

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Participating Sites

The sites included in the table below (except for Amphia) were originally member of an international consortium.

<i>Site</i>	<i>Country, city</i>	<i>Principal investigator</i>	<i>Number of participants included in intention-to-treat analysis</i>
Máxima Medical Center	Netherlands, Veldhoven	Gerrit D. Slooter	65
McGill University Health Center	Canada, Montreal	Prof. Francesco Carli	112
Hospital Clínic de Barcelona	Spain, Barcelona	Graciela Martínez Palli	48
Zealand University Hospital	Denmark, Roskilde	Prof. Ismail Gögenur	12
Slagelse Hospital	Denmark, Slagelse	Prof. Ismail Gögenur	9
St. Anna University Hospital	Italy, Ferrara	Prof. Carlo Feo	2
Amphia	Netherlands, Breda	Jennifer M.J. Schreinemakers	3

Two additional sites were approved to participate in the PREHAB trial. However, after approval the COVID-19 pandemic occurred and precluded them from enrolling patients.

<i>Site</i>	<i>Country, city</i>	<i>Principal investigator</i>
Mútua Terrassa University Hospital	Spain, Barcelona	Rosa Asbert Sagasti
Bernhoven	Netherlands, Uden	Wout van der Meij

eTable 1. Overview of Assessments

	Baseline	Preoperatively	4 Weeks after surgery	8 Weeks after surgery	52 Weeks after surgery
Domain					
Physical status	CPET 6MWT SCT STS Indirect 1-RM Activity questionnaire	CPET 6MWT SCT STS Indirect 1-RM Activity questionnaire	CPET 6MWT SCT STS Indirect 1-RM Activity questionnaire	6MWT SCT STS Indirect 1-RM Activity questionnaire	Activity questionnaire
Nutritional status	3-day food diary Height, weight, BMI HGS Skinfolds ^a Circumferences ^b PG-SGA	3-day food diary Height, weight, BMI HGS Skinfolds ^a Circumferences ^b PG-SGA	Height, weight, BMI HGS PG-SGA	Height, weight, BMI HGS PG-SGA	
Mental status	GAD-7 PHQ-9 Intake by site investigator	GAD-7 PHQ-9	GAD-7 PHQ-9	GAD-7 PHQ-9	GAD-7 PHQ-9
Other questionnaires ^c	G8 Fried Frailty Score EORTC QLQ-CR29 EORTC QLQ-C30 SF-36 iMTA-PCQ DASI ^d WHODAS 2.0 ^d	EORTC QLQ-CR29 EORTC QLQ-C30 SF-36 Programme evaluation iMTA-PCQ	EORTC QLQ-CR29 EORTC QLQ-C30 SF-36 iMTA-PCQ	EORTC QLQ-CR29 EORTC QLQ-C30 SF-36 iMTA-PCQ	EORTC QLQ-CR29 EORTC QLQ-C30 SF-36 DASI ^d WHODAS 2.0 ^d

All assessments at various time points. ^aSkinfolds were determined for biceps, triceps, subscapular, suprailiacal and calf. ^bCircumferences were determined for wrist, waist and upper arm. Wrist was only determined at baseline. ^cQuestionnaires were either sent by email or handed out in paper version, according to site preference. ^dDASI and WHODAS were added after trial commencement and were collected from January 2019. Abbreviations: 6MWT, 6-minute walk test; BMI, body mass index; CPET, cardiopulmonary exercise test; DASI, duke activity status index; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer, quality of life of cancer patients module; EORTC QLQ-CR29, European Organisation for Research and Treatment of Cancer, quality of life of cancer patients colorectal cancer module; G8, G8 geriatric screening tool; GAD-7, generalized anxiety disorder 7-item scale; HGS, handgrip strength; iMTA-PCQ, institute for medical technology assessment productivity cost questionnaire; indirect 1-RM, indirect 1-repetition maximum; PG-SGA, patient-generated subjective global assessment; PHQ-9, patient health questionnaire; SCT, stair climb test; SF-36, 36-item short form survey; STS, sit-to-stand test; WHODAS 2.0, world health organisation disability assessment schedule.

eTable 2. 30-Days Postoperative Complications.

