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Review Article

Quality and clinical generalizability of feasibility outcomes in exercise prehabilitation before colorectal cancer surgery – A systematic review

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ABSTRACT

Suboptimal quality of feasibility assessments might partially explain inconsistencies observed in the effectiveness of exercise prehabilitation before colorectal cancer (CRC) surgery. This systematic review aimed to assess the reporting quality and clinical generalizability of feasibility outcomes in feasibility studies addressing exercise prehabilitation before CRC surgery.

PubMed/Medline, Embase, Cochrane, and CINAHL were searched to identify all feasibility studies focussing on exercise prehabilitation in CRC surgery. Reporting quality was assessed using the Thabane et al. checklist and the Consolidated Standards of Reporting Trials extension for feasibility studies. Clinical generalizability was evaluated by appraising patient participation in all steps of the study and intervention.

Twelve studies were included. The main feasibility outcome in all studies was adherence to the intervention by the study sample. Based on adherence, 10 studies (83%) concluded exercise prehabilitation to be feasible. Six studies (50%) reported all details to assess patient participation showing retention rates between 18.4% and 58.2%, which was caused by non-participation and drop-out. Three feasibility studies (25%) discussed patient-reported barriers to participation and five additional studies (41%) described potential selection bias. Four studies (33%) reported lessons learned to solve issues hampering feasibility and clinical generalizability.

Results suggest that true feasibility of exercise prehabilitation before CRC surgery remains questionable due to poor reporting quality, insufficient clarity regarding the representativeness of the study sample for the target population, and limited attention for clinical generalizability. Feasibility of exercise prehabilitation might be improved by offering supervised community- or home-based interventions tailored to the physical and mental abilities of the patient.

1. Introduction

Surgery is the cornerstone of curative treatment of colorectal cancer (CRC); however, a relatively high rate of postoperative morbidity is observed with surgery [1]. Prehabilitation, an intervention to improve or, in case of neoadjuvant treatment, maintain a

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patient's health before surgery, is an emerging strategy to lower the risk of postoperative morbidity [2–4]. Nowadays, many prehabilitation programs are multimodal, thereby including interventions intended to improve preoperative physical fitness, nutritional status and mental well-being [5,6]. However, the basis of most programs is improving preoperative physical fitness through exercise prehabilitation.

It is well-established that patients with a lower preoperative physical fitness have a higher risk for postoperative morbidity after CRC surgery [3,7,8]. However, current results on the effectiveness of exercise prehabilitation appear inconsistent [9,10]. Although studies demonstrate that exercise prehabilitation leads to increased preoperative physical fitness in patients with CRC, its effectiveness to reduce postoperative morbidity has merely been established in high-risk patients based on a low preoperative physical fitness, high comorbidity burden, and/or high age [10–12].

To be clinically effective and relevant, exercise prehabilitation must be feasible for all patients who most likely benefit from the intervention. Therefore, a proper feasibility assessment targeting all steps needed to study and perform the exercise intervention is indispensable before assessing the effectiveness of exercise prehabilitation. The quality of feasibility studies in exercise prehabilitation including patients with CRC is currently unclear and could be part of the explanation why results of larger trials regarding the effectiveness of prehabilitation in improving postoperative outcomes seem inconsistent. Feasibility studies test the processes of the study, as well as the intervention, in order to detect and report how to overcome methodologic, logistic, and organizational problems that might affect the external validity of feasibility and future effectiveness outcomes [13–15]. A widespread problem in feasibility studies is not addressing or failing to detect these problems [16,17]. When left unrecognized, bias towards external validity might occur, which leads to ungeneralizable and clinically irrelevant effectiveness outcomes when proceeding to a full-scale trial or clinical implementation [14,15,18–23].

The reporting quality of feasibility studies is receiving increased attention by the publication of an extension to the Consolidated Standards of Reporting Trials (CONSORT) statement addressing items essential for good quality reporting of feasibility studies, as well as by the introduction of peer-reviewed journals solely focussing on feasibility studies [19]. Nevertheless, the actual reporting quality of feasibility studies remains poor [24–26]. Therefore, the aim of this systematic review was to assess the reporting quality and clinical generalizability of feasibility studies. In the current manuscript, feasibility studies addressing exercise prehabilitation in CRC surgery were used as an example.

