 65.2% | 49 | 68.1% |
| | | 1 | 3 | 11.5% | 6 | 13.0% | 9 | 12.5% |
| | | 2 | 2 | 7.7% | 10 | 21.7% | 12 | 16.7% |
| | | 3 | 2 | 7.7% | 0 | 0.0% | 2 | 2.8% |
| | Tenesmus | 0 | 8 | 30.8% | 11 | 23.9% | 19 | 26.4% |
| | | 1 | 4 | 15.4% | 6 | 13.0% | 10 | 13.9% |
| | | 2 | 8 | 30.8% | 15 | 32.6% | 23 | 31.9% |
| | | 3 | 6 | 23.1% | 14 | 30.4% | 20 | 27.8% |
| | Mucosal loss | 0 | 15 | 57.7% | 28 | 60.9% | 43 | 59.7% |
| | | 1 | 4 | 15.4% | 7 | 15.2% | 11 | 15.3% |
| | | 2 | 5 | 19.2% | 8 | 17.4% | 13 | 18.1% |
| | | 3 | 2 | 7.7% | 3 | 6.5% | 5 | 6.9% |
| Objective | Bleeding | 0 | 13 | 50.0% | 26 | 56.5% | 39 | 54.2% |
| | | 1 | 6 | 23.1% | 10 | 21.7% | 16 | 22.2% |
| | | 2 | 5 | 19.2% | 6 | 13.0% | 11 | 15.3% |
| | | 3 | 2 | 7.7% | 4 | 8.7% | 6 | 8.3% |
| | Stricture | 0 | 26 | 100.0% | 45 | 97.8% | 71 | 98.6% |
| | | 9 | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |
| | Ulceration | 0 | 26 | 100.0% | 45 | 97.8% | 71 | 98.6% |
| | | 9 | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |
| Management | Pain | 0 | 24 | 92.3% | 43 | 93.5% | 67 | 93.1% |
| | | 1 | 0 | 0.0% | 2 | 4.3% | 2 | 2.8% |
| | | 2 | 1 | 3.8% | 0 | 0.0% | 1 | 1.4% |
| | | 3 | 1 | 3.8% | 1 | 2.2% | 2 | 2.8% |
| | Tenis / frequency | 0 | 17 | 65.4% | 25 | 54.3% | 42 | 58.3% |
| | | 1 | 3 | 11.5% | 3 | 6.5% | 6 | 8.3% |
| | | 2 | 1 | 3.8% | 3 | 6.5% | 4 | 5.6% |
| | | 3 | 5 | 19.2% | 15 | 32.6% | 20 | 27.8% |
| | Bleeding | 0 | 24 | 92.3% | 33 | 71.7% | 57 | 79.2% |
| | | 1 | 2 | 7.7% | 12 | 26.1% | 14 | 19.4% |
| | | 2 | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |
| | Stricture | 0 | 25 | 96.2% | 46 | 100.0% | 71 | 98.6% |
| | | 1 | 1 | 3.8% | 0 | 0.0% | 1 | 1.4% |
| | Ulceration | 0 | 26 | 100.0% | 46 | 100.0% | 72 | 100.0% |
| | Sphincter control | 0 | 14 | 53.8% | 29 | 63.0% | 43 | 59.7% |
| | | 1 | 0 | 0.0% | 2 | 4.3% | 2 | 2.8% |
| | | 2 | 2 | 7.7% | 5 | 10.9% | 7 | 9.7% |
| | | 3 | 10 | 38.5% | 10 | 21.7% | 20 | 27.8% |

A2.4 Maximum grade reported for each scale at baseline

| Maximum grade per scale at baseline | | HBO N=55 | | Control N=29 | | Total N=84 | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| Subjective | 0 | 1 | 1.8% | 0 | 0.0% | 1 | 1.2% |
| | 1 | 7 | 12.7% | 4 | 13.8% | 11 | 13.1% |
| | 2 | 19 | 34.5% | 8 | 27.6% | 27 | 32.1% |
| | 3 | 28 | 50.9% | 17 | 58.6% | 45 | 53.6% |
| Objective | 0 | 27 | 49.1% | 11 | 37.9% | 38 | 45.2% |
| | 1 | 6 | 10.9% | 5 | 17.2% | 11 | 13.1% |
| | 2 | 8 | 14.5% | 4 | 13.8% | 12 | 14.3% |
| | 3 | 14 | 25.5% | 9 | 31.0% | 23 | 27.4% |
| Management | 0 | 8 | 14.5% | 7 | 24.1% | 15 | 17.9% |
| | 1 | 9 | 16.4% | 2 | 6.9% | 11 | 13.1% |
| | 2 | 10 | 18.2% | 3 | 10.3% | 13 | 15.5% |
| | 3 | 28 | 50.9% | 17 | 58.6% | 45 | 53.6% |