	Prehab (n=123)	Control (n=128)	OR	95%CI OR	p-value
All (CCI)	39	54	0.62	(0.37, 1.05)	0.07
Severe (CCI>20)	21	38	0.47	(0.26, 0.87)	0.02
Medical	19	35	0.48	(0.26, 0.89)	0.02
Surgical	26	35	0.71	(0.40, 1.27)	0.25
Medical & surgical	6	16	0.36	(0.14, 0.95)	0.03

Incidence and odds ratio of different types of complications in the two study arms within 30 days after surgery in the intention-to-treat population (n=251).

eTable 3. 30-Days Postoperative Complications Specified.

	Prehab (n=123)	Control (n=128)	p-value
Number of patients with medical complication ^a , No. (%)	19 (15.4%)	35 (27.3%)	0.02
Number of patients with surgical complication ^a , No. (%)	26 (21.1%)	35 (27.3%)	0.25
Number of patients with both medical and surgical complication, No. (%)	6 (4.9%)	16 (12.5%)	0.03
Number of complications ^b			0.19
1	26 (21.1%)	29 (22.7%)	
2	10 (8.1%)	16 (12.5%)	
3	3 (2.4%)	4 (3.1%)	
4	0	4 (3.1%)	
5	0	1 (0.8%)	
Total number of medical complications ^c , No. (%)			0.05
Cardiovascular, No. (%)	5 (4.1%)	12 (9.4%)	
Respiratory, No. (%)	3 (2.4%)	7 (5.5%)	
Urogenital, No. (%)	8 (6.5%)	11 (8.6%)	
Neurological, No. (%)	0	3 (2.3%)	
Other, No. (%)	6 (4.9%)	11 (8.6%)	
Total number of surgical complications ^c , No. (%)			0.39
Wound or stoma related, No. (%)	8 (6.5%)	11 (8.6%)	
Blood loss, No. (%)	5 (4.1%)	5 (3.9%)	
Ileus/ gastroparesis, No. (%)	13 (10.6%)	19 (14.8%)	
CAL, No. (%)	2 (1.6%)	5 (3.9%)	
Abscess, No. (%)	1 (0.8%)	5 (3.9%)	
Other, No. (%)	4 (3.3%)	5 (3.9%)	

Specification of complications within 30 days after surgery in the intention-to-treat population (n=251). ^aSubjects with at least one medical, surgical, or both medical and surgical complications. ^bPer patient. ^cAll complications specified per subtype: 93 Subjects had a total of 149 complications. Abbreviations: CAL, colorectal anastomotic leakage.