2. Materials and methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [27]. Before initiating the review process, eligibility criteria, outcome measurements, and methods for analysis were documented in a review protocol (Supplementary Table 1).

2.1. In- and exclusion criteria

All studies focussing on the feasibility of exercise prehabilitation programs in patients with CRC scheduled for elective surgery, with or without neoadjuvant chemoradiotherapy (NACRT), were eligible for inclusion. Exercise prehabilitation was defined as a preoperative physical exercise training intervention aiming to maintain or improve preoperative physical fitness. Feasibility studies for multimodal prehabilitation programs were also included when preoperative physical exercise training was incorporated. Feasibility studies were defined as studies primarily designed to assess the feasibility of the prehabilitation intervention, as well as the feasibility to execute the prehabilitation study itself. Secondarily, these studies provide preliminary results of the hypothesized effects. Feasibility studies were typically performed before moving forward to an adequately powered randomized clinical trial or clinical implementation. The terms “pilot” and “feasibility” are used interchangeably in literature. Pilot studies usually carry out all parts of the future trial or clinical implementation and can be regarded as feasibility studies [14]. Throughout this systematic review, the term feasibility study is used to refer to both feasibility and pilot studies.

Feasibility studies were included when participants were adults (aged $\geq$18 years), diagnosed with CRC, scheduled for surgery with or without NACRT, and when a physical exercise training intervention was conducted prior to surgery, or prior to or during NACRT. Studies not assessing a physical exercise training intervention were excluded. Because the term “pilot” or “feasibility” study is often used as a justification for a small sample size, pilot or feasibility studies only focussing on effectiveness without any feasibility objectives were not considered feasibility studies and therefore excluded.

2.2. Data sources and search strategy

A comprehensive literature search was performed across PubMed/Medline, Embase, Cochrane Library, and CINAHL databases. The search strategy was verified by an experienced librarian. The last search was performed on June 12, 2020. The following keyword search terms or synonyms of these terms were used: “Colorectal neoplasm” AND “surgery” OR “neoadjuvant therapy” AND “prehabilitation” OR “exercise” AND “feasibility” OR “pilot”. A detailed description of the search strategies can be found in Supplementary Table 1.

2.3. Study selection

After removal of duplicates, two reviewers (AC and FL) independently screened all articles for eligibility based on title and abstract. When information in the title or abstract was insufficient to exclude the study, the full article was reviewed. After the initial screening procedure was completed, two reviewers (AC and FL) independently reviewed the full text of the possible eligible articles to determine final inclusion. A third reviewer (BB) determined eligibility and inclusion if the first two reviewers did not reach consensus. In addition to the primary search, bibliographies of included articles were reviewed to identify additional relevant articles that might be eligible for inclusion. No studies were excluded based on quality and no risk of bias assessment was performed because the aim was to assess reporting quality.

2.4. Assessment of reporting quality

Reporting quality of all included studies was assessed using the checklist of information to include when reporting a pilot study as published by Thabane et al. [23] and based on the CONSORT 2010 statement extension to randomized pilot and feasibility trials [19]. Item 4c of the CONSORT statement extension to randomized pilot and feasibility trials (“*How participants were identified and consented*”) was added to the checklist as it was not included by Thabane et al. [19,23]. A detailed description of the used checklist is displayed in Supplementary Table 2.

2.5. Assessment of clinical generalizability

Clinical generalizability of the feasibility outcomes was appraised based on the methodological quality of the feasibility assessments and patient-reported reasons for non-participation, dropout, and non-adherence. Methodological quality regarding the feasibility assessments of a full-scale trial and feasibility of the studied prehabilitation intervention was evaluated using process and scientific feasibility outcomes.