A2.5 Maximum grade reported for each scale at 2 weeks

| Maximum grade per scale at 2 weeks | | HBO N=50 | | Control N=28 | | Total N=78 | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| Subjective | 0 | 4 | 8.0% | 2 | 7.1% | 6 | 7.7% |
| | 1 | 11 | 22.0% | 5 | 17.9% | 16 | 20.5% |
| | 2 | 15 | 30.0% | 13 | 46.4% | 28 | 35.9% |
| | 3 | 20 | 40.0% | 8 | 28.6% | 28 | 35.9% |
| Objective | 0 | 23 | 46.0% | 10 | 35.7% | 33 | 42.3% |
| | 1 | 9 | 18.0% | 6 | 21.4% | 15 | 19.2% |
| | 2 | 11 | 22.0% | 3 | 10.7% | 14 | 17.9% |
| | 3 | 6 | 12.0% | 6 | 21.4% | 12 | 15.4% |
| | Missing | 1 | 2.0% | 3 | 10.7% | 4 | 5.1% |
| Management | 0 | 11 | 22.0% | 8 | 28.6% | 19 | 24.4% |
| | 1 | 7 | 14.0% | 5 | 17.9% | 12 | 15.4% |
| | 2 | 7 | 14.0% | 1 | 3.6% | 8 | 10.3% |
| | 3 | 25 | 50.0% | 14 | 50.0% | 39 | 50.0% |

A2.6 Maximum grade reported for each scale at 12 months

| Maximum grade per scale at 12 months | | HBO N=46 | | Control N=26 | | Total N=72 | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| Subjective | 0 | 2 | 4.3% | 2 | 7.7% | 4 | 5.6% |
| | 1 | 11 | 23.9% | 6 | 23.1% | 17 | 23.6% |
| | 2 | 11 | 23.9% | 9 | 34.6% | 20 | 27.8% |
| | 3 | 22 | 47.8% | 9 | 34.6% | 31 | 43.1% |
| Objective | 0 | 26 | 56.5% | 13 | 50.0% | 39 | 54.2% |
| | 1 | 9 | 19.6% | 6 | 23.1% | 15 | 20.8% |
| | 2 | 6 | 13.0% | 5 | 19.2% | 11 | 15.3% |
| | 3 | 4 | 8.7% | 2 | 7.7% | 6 | 8.3% |
| | Missing | 1 | 2.2% | 0 | 0.0% | 1 | 1.4% |
| Management | 0 | 14 | 30.4% | 8 | 30.8% | 22 | 30.6% |
| | 1 | 7 | 15.2% | 4 | 15.4% | 11 | 15.3% |
| | 2 | 5 | 10.9% | 1 | 3.8% | 6 | 8.3% |
| | 3 | 20 | 43.5% | 13 | 50.0% | 33 | 45.8% |

A2.7 Maximum overall rectal LENT SOMA grade reported at baseline

| Maximum overall grade at baseline | HBO N=55 | | Control N=29 | | Total N=84 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| 1 | 1 | 1.8% | 0 | 0.0% | 1 | 1.2% |
| 2 | 9 | 16.4% | 3 | 10.3% | 12 | 14.3% |
| 3 | 45 | 81.8% | 26 | 89.7% | 71 | 84.5% |

A2.8 Maximum overall rectal LENT SOMA grade reported at 2 weeks

| Maximum overall grade at 2 weeks | HBO N=50 | | Control N=28 | | Total N=78 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| 1 | 3 | 6.0% | 2 | 7.1% | 5 | 6.4% |
| 2 | 15 | 30.0% | 6 | 21.4% | 21 | 26.9% |
| 3 | 32 | 64.0% | 20 | 71.4% | 52 | 66.7% |

A2.9 Maximum overall rectal LENT SOMA grade reported at 12 months

| Maximum overall grade at 12 months | HBO N=46 | | Control N=26 | | Total N=72 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| 0 | 1 | 2.2% | 2 | 7.7% | 3 | 4.2% |
| 1 | 6 | 13.0% | 2 | 7.7% | 8 | 11.1% |
| 2 | 9 | 19.6% | 5 | 19.2% | 14 | 19.4% |
| 3 | 30 | 65.2% | 17 | 65.4% | 47 | 65.3% |