1 **eTable 4. Secondary Functional Outcomes**

	Baseline		Preoperatively		4 Weeks after surgery		8 Weeks after surgery	
	Prehab	Control	Prehab	Control	Prehab	Control	Prehab	Control
6MWD, meters	514.0 [450.0, 578.0]	512.5 [435.0, 572.0]	551.0 [464.0, 630.0]	534.0 [458.5, 594.0]	536 [470, 603]	514 [428, 568]	558.5 [482.5, 625.0]	528.5 [457.0, 594.0]
Missing, No. (%)	1 (0.8%)	2 (1.6%)	18 (14.6%)	24 (18.8%)	38 (30.9%)	45 (35.2%)	43 (35.0%)	50 (39.1%)
VO ₂ AT, ml·kg ⁻¹ ·min ⁻¹	12.3 [10.9, 15.0]	12.9 [10.3, 15.0]	13.7 [11.2, 16.7]	12.6 [11.0, 14.5]	12.9 [11.4, 15.4]	11.5 [10.0, 12.7]		
Missing, No. (%)	14 (11.4%)	17 (13.3%)	33 (26.8%)	43 (33.6%)	55 (44.7%)	59 (46.1%)		
peakVO ₂ , ml·kg ⁻¹ ·min ⁻¹	18.0 [15.0, 21.9]	19.0 [15.0, 22.3]	19.0 [16.0, 26.2]	20.0 [15.7, 23.5]	19.3 [15.9, 24.9]	18.0 [14.5, 20.6]		
Missing, No. (%)	10 (8.1%)	13 (10.2%)	33 (26.8%)	40 (31.3%)	54 (43.9%)	57 (44.5%)		
1-RM chest press, kilograms	15.9 [9.1, 28.8]	18.8 [11.8, 30.0]	20.2 [13.0, 33.5]	22.5 [13.3, 32.1]	20.0 [11.4, 31.9]	20.9 [13.7, 34.5]	21.1 [13.3, 33.3]	20.0 [11.8, 34.6]
Missing, No. (%)	5 (4.1%)	32 (25.0%)	27 (22.0%)	53 (41.4%)	44 (35.8%)	68 (53.1%)	49 (39.8%)	73 (57.0%)
Handgrip strength, kilograms	28.0 [21.5, 38.0]	30.5 [23.5, 38.0]	31.5 [22.9, 38.0]	30.0 [24.0, 37.7]	28.3 [22.0, 38.0]	29.0 [22.9, 34.5]	30.0 [22.0, 40.0]	30.0 [24.0, 36.3]
Missing, No. (%)	3 (2.4%)	4 (3.1%)	19 (15.4%)	23 (18.0%)	40 (32.5%)	48 (37.5%)	45 (36.6%)	55 (43.0%)
PG-SGA-SF	1 [0, 4]	1 [0, 3]	0 [0, 2]	0 [0, 2]	1 [0, 4]	1 [0, 4]	0 [0, 1]	0 [0, 3]
Missing, No. (%)	8 (6.5%)	10 (7.8%)	34 (27.6%)	42 (32.8%)	59 (48.0%)	61 (47.7%)	71 (57.7%)	79 (61.7%)
GAD-7	2 [0, 5]	3 [0, 6]	1 [0, 4]	2 [0, 5]	1 [0, 3]	1 [0, 5]	0 [0, 3]	1 [0, 3]
Missing, No. (%)	6 (4.9%)	3 (1.7%)	26 (21.1%)	28 (21.9%)	38 (30.9%)	46 (35.9%)	43 (35.0%)	49 (38.3%)
PHQ-9	2 [0, 6]	2 [0, 5]	1 [0, 4]	2 [0, 4]	2 [0, 5]	3 [1, 5]	1 [0, 4]	2 [1, 4]
Missing, No. (%)	8 (6.5%)	2 (1.6%)	25 (20.3%)	32 (25.0%)	40 (32.5%)	47 (36.7%)	44 (35.8%)	49 (38.3%)
EORTC QLQ-C30, global health status	66 [66, 83]	66 [50, 83]	66 [66, 83]	66 [50, 83]	66 [66, 83]	66 [50, 83]	83 [66, 83]	66 [66, 83]
Missing, No. (%)	2 (1.6%)	1 (0.8%)	24 (19.5%)	28 (21.9%)	37 (30.1%)	44 (34.4%)	42 (34.1%)	49 (38.3%)

2 Secondary functional outcomes in the intention-to-treat population (n=251). Values are displayed per time point in median [IQR]. Abbreviations: 1-RM, indirect 1 repetition maximum; 6MWD, 6-
3 minute walking distance; EORTC QLQ-C30, european organisation for research and treatment of cancer, quality of life of cancer patients module; GAD-7, generalized anxiety disorder 7-item
4 scale; IQR, interquartile range; kg, kilograms; ml, milliliter; min, minute; peakVO₂, oxygen consumption at peak exercise; PG-SGA-SF, patient-generated subjective global assessment short
5 form; PHQ-9, patient health questionnaire; VO₂AT, oxygen consumption at the anaerobic threshold.