Process feasibility assesses the feasibility of participation in all steps that need to take place as part of the study itself and the studied prehabilitation intervention, and is measured using different participation rates [23]. Process feasibility outcomes of the study included the stated eligibility criteria (clear, sufficient, and not too restrictive), eligibility rates, and recruitment rates. Eligibility rates were calculated as the percentage of potentially eligible patients who were eligible to participate in the study. Recruitment rates were calculated as the percentage of eligible patients who were included in the study. Process feasibility outcomes of the studied prehabilitation intervention included retention rates and adherence rates [23]. Retention rates were calculated in two ways: first as the percentage of recruited (included) patients who completed the study, and second as the percentage of eligible patients who completed the study. Adherence rates were measured by the percentage of exercise sessions attended by the study participants. When participants were divided into an intervention and control group, adherence by the participants allocated to the intervention group was calculated.

Scientific feasibility of the prehabilitation intervention focusses on the safety of the intervention and the estimate of the treatment effect [23]. Scientific feasibility outcomes were program safety, as measured by the number of adverse events, and the preliminary effect of the prehabilitation intervention on preoperative physical fitness of the included patients, as assessed in the individual studies.

2.6. Data extraction and analysis

Reporting quality was assessed independently by two reviewers (AC and FL). All items of the reporting quality checklist were scored as *good*, *moderate*, or *poor*. Discrepancies were discussed until consensus was reached, with the consultation of a third reviewer (BB) when necessary. Inter-rater reliability for reporting quality was assessed by calculating inter-rater agreement and Cohen's Kappa. Inter-rater agreement was calculated using Microsoft Excel, version 2016 for Windows. Cohen's Kappa was calculated using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

A data extraction sheet was developed reporting general study characteristics (e.g., author, year and country of publication, study design, target population, sample size, study setting, intervention characteristics, and outcome measures) and demographics of the study populations (including age, tumour location, American Society of Anesthesiologists (ASA) physical status classification, and comorbidities). Separate extraction sheets were made for feasibility and preliminary effectiveness outcomes. Data extraction was performed independently by two reviewers (AC and FL). Afterwards, extraction sheets were exchanged and checked for errors. Disagreements were resolved by bilateral consensus and after consultation of a third reviewer (BB).

3. Results

The systematic database search provided 1015 records. Two additional records were identified by reviewing the reference lists. Based on screening titles and abstracts, 37 articles were identified for full text review. A total of 12 articles met the inclusion criteria and were included in the systematic review. Fig. 1 shows the PRISMA flow diagram for evidence acquisition. All included studies were prospective cohort feasibility studies or randomized controlled feasibility trials and were published between October 2009 and November 2019 [28–39]. General study characteristics, outcome measures, and demographics of the study samples are summarized in Table 1. Table 2 provides a detailed overview of the intervention characteristics of the included studies.

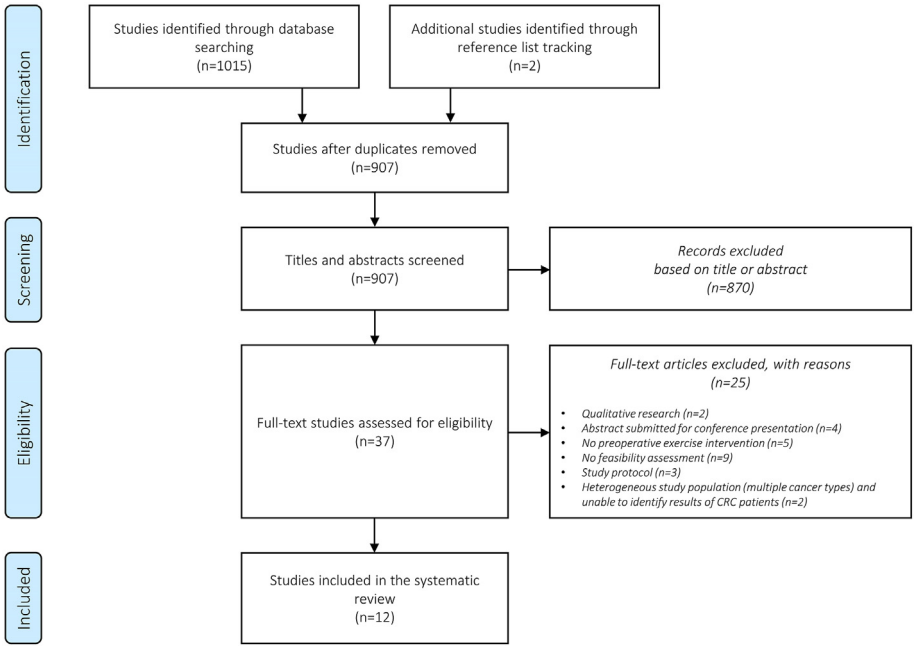

Fig. 1. PRISMA flow chart for evidence acquisition.