## Appendix 3 LENTSOMA – Intestine

A3.1: Number of patients with grade 0-4 intestinal LENT SOMA by toxicity at baseline

| | | | Control N=29 | | HBO N=55 | | Total N=84 | |
|---|---|---|---|---|---|---|---|---|
| | | | N | % | N | % | N | % |
| Subjective | Stool frequency | 0 | 4 | 13.8% | 5 | 9.1% | 9 | 10.7% |
| | | 1 | 18 | 62.1% | 27 | 49.1% | 45 | 53.6% |
| | | 2 | 6 | 20.7% | 21 | 38.2% | 27 | 32.1% |
| | | 3 | 1 | 3.4% | 2 | 3.6% | 3 | 3.6% |
| | Stool consistency | 0 | 21 | 72.4% | 32 | 58.2% | 53 | 63.1% |
| | | 1 | 3 | 10.3% | 2 | 3.6% | 5 | 6.0% |
| | | 2 | 5 | 17.2% | 21 | 38.2% | 26 | 31.0% |
| | Pain | 0 | 16 | 55.2% | 18 | 32.7% | 34 | 40.5% |
| | | 1 | 4 | 13.8% | 7 | 12.7% | 11 | 13.1% |
| | | 2 | 6 | 20.7% | 17 | 30.9% | 23 | 27.4% |
| | | 3 | 3 | 10.3% | 13 | 23.6% | 16 | 19.0% |
| | Constipation | 0 | 28 | 96.6% | 53 | 96.4% | 81 | 96.4% |
| | | 1 | 1 | 3.4% | 2 | 3.6% | 3 | 3.6% |
| Objective | Melena | 0 | 24 | 82.8% | 48 | 87.3% | 72 | 85.7% |
| | | 1 | 3 | 10.3% | 3 | 5.5% | 6 | 7.1% |
| | | 2 | 1 | 3.4% | 4 | 7.3% | 5 | 6.0% |
| | | 3 | 1 | 3.4% | 0 | 0.0% | 1 | 1.2% |
| | Weight loss | 0 | 28 | 96.6% | 53 | 96.4% | 81 | 96.4% |
| | | 2 | 1 | 3.4% | 1 | 1.8% | 2 | 2.4% |
| | | 3 | 0 | 0.0% | 1 | 1.8% | 1 | 1.2% |
| | Stricture | 0 | 29 | 100.0% | 54 | 98.2% | 83 | 98.8% |
| | | 1 | 0 | 0.0% | 1 | 1.8% | 1 | 1.2% |
| | Ulceration | 0 | 29 | 100.0% | 55 | 100.0% | 84 | 100.0% |
| Management | Pain | 0 | 22 | 75.9% | 40 | 72.7% | 62 | 73.8% |
| | | 1 | 2 | 6.9% | 10 | 18.2% | 12 | 14.3% |
| | | 2 | 4 | 13.8% | 3 | 5.5% | 7 | 8.3% |
| | | 3 | 1 | 3.4% | 2 | 3.6% | 3 | 3.6% |
| | Stool consistency / frequency | 0 | 9 | 31.0% | 14 | 25.5% | 23 | 27.4% |
| | | 1 | 9 | 31.0% | 15 | 27.3% | 24 | 28.6% |
| | | 2 | 10 | 34.5% | 24 | 43.6% | 34 | 40.5% |
| | | 3 | 1 | 3.4% | 2 | 3.6% | 3 | 3.6% |
| | Bleeding | 0 | 28 | 96.6% | 53 | 96.4% | 81 | 96.4% |
| | | 1 | 1 | 3.4% | 2 | 3.6% | 3 | 3.6% |
| | Stricture | 0 | 29 | 100.0% | 55 | 100.0% | 84 | 100.0% |
| | Ulceration | 0 | 29 | 100.0% | 55 | 100.0% | 84 | 100.0% |

A3.2: Number of patients with grade 0-4 intestinal LENT SOMA by toxicity at 2 weeks