6 eTable 5. Results of the GEE Analysis

	Baseline mean diff (95%CI)	Preoperatively mean diff (95%CI)	4 Weeks after surgery mean diff (95%CI)	8 Weeks after surgery mean diff (95%CI)
6MWD, meters	10.61 (-14.93, 36.16)	10.58 (-1.67, 22.83)	15.58 (-1.44, 32.59)	22.15 (6.63, 37.66)
p-value, corrected for baseline	0.42*	0.09	0.07	0.01
Handgrip strength, kilograms	-1.32 (-3.88, 1.25)	1.00 (-0.25, 2.26)	1.23 (-0.06, 2.51)	1.86 (0.57, 3.16)
p-value, corrected for baseline	0.32*	0.12	0.06	<.01
EORTC QLQ-C30, global health status	4.29 (-0.42, 90.1)	-0.54 (-1.86, 0.77)	-0.88 (-6.66, 4.90)	0.46 (-5.12, 6.05)
p-value, corrected for baseline	0.07*	0.42	0.77	0.87
	Baseline Median ratio (95%CI)	Preoperatively Median ratio (95%CI)	4 Weeks after surgery Median ratio (95%CI)	8 Weeks after surgery Median ratio (95%CI)
VO ₂ AT, ml·kg ⁻¹ ·min ⁻¹	1.01 (0.95, 1.07)	1.06 (0.99, 1.12)	1.08 (1.02, 1.16)	
p-value, corrected for baseline	0.75*	0.08	0.02	
peakVO ₂ , ml·kg ⁻¹ ·min ⁻¹	1.02 (0.95, 1.1)	1.04 (1.00, 1.09)	1.07 (1.02, 1.12)	
p-value, corrected for baseline	0.60*	0.07	0.01	
1-RM chest press, kilograms	0.88 (0.77, 1.01)	1.18 (1.11, 1.25)	1.17 (1.09, 1.25)	1.14 (1.06, 1.23)
p-value, corrected for baseline	0.07*	<.01	<.01	<.01
PG-SGA-SF	0.97 (0.77, 1.24)	1.11 (0.82, 1.52)	0.98 (0.67, 1.45)	0.86 (0.51, 1.44)
p-value, corrected for baseline	0.82*	0.50	0.94	0.56
GAD-7	0.93 (0.72, 1.18)	1.06 (0.81, 1.40)	0.87 (0.61, 1.23)	1.11 (0.78, 1.58)
p-value, corrected for baseline	0.54*	0.66	0.44	0.56
PHQ-9	0.97 (0.77, 1.23)	0.98 (0.77, 1.25)	0.87 (0.65, 1.15)	0.99 (0.75, 1.31)
p-value, corrected for baseline)	0.83*	0.88	0.32	0.95

7 Estimates, 95% confidence intervals and p-values from the GEE analyses. The 6MWD, handgrip strength and EORTC QLQ-C30 are analyzed in the original scale, and the estimates refer thus
8 to the mean difference between the two groups per time point, corrected for baseline. For all other variables, analyzed in the logarithmic scale because of a skewed distribution, estimates refer
9 to the median ratio between the two groups per time point, with respect to baseline. P-values at baseline are marked with a star (*) because these refer to the mean difference/median ratio not
10 corrected for baseline. Abbreviations: 6MWD, 6-minute walking distance; VO₂AT, oxygen consumption at the anaerobic threshold; peakVO₂, oxygen consumption at peak exercise; 1-RM,
11 indirect 1 repetition maximum; PG-SGA-SF, patient-generated subjective global assessment short form; GAD-7, generalized anxiety disorder 7-item scale; PHQ-9, patient health questionnaire;
12 EORTC QLQ-C30, European organisation for research and treatment of cancer, quality of life of cancer patients module; GEE generalized estimating equations; kg, kilogram; ml, milliliter; min,
13 minute.

14

15 **eTable 6. Sensitivity and Per-Protocol Analyses**

16 SUBGROUP ANALYSIS

17 High risk vs. low risk population based on CPET-derived variables.

18 High risk population (n=114; pre-operative risk assessment based on CPET variables: high risk = $VO_2AT < 11 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ and/
19 or $\text{peak}VO_2 < 18 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)

	Prehab (n=58)	Control (n=56)	p-value
Number of complications, No. (%)	21 (36.2%)	29 (51.8%)	0.09
CCI>20	12 (20.7%)	23 (41.1%)	0.02
Number of patients with medical complication, No. (%)	9 (15.5%)	22 (39.3%)	<.01
Number of patients with surgical complication, No. (%)	16 (27.59%)	19 (33.9%)	0.46
Number of patients with both medical and surgical complication, No. (%)	4 (6.9%)	12 (21.4%)	0.03
6MWD four weeks postoperatively, median [IQR]	475.0 [412.0, 517.0]	450 [355.0, 515.0]	0.25

20 Abbreviations: 6MWD, 6-minute walking distance; CCI, comprehensive complication index; CPET, cardiopulmonary exercise
21 test; IQR, interquartile range; kg, kilogram; ml, milliliter; min, minute; $\text{peak}VO_2$, oxygen consumption at peak exercise; VO_2AT ,
22 oxygen consumption at the anaerobic threshold.