Table 1
General study characteristics.

Authors (year) Country	Study design *Period*	Target population	Study sample	Process feasibility outcome measures	Scientific feasibility outcome measures (preliminary effectiveness)
Alejo et al. (2019) Spain	Prospective cohort *Period*: NR	Patients with rectal cancer	n = 12 (male 25%) Age: 61 ± 7 yrs ASA: NR Comorbidities: NR	**Adherence**	*Aerobic fitness:* CPET *Functional performance:* HGS, 5-STS *Physical activity level*: Inactivity (min/week), MVPA *Body composition*: BMI *HR-QoL:* EORTC-QoL-C30 *Psychological distress*: HADS
Bruns et al. (2019) The Netherlands	Prospective cohort *Period:* February 2017 –February 2018	(Pre-)frail[a] patients with colorectal cancer (>70 years)	n = 14 (male 36%) Age: 79 [74–86] yrs ASA: 2 [2,3] Comorbidities: CVD[b]: 10 DM: 5 Pulmonary[c]: 1	**Retention** **Adherence**	***Safety*: adverse events** *Frailty*: Fried Frailty Index and Clinical Frailty Scale *Functional performance*: 4-m GS, SBBP *Muscle strength*: HGS *HR-QoL*: EORTC-QoL-C29/30
Dronkers et al. (2009) The Netherlands	RCT *Period*: NR	Elderly patients with colorectal cancer (>60 years)	*Intervention:* n = 22 (male 68.2%) Age: 71.1 ± 6.3 yrs ASA: NR Comorbidities: DM: 8 Pulmonary[c]: 3 *Control:* n = 20 (male 80%) Age: 68.8 ± 6.4 yrs ASA: NR Comorbidities: DM: 7 Pulmonary[c]: 3	**Adherence** **Appreciation**	***Safety*: adverse events** ***Aerobic fitness*: PWC170** ***Muscle strength*: MIP** ***Functional mobility*: CRT, TUG** *Self-reported activity* LAPAQ *HR-QoL:* EORTC-QoL-C30 *Postoperative outcome*: complications, functional recovery *Fatigue: AFQ*
Heldens et al. (2016) The Netherlands	Prospective cohort *Period:* April 2014 –April 2015	Patients with rectal cancer	n = 9 (male 89%) Age: 64.4 ± 10.9 yrs ASA I: 5, II: 3, III: 1 Comorbidities: CVD[b]: 4 DM: 1 Pulmonary[c]: 1 Orthopaedic[d]:1	**Adherence** **Patient motivation and satisfaction**	***Safety*: adverse events** *Functional performance*: 6MWT *Muscle strength*: arm and leg press *HR-QoL*: SF-36 *Fatigue: MFI*
Karlsson et al. (2019) Sweden	RCT *Period:* September 2016–June 2018	Elderly patients with colorectal cancer (>70 years)	*Intervention:* n = 10 (male 40%) Age: 83.5 [76; 85] yrs ASA: NR Comorbidities: CCI 2 [1–3] *Control:* n = 11 (male 36%) Age: 74.0 [73; 76] yrs ASA: NR Comorbidities: CCI 1 [0–3]	**Recruitment** **Adherence** **Acceptability**	*Safety*: adverse events *Functional performance*: walking distance, gait speed *Muscle strength*: leg strength, MIP *Postoperative outcome*: complications, LOS, PRP
Loughney et al. (2019) Ireland	Prospective cohort *Period:* June 2016 –June 2018	Patients with colorectal cancer	n = 17 (male 76.5%) Age: 60.5 ± 12.1 yrs ASA: NR Comorbidities: Any comorbidity: 7	**Retention** **Adherence**	*Functional performance*: 6MWT, HGS, 10 repetitions sit to stand *HR-QoL*: EORTC QLQ-C30 and EQ-5D
Morielli et al. (2016) Canada	Prospective cohort *Period:* April 2014 –October 2014	Patients with rectal cancer	n = 18 (male 66.6%) Age: 57.5 ± 10.4 yrs ASA: NR Comorbidities: 1-2 comorbidities: 7	**Eligibility** **Recruitment** **Retention** **Adherence**	***Safety*: adverse events** *Aerobic fitness*: CPET *Functional performance*: Senior's Fitness Test (6MWT, 30-s chair stand, 30-s arm curl, sit-and-reach, back scratch, 8-foot up-and-go) *HR-QoL*: SF-36, FACT-C *Psychological distress*: CES-D, SSAS, PSS, PSQI, RSES