| | | | Control N=28 | | HBO N=50 | | Total N=78 | |
|---|---|---|---|---|---|---|---|---|
| | | | N | % | N | % | N | % |
| Subjective | Stool frequency | 0 | 6 | 21.4% | 13 | 26.0% | 19 | 24.4% |
| | | 1 | 18 | 64.3% | 26 | 52.0% | 44 | 56.4% |
| | | 2 | 4 | 14.3% | 9 | 18.0% | 13 | 16.7% |
| | | 3 | 0 | 0.0% | 2 | 4.0% | 2 | 2.6% |
| | Stool consistency | 0 | 25 | 89.3% | 42 | 84.0% | 67 | 85.9% |
| | | 1 | 0 | 0.0% | 2 | 4.0% | 2 | 2.6% |
| | | 2 | 3 | 10.7% | 5 | 10.0% | 8 | 10.3% |
| | | 3 | 0 | 0.0% | 1 | 2.0% | 1 | 1.3% |
| | Pain | 0 | 16 | 57.1% | 22 | 44.0% | 38 | 48.7% |
| | | 1 | 4 | 14.3% | 10 | 20.0% | 14 | 17.9% |
| | | 2 | 5 | 17.9% | 14 | 28.0% | 19 | 24.4% |
| | | 3 | 3 | 10.7% | 3 | 6.0% | 6 | 7.7% |
| | | 4 | 0 | 0.0% | 1 | 2.0% | 1 | 1.3% |
| | Constipation | 0 | 27 | 96.4% | 49 | 98.0% | 76 | 97.4% |
| | | 1 | 1 | 3.6% | 1 | 2.0% | 2 | 2.6% |
| Objective | Melena | 0 | 26 | 92.9% | 47 | 94.0% | 73 | 93.6% |
| | | 1 | 2 | 7.1% | 3 | 6.0% | 5 | 6.4% |
| | Weight loss | 0 | 26 | 92.9% | 49 | 98.0% | 75 | 96.2% |
| | | Missing | 2 | 7.1% | 1 | 2.0% | 3 | 3.8% |
| | Stricture | 0 | 25 | 89.3% | 49 | 98.0% | 74 | 94.9% |
| | | Missing | 3 | 10.7% | 1 | 2.0% | 4 | 5.1% |
| | Ulceration | 0 | 25 | 89.3% | 49 | 98.0% | 74 | 94.9% |
| | | Missing | 3 | 10.7% | 1 | 2.0% | 4 | 5.1% |
| Management | Pain | 0 | 22 | 78.6% | 35 | 70.0% | 57 | 73.1% |
| | | 1 | 3 | 10.7% | 11 | 22.0% | 14 | 17.9% |
| | | 2 | 3 | 10.7% | 3 | 6.0% | 6 | 7.7% |
| | | 3 | 0 | 0.0% | 1 | 2.0% | 1 | 1.3% |
| | Stool consistency / frequency | 0 | 10 | 35.7% | 12 | 24.0% | 22 | 28.2% |
| | | 1 | 11 | 39.3% | 13 | 26.0% | 24 | 30.8% |
| | | 2 | 6 | 21.4% | 24 | 48.0% | 30 | 38.5% |
| | | 3 | 1 | 3.6% | 1 | 2.0% | 2 | 2.6% |
| | Bleeding | 0 | 25 | 89.3% | 48 | 96.0% | 73 | 93.6% |
| | | 1 | 3 | 10.7% | 2 | 4.0% | 5 | 6.4% |
| | Stricture | 0 | 25 | 89.3% | 50 | 100.0% | 75 | 96.2% |
| | | 1 | 1 | 3.6% | 0 | 0.0% | 1 | 1.3% |
| | | Missing | 2 | 7.1% | 0 | 0.0% | 2 | 2.6% |
| | Ulceration | 0 | 26 | 92.9% | 50 | 100.0% | 76 | 97.4% |
| | | Missing | 2 | 7.1% | 0 | 0.0% | 2 | 2.6% |

A3.3: Number of patients with grade 0-4 intestinal LENT SOMA by toxicity at 12 months

| | | | Control N=26 | | HBO N=46 | | Total N=72 | |
|---|---|---|---|---|---|---|---|---|
| | | | N | % | N | % | N | % |
| Subjective | Stool frequency | 0 | 7 | 26.9% | 8 | 17.4% | 15 | 20.8% |
| | | 1 | 12 | 46.2% | 24 | 52.2% | 36 | 50.0% |
| | | 2 | 5 | 19.2% | 11 | 23.9% | 16 | 22.2% |
| | | 3 | 2 | 7.7% | 3 | 6.5% | 5 | 6.9% |
| | Stool consistency | 0 | 22 | 84.6% | 32 | 69.6% | 54 | 75.0% |
| | | 1 | 1 | 3.8% | 3 | 6.5% | 4 | 5.6% |
| | | 2 | 3 | 11.5% | 11 | 23.9% | 14 | 19.4% |
| | Pain | 0 | 14 | 53.8% | 20 | 43.5% | 34 | 47.2% |
| | | 1 | 3 | 11.5% | 6 | 13.0% | 9 | 12.5% |
| | | 2 | 6 | 23.1% | 15 | 32.6% | 21 | 29.2% |
| | | 3 | 2 | 7.7% | 5 | 10.9% | 7 | 9.7% |
| | | 4 | 1 | 3.8% | 0 | 0.0% | 1 | 1.4% |
| | Constipation | 0 | 26 | 100.0% | 46 | 100.0% | 72 | 100.0% |
| Objective | Melena | 0 | 25 | 96.2% | 45 | 97.8% | 70 | 97.2% |
| | | 1 | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |
| | | 2 | 1 | 3.8% | 0 | 0.0% | 1 | 1.4% |
| | Weight loss | 0 | 26 | 100.0% | 46 | 100.0% | 72 | 100.0% |
| | Stricture | 0 | 26 | 100.0% | 45 | 97.8% | 71 | 98.6% |
| | | Missing | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |
| | Ulceration | 0 | 26 | 100.0% | 45 | 97.8% | 71 | 98.6% |
| | | Missing | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |
| Management | Pain | 0 | 22 | 84.6% | 36 | 78.3% | 58 | 80.6% |
| | | 1 | 2 | 7.7% | 6 | 13.0% | 8 | 11.1% |
| | | 2 | 1 | 3.8% | 2 | 4.3% | 3 | 4.2% |
| | | 3 | 1 | 3.8% | 2 | 4.3% | 3 | 4.2% |
| | Stool consistency / frequency | 0 | 11 | 42.3% | 19 | 41.3% | 30 | 41.7% |
| | | 1 | 10 | 38.5% | 8 | 17.4% | 18 | 25.0% |
| | | 2 | 5 | 19.2% | 18 | 39.1% | 23 | 31.9% |
| | | 3 | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |
| | Bleeding | 0 | 26 | 100.0% | 44 | 95.7% | 70 | 97.2% |
| | | 1 | 0 | 0.0% | 2 | 4.3% | 2 | 2.8% |
| | Stricture | 0 | 26 | 100.0% | 46 | 100.0% | 72 | 100.0% |
| | Ulceration | 0 | 26 | 100.0% | 46 | 100.0% | 72 | 100.0% |