23 Low risk population (n=114; pre-operative risk assessment based on CPET variables: low risk = $VO_2AT \geq 11 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$
24 and/or $\text{peak}VO_2 \geq 18 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)

	Prehab (n=55)	Control (n=59)	p-value
Number of complications, No. (%)	14 (25.5%)	19 (32.2%)	0.43
CCI>20	7 (12.7%)	10 (17.0%)	0.53
Number of patients with medical complication, No. (%)	7 (12.7%)	11 (18.6%)	0.39
Number of patients with surgical complication, No. (%)	8 (15.6%)	12 (20.3%)	0.42
Number of patients with both medical and surgical complication, No. (%)	1 (1.8%)	4 (6.8%)	0.37
6MWD four weeks postoperatively, median [IQR]	584.5 [533.0, 663.0]	552.0 [510.0, 616.0]	0.05

25 Abbreviations: 6MWD, 6-minute walking distance; CCI, comprehensive complication index; CPET, cardiopulmonary exercise
26 test; IQR, interquartile range; kg, kilogram; ml, milliliter; min, minute; $\text{peak}VO_2$, oxygen consumption at peak exercise; VO_2AT ,
27 oxygen consumption at the anaerobic threshold.

28 Colonic vs. rectal cancer.

29 Participants with colonic cancer (n=206, 82%)

	Prehab (n=101)	Control (n=105)	p-value
Number of complications, No. (%)	30 (29.7%)	42 (40.0%)	0.12
CCI>20	16 (15.8%)	28 (26.7%)	0.06
Number of patients with medical complication, No. (%)	16 (15.8%)	29 (27.6%)	0.04
Number of patients with surgical complication, No. (%)	19 (18.8%)	25 (23.8%)	0.38
Number of patients with both medical and surgical complication, No. (%)	5 (5.0%)	12 (11.4%)	0.09
6MWD four weeks postoperatively, median [IQR]	517.0 [451.0, 608.0]	514.5 [420.0, 568.0]	0.12

30 Abbreviations: 6MWD, 6-minute walking distance; CCI, comprehensive complication index; IQR, interquartile range.

31 Participants with rectal cancer (n=45, 18%)

	Prehab (n=22)	Control (n=23)	p-value
Number of complications, No. (%)	9 (40.9%)	12 (51.2%)	0.45
CCI>20	5 (22.7%)	10 (43.5%)	0.14
Number of patients with medical complication, No. (%)	3 (13.6%)	6 (26.1%)	0.46
Number of patients with surgical complication, No. (%)	7 (31.8%)	10 (43.5%)	0.42
Number of patients with both medical and surgical complication, No. (%)	1 (4.6%)	4 (17.4%)	0.35
6MWD four weeks postoperatively, median [IQR]	552.5 [536.0, 595.0]	513.0 [469.0, 554.0]	0.31

32 Abbreviations: 6MWD, 6-minute walking distance; CCI, comprehensive complication index; IQR, interquartile range.

33 SENSITIVITY ANALYSES

34 Excluding participants included in the Danish hospitals (n=230). The two Danish centers only included patients with a ECOG
35 performance status >0. This resulted in a subgroup with statistically different baseline results (poorer condition).

	Prehab (n=113)	Control (n=117)	p-value
Number of complications, No. (%)	33 (29.2%)	46 (39.3%)	0.09
CCI>20	17 (15.0%)	31 (26.5%)	0.03
Number of patients with medical complication, No. (%)	17 (15.0%)	30 (25.6%)	0.04
Number of patients with surgical complication, No. (%)	21 (18.6%)	31 (26.5%)	0.15
Number of patients with both medical and surgical complication, No. (%)	5 (4.42%)	15 (12.8%)	0.02
6MWD 4W postop, median [IQR]	546 [475, 608]	525 [450, 579]	0.02

36 Abbreviations: 6MWD, 6-minute walking distance; CCI, comprehensive complication index; ECOG, Eastern Cooperative
37 Oncology Group; IQR, interquartile range.