Table 1 (*continued*)

Authors (year) Country	Study design *Period*	Target population	Study sample	Process feasibility outcome measures	Scientific feasibility outcome measures (preliminary effectiveness)
			3+ comorbidities: 4		
Moug et al. (2018) United Kingdom	RCT *Period:* August 2014 –March 2016	Patients with rectal cancer	*Intervention:* n = 24 (male 75%) Age: 65.2 ± 11.4 yrs ASA II: 18, III: 5 Comorbidities: CVD[b]: 9 DM: 2 Pulmonary[c]: 1 CVA: 1 Orthopaedic[d]: 3 *Control:* n = 11 (male 54%) Age: 66.5 ± 9.6 yrs ASA II: 14, III: 10 Comorbidities: CVD[b]: 8 Pulmonary[c]: 1 Orthopaedic[d]: 5	**Eligibility** **Recruitment** **Retention** **Adherence** **Acceptability**	*Functional performance*: median step count/day, 6MWT, 30-s chair stand *Body composition*: weight, BMI, waist circumference *Self-reported activity*: % activity and sedentary/week *HR-QoL*: EORTC QLQ-C 29/30 *Psychological distress*: BDI-II, PANAS, FACT-C
Northgraves et al. (2019) United Kingdom	RCT *Period*: NR	Patients with colorectal cancer	*Intervention:* n = 10 (male 40%) Age: 64.1 [46; 79] yrs ASA; NR Comorbidities: NR *Control:* n = 11 (male 63.6%) Age: 63.5 [37; 83] yrs ASA: NR Comorbidities: NR	Recruitment Adherence	*Safety*: adverse events *Functional performance*: TUG, 5-STS, SCT, HGS, 6MWT ***Postoperative outcome*: complications, LOS** *HR-QoL*: EORTC QLQ-C30 *Psychological distress: HADS*
Singh et al. (2017) Australia	Prospective cohort *Period*: NR	Patients with rectal cancer	n = 10 (male 50%) Age: 54.4 ± 12.9 yrs ASA: NR Comorbidities: No: 0.8 (1.2)	Adherence	*Safety*: adverse events ***Muscle strength*: chest press, leg press, seated row, leg extension, *Muscle endurance*: chest and leg press** *Functional performance*: 6-m usual, fast and backward walk, 400-m walk, CRT, SCT *Self-reported activity*: Godin Leisure-time *Body composition*: LM, FM *HR-QoL:* EORTC-QLQ C30, SF-36 *Fatigue*: MFSI-SF *Postoperative outcome: LOS*
Singh et al. (2018) Australia	Prospective cohort *Period*: NR	Patients with rectal cancer	n = 10 (male 70%) Age: 54.6 ± 14.1 yrs ASA: NR Comorbidities: No: 0.7 (1.1)	**Recruitment** **Retention** **Adherence**	*Safety*: adverse events *Muscle strength*: chest press, leg press, seated row, leg extension *Muscle endurance*: chest and leg press *Functional performance*: 6-m usual, fast and backward walk, 400-m walk, CRT, SCT *Self-reported activity*: Godin Leisure-time *Body composition*: LM, FM *HR-QoL:* EORTC-QLQ C30 *Fatigue*: MFSI-SF
Van Rooijen et al. (2019) The Netherlands	Prospective case-control *Period:* June 2016 –June 2017	Patients with colorectal cancer	*Intervention:* n = 20 (male 50%) Age: 75 [62; 89] yrs ASA: I: 6, II: 8, III: 6 Comorbidities: CCI 3 [2,7] *Control:* n = 30 (male 57%) Age: 71 [46; 84] yrs ASA I: 10, II: 5,	**Retention** **Adherence**	***Safety*: adverse events** *Functional performance*: 6MWT, SCT, sit to stand *Muscle strength*: HGS *Muscle endurance*: leg press, chest press and lateral pull down *Aerobic fitness*: CPET *Physical activity level*: mCHAMPS *Nutritional status*: BMI, food diary, skin fold, anthropometry, PG-SGA *HR-QoL*: EORTC-QoL-C29/30 *Psychological distress*: GAD-7, PHQ-9 *Frailty*: Fried Frailty Index, G8 *Postoperative outcome*: complications, LOS reintervention, readmission, mortality