A3.4 Maximum grade reported for each scale at baseline

| Maximum grade at baseline | | Control N=29 | | HBO N=55 | | Total N=84 | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| Subjective | 0 | 2 | 6.9% | 3 | 5.5% | 5 | 6.0% |
| | 1 | 13 | 44.8% | 10 | 18.2% | 23 | 27.4% |
| | 2 | 10 | 34.5% | 28 | 50.9% | 38 | 45.2% |
| | 3 | 4 | 13.8% | 14 | 25.5% | 18 | 21.4% |
| Objective | 0 | 23 | 79.3% | 45 | 81.8% | 68 | 81.0% |
| | 1 | 3 | 10.3% | 4 | 7.3% | 7 | 8.3% |
| | 2 | 2 | 6.9% | 5 | 9.1% | 7 | 8.3% |
| | 3 | 1 | 3.4% | 1 | 1.8% | 2 | 2.4% |
| Management | 0 | 8 | 27.6% | 12 | 21.8% | 20 | 23.8% |
| | 1 | 8 | 27.6% | 16 | 29.1% | 24 | 28.6% |
| | 2 | 11 | 37.9% | 23 | 41.8% | 34 | 40.5% |
| | 3 | 2 | 6.9% | 4 | 7.3% | 6 | 7.1% |

A3.5 Maximum grade reported for each scale at 2 weeks

| Maximum grade at 2 weeks | | Control N=28 | | HBO N=50 | | Total N=78 | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| Subjective | 0 | 5 | 17.9% | 7 | 14.0% | 12 | 15.4% |
| | 1 | 11 | 39.3% | 17 | 34.0% | 28 | 35.9% |
| | 2 | 9 | 32.1% | 20 | 40.0% | 29 | 37.2% |
| | 3 | 3 | 10.7% | 5 | 10.0% | 8 | 10.3% |
| | 4 | 0 | 0.0% | 1 | 2.0% | 1 | 1.3% |
| Objective | 0 | 23 | 82.1% | 46 | 92.0% | 69 | 88.5% |
| | 1 | 2 | 7.1% | 3 | 6.0% | 5 | 6.4% |
| | Missing | 3 | 10.7% | 1 | 2.0% | 4 | 5.1% |
| Management | 0 | 6 | 21.4% | 11 | 22.0% | 17 | 21.8% |
| | 1 | 12 | 42.9% | 14 | 28.0% | 26 | 33.3% |
| | 2 | 7 | 25.0% | 23 | 46.0% | 30 | 38.5% |
| | 3 | 1 | 3.6% | 2 | 4.0% | 3 | 3.8% |
| | Missing | 2 | 7.1% | 0 | 0.0% | 2 | 2.6% |

A3.6 Maximum grade reported for each scale at 12 months

| Maximum grade at 12 months | | Control N=26 | | HBO N=46 | | Total N=72 | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| Subjective | 0 | 6 | 23.1% | 5 | 10.9% | 11 | 15.3% |
| | 1 | 9 | 34.6% | 16 | 34.8% | 25 | 34.7% |
| | 2 | 7 | 26.9% | 19 | 41.3% | 26 | 36.1% |
| | 3 | 3 | 11.5% | 6 | 13.0% | 9 | 12.5% |
| | 4 | 1 | 3.8% | 0 | 0.0% | 1 | 1.4% |
| Objective | 0 | 25 | 96.2% | 44 | 95.7% | 69 | 95.8% |
| | 1 | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |
| | 2 | 1 | 3.8% | 0 | 0.0% | 1 | 1.4% |
| | Missing | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |
| Management | 0 | 10 | 38.5% | 17 | 37.0% | 27 | 37.5% |
| | 1 | 9 | 34.6% | 9 | 19.6% | 18 | 25.0% |
| | 2 | 6 | 23.1% | 18 | 39.1% | 24 | 33.3% |
| | 3 | 1 | 3.8% | 2 | 4.3% | 3 | 4.2% |