38 Excluding two major protocol deviations (n=249). The two major protocol deviations consisted of two patients who enrolled in
 39 the standard care group, instead completed the prehabilitation program.

	Prehab (n=123)	Control (n=126)	p-value
Number of complications, No. (%)	39 (31.7%)	54 (42.9%)	0.07
CCI>20	21 (17.1%)	38 (30.2%)	0.02
Number of patients with medical complication, No. (%)	19 (15.5%)	35 (27.78%)	0.02
Number of patients with surgical complication, No. (%)	26 (21.1%)	35 (27.8%)	0.25
Number of patients with both medical and surgical complication, No. (%)	6 (4.9%)	16 (12.7%)	0.03
6MWD 4W postop, median [IQR]	536.0 [470.0, 603.0]	514.5 [428.0, 568.0]	0.06

40 Abbreviations: 6MWD, 6-minute walking distance; CCI, comprehensive complication index; IQR, interquartile range.

41 Per-protocol analysis (n=166) only including participants from both groups with a preoperative period, determined as the number
 42 of weeks between baseline and presurgery assessment, consisting of minimal three and maximal eight weeks. Additionally, only
 43 compliant participants (≥9 training sessions) from the prehabilitation were selected.

	Prehab (n=83)	Control (n=83)	p-value
Number of complications, No. (%)	25 (30.1%)	32 (38.6%)	0.09
CCI>20	12 (14.5%)	21 (25.3%)	0.03
Number of patients with medical complication, No. (%)	14 (16.9%)	20 (24.1%)	0.16
Number of patients with surgical complication, No. (%)	16 (19.3%)	21 (25.3%)	0.19
Number of patients with both medical and surgical complication, No. (%)	5 (6.0%)	9 (10.8%)	0.26
6MWD 4W postop, median [IQR]	534.5 [475.0, 598.0]	515.0 [428.0, 573.0]	0.68

44 Abbreviations: 6MWD, 6-minute walking distance; CCI, comprehensive complication index; IQR, interquartile range.

45 Two participants were assessed as ASA III at time of inclusion, instead were eventually scored as ASA IV. Since ASA IV is one
 46 of the exclusion criteria, sensitivity analysis excluding these two participants were performed (n=249).

	Prehab (n=122)	Control (n=127)	p-value
Number of complications, No. (%)	39 (32.0%)	53 (41.7%)	0.11
CCI>20	21 (17.2%)	37 (29.1%)	0.03
Number of patients with medical complication, No. (%)	19 (15.6%)	34 (26.8%)	0.03
Number of patients with surgical complication, No. (%)	26 (21.3%)	35 (27.6%)	0.26
Number of patients with both medical and surgical complication, No. (%)	6 (4.9%)	16 (12.6%)	0.03
6MWD 4W postop, median [IQR]	534.5 [467.5, 605.5]	514.0 [428.0, 568.0]	0.08

47 Abbreviations: 6MWD, 6-minute walking distance; ASA, American Society of Anesthesiologists; CCI, comprehensive
 48 complication index; IQR, interquartile range.

49 Two participants eventually received minimal invasive surgery with transanal endoscopic microsurgery and endoscopic excision
 50 of the tumor. Sensivity analysis excluding these two participants is displayed below (n=249).

	Prehab (n=122)	Control (n=127)	p-value
Number of complications, No. (%)	39 (32.0%)	54 (42.5%)	0.07
CCI>20	21 (17.2%)	38 (29.9%)	0.01
Number of patients with medical complication, No. (%)	19 (15.6%)	35 (27.6%)	0.02
Number of patients with surgical complication, No. (%)	26 (21.3%)	35 (27.6%)	0.24
Number of patients with both medical and surgical complication, No. (%)	6 (4.9%)	16 (12.6%)	0.03
6MWD 4W postop, median [IQR]	534.5 [467.5, 605.5]	514.0 [428.0, 568.0]	0.08

51 Abbreviations: 6MWD, 6-minute walking distance; CCI, comprehensive complication index; IQR, interquartile range.