(*continued on next page*)

Table 1 (*continued*)

Authors (year) Country	Study design *Period*	Target population	Study sample	Process feasibility outcome measures	Scientific feasibility outcome measures (preliminary effectiveness)
			III: 13, IV: 1 Comorbidities: CCI 2 [2,7]		

Abbreviations: AFQ: abbreviated fatigue questionnaire, ASA: American Society of Anesthesiologists, BDI-II: Becks depression inventory, BMI: body mass index, CCI: Charlson comorbidity index, CES-D: 10-item Centre for Epidemiologic Studies depression scale, CPET: cardiopulmonary exercise testing, CRT: chair rise time, CVA: cerebrovascular attack, CVD: cardiovascular disease, DM: diabetes mellitus, EORTC QLQ-C 29/30: European organization for research and treatment of cancer quality of life questionnaire, EQ-5D: EuroQol 5D, ERAS: enhanced recovery after surgery, FACT-C: functional assessment of cancer therapy-colorectal, FM: fat mass, GAD-7: generalized anxiety disorder 7, HADS: hospital anxiety and depression scale, HGS: handgrip strength, HR-QoL: health-related quality of life, LAPAQ: LASA physical activity questionnaire, LM: total body lean mass, LOS: length of stay, mCHAMPS: modified community healthy activities model program for seniors, MFI: multidimensional fatigue index, MFSI-SF: multidimensional fatigue symptom inventory, MIP: maximal inspiratory pressure, MVPA: mean levels of moderate to vigorous physical activity, NACRT: neoadjuvant chemoradiotherapy, NR: not reported, PANAS: positive and negative affect schedule, PG-SGA: patient-generated subjective global assessment, PHQ-9: patient health questionnaire 9, PRP: 17-item postoperative recovery profile, PSQI: Pittsburgh sleep quality index, PSS: 14-item perceived stress scale, PWC170: physical work capacity 170, RCT: randomized controlled trial, RSES: 10-item Rosenberg self-esteem scale, SCT: stair climb test, SF-36: short-form 36 health survey, SPPB: short physical performance battery, SSAS: 10-item Spielberger state anxiety scale, TUG: timed up-and-go test, 4-m GS: 4-m gait speed, 5-STS: five times sit-to-stand test, 6MWT: 6-min walk test.
Values are reported as Mean ± SD, Median [IQR] or absolute number (%) as reported in original publications. Primary outcome measures are highlighted in bold.
[a] (Pre-)frailty was defined according to the current Dutch guidelines stating either a VeiligheidsManagementSysteem (Safety Management System, VMS) score of 1 or higher or an Identification of Seniors at Risk-Hospitalized Patients score of 2 or higher.
[b] "CVD" includes hypertension, myocardial infarction, heart failure and unspecified cardiac disease.
[c] "Pulmonary" included asthma and chronic obstructive pulmonary disease.
[d] "Orthopaedic" includes arthritis and unspecified orthopaedic conditions.

3.1. Assessment of the reporting quality (by checklist items)

The quality of reporting assessment is shown in Fig. 2. There was 88.5% agreement between AC and FL for the initial assessment of the reporting quality, with a Cohen's Kappa of 0.74 indicating substantial agreement (Supplementary Table 3).