A3.7 Maximum overall intestinal LENT SOMA grade reported at baseline

| Maximum score at baseline | Control N=29 | | HBO N=55 | | Total N=84 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| 0 | 1 | 3.4% | 3 | 5.5% | 4 | 4.8% |
| 1 | 9 | 31.0% | 5 | 9.1% | 14 | 16.7% |
| 2 | 13 | 44.8% | 31 | 56.4% | 44 | 52.4% |
| 3 | 6 | 20.7% | 16 | 29.1% | 22 | 26.2% |

A3.8 Maximum overall intestinal LENT SOMA grade reported at 2 weeks

| Maximum score at 2 weeks | Control N=28 | | HBO N=50 | | Total N=78 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| 0 | 3 | 10.7% | 6 | 12.0% | 9 | 11.5% |
| 1 | 12 | 42.9% | 14 | 28.0% | 26 | 33.3% |
| 2 | 9 | 32.1% | 23 | 46.0% | 32 | 41.0% |
| 3 | 4 | 14.3% | 6 | 12.0% | 10 | 12.8% |
| 4 | 0 | 0.0% | 1 | 2.0% | 1 | 1.3% |

A3.9 Maximum overall intestinal LENT SOMA grade reported at 12 months

| Maximum score at 12 months | Control N=26 | | HBO N=46 | | Total N=72 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| 0 | 5 | 19.2% | 4 | 8.7% | 9 | 12.5% |
| 1 | 9 | 34.6% | 13 | 28.3% | 22 | 30.6% |
| 2 | 8 | 30.8% | 23 | 50.0% | 31 | 43.1% |
| 3 | 3 | 11.5% | 6 | 13.0% | 9 | 12.5% |
| 4 | 1 | 3.8% | 0 | 0.0% | 1 | 1.4% |

## Appendix 4 CTCAE

The number and proportion of patients with each grade of each toxicity are shown split by treatment group at each time point

A4.1 Baseline CTCAE toxicities

| | | Control N=29 | | HBO N=54 | | Total N=83 | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| Abdominal pain | 0 | 15 | 53.6% | 21 | 38.9% | 36 | 43.4% |
| | 1 | 10 | 35.7% | 16 | 29.6% | 26 | 31.3% |
| | 2 | 1 | 3.6% | 10 | 18.5% | 11 | 13.3% |
| | 3 | 3 | 10.7% | 7 | 13.0% | 10 | 12.0% |
| Bloating | 0 | 17 | 60.7% | 26 | 48.1% | 43 | 51.8% |
| | 1 | 8 | 28.6% | 17 | 31.5% | 25 | 30.1% |
| | 2 | 4 | 14.3% | 11 | 20.4% | 15 | 18.1% |
| Constipation | 0 | 26 | 92.9% | 49 | 90.7% | 75 | 90.4% |
| | 1 | 3 | 10.7% | 4 | 7.4% | 7 | 8.4% |
| | 2 | 0 | 0.0% | 1 | 1.9% | 1 | 1.2% |
| Diarrhoea | 0 | 21 | 75.0% | 39 | 72.2% | 60 | 72.3% |
| | 1 | 1 | 3.6% | 1 | 1.9% | 2 | 2.4% |
| | 2 | 6 | 21.4% | 12 | 22.2% | 18 | 21.7% |
| | 3 | 1 | 3.6% | 1 | 1.9% | 2 | 2.4% |
| | 4 | 0 | 0.0% | 1 | 1.9% | 1 | 1.2% |
| Faecal incontinence | 0 | 9 | 32.1% | 18 | 33.3% | 27 | 32.5% |
| | 1 | 6 | 21.4% | 19 | 35.2% | 25 | 30.1% |
| | 2 | 14 | 50.0% | 16 | 29.6% | 30 | 36.1% |
| | 3 | 0 | 0.0% | 1 | 1.9% | 1 | 1.2% |
| Flatulence | 0 | 9 | 32.1% | 20 | 37.0% | 29 | 34.9% |
| | 1 | 11 | 39.3% | 25 | 46.3% | 36 | 43.4% |
| | 2 | 9 | 32.1% | 9 | 16.7% | 18 | 21.7% |
| Frequency | 0 | 11 | 39.3% | 11 | 20.4% | 22 | 26.5% |
| | 1 | 6 | 21.4% | 17 | 31.5% | 23 | 27.7% |
| | 2 | 11 | 39.3% | 26 | 48.1% | 37 | 44.6% |
| | 3 | 1 | 3.6% | 0 | 0.0% | 1 | 1.2% |
| Rectal bleeding | 0 | 10 | 35.7% | 27 | 50.0% | 37 | 44.6% |
| | 1 | 7 | 25.0% | 6 | 11.1% | 13 | 15.7% |
| | 2 | 11 | 39.3% | 16 | 29.6% | 27 | 32.5% |
| | 3 | 1 | 3.6% | 5 | 9.3% | 6 | 7.2% |
| Rectal pain | 0 | 22 | 78.6% | 48 | 88.9% | 70 | 84.3% |
| | 1 | 4 | 14.3% | 2 | 3.7% | 6 | 7.2% |
| | 2 | 2 | 7.1% | 4 | 7.4% | 6 | 7.2% |
| | 3 | 1 | 3.6% | 0 | 0.0% | 1 | 1.2% |
| Tenesmus | 0 | 6 | 21.4% | 17 | 31.5% | 23 | 27.7% |
| | 1 | 13 | 46.4% | 16 | 29.6% | 29 | 34.9% |
| | 2 | 10 | 35.7% | 21 | 38.9% | 31 | 37.3% |
| Urgency | 0 | 3 | 10.7% | 5 | 9.3% | 8 | 9.6% |
| | 1 | 3 | 10.7% | 10 | 18.5% | 13 | 15.7% |
| | 2 | 21 | 75.0% | 37 | 68.5% | 58 | 69.9% |
| | 3 | 2 | 7.1% | 2 | 3.7% | 4 | 4.8% |
| GI disorders | 0 | 27 | 96.4% | 47 | 87.0% | 74 | 89.2% |
| | 1 | 1 | 3.6% | 6 | 11.1% | 7 | 8.4% |
| | 2 | 1 | 3.6% | 1 | 1.9% | 2 | 2.4% |

A4.2 2 week CTCAE toxicities

| | | HBO N=50 | | Control N=28 | | Total N=78 | |
|---|---|---|---|---|---|---|---|
| | | N | % | N | % | N | % |
| Abdominal pain | 0 | 27 | 54.0% | 15 | 53.6% | 42 | 53.8% |
| | 1 | 12 | 24.0% | 8 | 28.6% | 20 | 25.6% |
| | 2 | 7 | 14.0% | 3 | 10.7% | 10 | 12.8% |
| | 3 | 4 | 8.0% | 2 | 7.1% | 6 | 7.7% |
| Bloating | 0 | 27 | 54.0% | 17 | 60.7% | 44 | 56.4% |
| | 1 | 20 | 40.0% | 6 | 21.4% | 26 | 33.3% |
| | 2 | 3 | 6.0% | 5 | 17.9% | 8 | 10.3% |
| Constipation | 0 | 47 | 94.0% | 24 | 85.7% | 71 | 91.0% |
| | 1 | 3 | 6.0% | 4 | 14.3% | 7 | 9.0% |
| Diarrhoea | 0 | 40 | 80.0% | 24 | 85.7% | 64 | 82.1% |
| | 1 | 6 | 12.0% | 0 | 0.0% | 6 | 7.7% |
| | 2 | 3 | 6.0% | 4 | 14.3% | 7 | 9.0% |
| | 3 | 1 | 2.0% | 0 | 0.0% | 1 | 1.3% |
| Faecal incontinence | 0 | 23 | 46.0% | 9 | 32.1% | 32 | 41.0% |
| | 1 | 13 | 26.0% | 6 | 21.4% | 19 | 24.4% |
| | 2 | 14 | 28.0% | 12 | 42.9% | 26 | 33.3% |
| | 3 | 0 | 0.0% | 1 | 3.6% | 1 | 1.3% |
| Flatulence | 0 | 20 | 40.0% | 11 | 39.3% | 31 | 39.7% |
| | 1 | 19 | 38.0% | 12 | 42.9% | 31 | 39.7% |
| | 2 | 11 | 22.0% | 5 | 17.9% | 16 | 20.5% |
| Frequency | 0 | 27 | 54.0% | 11 | 39.3% | 38 | 48.7% |
| | 1 | 11 | 22.0% | 11 | 39.3% | 22 | 28.2% |
| | 2 | 11 | 22.0% | 6 | 21.4% | 17 | 21.8% |
| | 3 | 1 | 2.0% | 0 | 0.0% | 1 | 1.3% |
| Rectal bleeding | 0 | 23 | 46.0% | 12 | 42.9% | 35 | 44.9% |
| | 1 | 17 | 34.0% | 11 | 39.3% | 28 | 35.9% |
| | 2 | 8 | 16.0% | 5 | 17.9% | 13 | 16.7% |
| | 3 | 2 | 4.0% | 0 | 0.0% | 2 | 2.6% |
| Rectal pain | 0 | 41 | 82.0% | 22 | 78.6% | 63 | 80.8% |
| | 1 | 8 | 16.0% | 5 | 17.9% | 13 | 16.7% |
| | 2 | 1 | 2.0% | 1 | 3.6% | 2 | 2.6% |
| Tenesmus | 0 | 21 | 42.0% | 11 | 39.3% | 32 | 41.0% |
| | 1 | 17 | 34.0% | 9 | 32.1% | 26 | 33.3% |
| | 2 | 12 | 24.0% | 8 | 28.6% | 20 | 25.6% |
| Urgency | 0 | 10 | 20.0% | 5 | 17.9% | 15 | 19.2% |
| | 1 | 20 | 40.0% | 9 | 32.1% | 29 | 37.2% |
| | 2 | 20 | 40.0% | 14 | 50.0% | 34 | 43.6% |
| GI disorders | 0 | 48 | 96.0% | 27 | 96.4% | 75 | 96.2% |
| | 1 | 2 | 4.0% | 1 | 3.6% | 3 | 3.8% |

A4.3 12 month CTCAE toxicities

| | | Control N=26 | | HBO N=46 | | Total N=72 | |
|---|---|---|---|---|---|---|---|
| | | N | % | HBO | % | N | % |
| Abdominal pain | 0 | 14 | 53.8% | 20 | 43.5% | 34 | 47.2% |
| | 1 | 7 | 26.9% | 12 | 26.1% | 19 | 26.4% |
| | 2 | 1 | 3.8% | 9 | 19.6% | 10 | 13.9% |
| | 3 | 4 | 15.4% | 5 | 10.9% | 9 | 12.5% |
| Bloating | 0 | 12 | 46.2% | 22 | 47.8% | 34 | 47.2% |
| | 1 | 10 | 38.5% | 20 | 43.5% | 30 | 41.7% |
| | 2 | 4 | 15.4% | 4 | 8.7% | 8 | 11.1% |
| Constipation | 0 | 25 | 96.2% | 43 | 93.5% | 68 | 94.4% |
| | 1 | 1 | 3.8% | 2 | 4.3% | 3 | 4.2% |
| | 2 | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |
| Diarrhoea | 0 | 23 | 88.5% | 39 | 84.8% | 62 | 86.1% |
| | 1 | 1 | 3.8% | 1 | 2.2% | 2 | 2.8% |
| | 2 | 0 | 0.0% | 6 | 13.0% | 6 | 8.3% |
| | 3 | 2 | 7.7% | 0 | 0.0% | 2 | 2.8% |
| Faecal incontinence | 0 | 10 | 38.5% | 18 | 39.1% | 28 | 38.9% |
| | 1 | 5 | 19.2% | 14 | 30.4% | 19 | 26.4% |
| | 2 | 10 | 38.5% | 13 | 28.3% | 23 | 31.9% |
| | 3 | 1 | 3.8% | 1 | 2.2% | 2 | 2.8% |
| Flatulence | 0 | 10 | 38.5% | 16 | 34.8% | 26 | 36.1% |
| | 1 | 11 | 42.3% | 15 | 32.6% | 26 | 36.1% |
| | 2 | 5 | 19.2% | 15 | 32.6% | 20 | 27.8% |
| Frequency | 0 | 12 | 46.2% | 17 | 37.0% | 29 | 40.3% |
| | 1 | 7 | 26.9% | 13 | 28.3% | 20 | 27.8% |
| | 2 | 6 | 23.1% | 16 | 34.8% | 22 | 30.6% |
| | 3 | 1 | 3.8% | 0 | 0.0% | 1 | 1.4% |
| Rectal bleeding | 0 | 11 | 42.3% | 25 | 54.3% | 36 | 50.0% |
| | 1 | 13 | 50.0% | 14 | 30.4% | 27 | 37.5% |
| | 2 | 2 | 7.7% | 6 | 13.0% | 8 | 11.1% |
| | 3 | 0 | 0.0% | 1 | 2.2% | 1 | 1.4% |
| Rectal pain | 0 | 20 | 76.9% | 35 | 76.1% | 55 | 76.4% |
| | 1 | 3 | 11.5% | 11 | 23.9% | 14 | 19.4% |
| | 2 | 1 | 3.8% | 0 | 0.0% | 1 | 1.4% |
| | 3 | 2 | 7.7% | 0 | 0.0% | 2 | 2.8% |
| Tenesmus | 0 | 17 | 65.4% | 20 | 43.5% | 37 | 51.4% |
| | 1 | 4 | 15.4% | 15 | 32.6% | 19 | 26.4% |
| | 2 | 5 | 19.2% | 11 | 23.9% | 16 | 22.2% |
| Urgency | 0 | 6 | 23.1% | 13 | 28.3% | 19 | 26.4% |
| | 1 | 8 | 30.8% | 5 | 10.9% | 13 | 18.1% |
| | 2 | 11 | 42.3% | 24 | 52.2% | 35 | 48.6% |
| | 3 | 1 | 3.8% | 4 | 8.7% | 5 | 6.9% |
| GI disorders | 0 | 22 | 84.6% | 42 | 91.3% | 64 | 88.9% |
| | 1 | 1 | 3.8% | 2 | 4.3% | 3 | 4.2% |
| | 2 | 3 | 11.5% | 2 | 4.3% | 5 | 6.9% |