3.1.1. Background, objectives, and outcome measures

All studies indicated to be a pilot or feasibility study (item 1), of which eight studies (67%) provided a clear background and rationale for conducting a feasibility assessment (item 2) [29,31,32,34–36,38,39]. Feasibility was a primary aim in 11 studies (92%) [28–35,37–39], of which five studies (42%) [29,32–35] provided feasibility objectives (item 5b), and nine studies (75%) [28–32,34,35,37,39] clarified their feasibility outcome measures (item 6b). To compare, nine studies (75%) [30–38] explained the objectives regarding the potential effectiveness of exercise prehabilitation (item 5a), and 11 studies explained their effectiveness outcome measures (item 6a) [28,30–39], such as the potential effect on preoperative physical fitness (Table 1). Four studies (33%) [28,29,32,34] formulated threshold criteria to conclude feasibility of the prehabilitation intervention (item 8), with adherence rate thresholds ranging from ≥60 to ≥80%. Morielli et al. [34] also described a recruitment rate >20% as feasibility threshold for feasibility of a full-scale trial.

3.1.2. Settings, intervention details and participant flow

Eligibility criteria (item 3a) and intervention details (item 4) were provided in all studies, of which identification, recruitment, and consent procedures of potentially eligible patients (item 3c) were reported completely in four studies (33%) [32–35], and the participant flow (item 11) was reported completely in five studies (42%) [29,32,34–36]. Seven studies (58%) [29–32,34,35] fully explained the setting of recruitment and data collection (item 3b), where 42% [28,30,36–38] provided no recruitment and follow-up periods (item 12).

3.1.3. Analysis and interpretation of study results

Except for two studies (17%) [33,36], all authors concluded participation in the intervention to be feasible. In three of these studies [28,29,38], no clear explanation was given to justify their conclusion (item 15a). Feasibility of participation in the study was addressed by five studies (42%). Two studies (17%) [34,35] concluded that the study was feasible based on sufficiently high eligibility and recruitment rates as considered by the authors (eligibility rates of 71.1% and 26.1%, and recruitment rates of 56.3% and 61.5%, respectively), whereas three studies (25%) [31,32,36] encountered problems with patient recruitment and highlighted the risk of selection bias. An additional five studies (42%) [28,29,33,37,38] mentioned selection bias as a limitation due to the inability to include all eligible patients [29], including only motivated patients [33], or working with volunteers who might not represent all patients scheduled for surgery [37,38]. Six studies (50%) [29,31,32,34–36] discussed generalizability of the feasibility outcomes, of which four studies (33%) [29,31,32,36] explained the lessons learned how to overcome potential bias and maintain clinical generalizability towards future patients (item 16). Compared to feasibility outcomes, which were discussed in depth by 50% of all studies [29,31–35], preliminary effectiveness outcomes were discussed in detail by all authors (item 17), including caveats about possible imprecision in the observed effectiveness due to lack of power (11 studies, 92%) [27,30–39] (item 7).

3.2. Clinical generalizability of prehabilitation feasibility outcomes

The majority of the studies included patients aged ≥18 years diagnosed with non-metastatic CRC and excluded patients with contraindications or comorbidities impeding exercise (Table 3). Retention and adherence rates were primary feasibility outcomes in six [29,33–35,37,39] and 10 studies [28–35,37,39], respectively (Table 1). Overall, retention rates ranged from 18.4% to 90.5%. Patient dropout from the studies was predominantly caused by "side effects of NACRT", "personal issues (e.g., work commitments, a lack of time), participating in the program was "too stressful", "travel distance", and "not feeling well" (Table 3). As visualized in Fig. 3, the number of patients completing each of the included feasibility studies (retained patients) reflected only a small part of the total number of (potentially) eligible patients. Six studies showed all participation details (50.0%). These studies reported retention rates ranging from 18.4% to 58.2% [29,32,34–36,38]. Among the patients participating in the studies, adherence to the intervention ranged from 75.0% to 100% (Table 3). Most of the interventions consisted of supervised moderate-to high-intensity exercise training two or more days a week and were conducted in settings outside the patient's home (Table 2). Reasons for patients being unable or unwilling to adhere to the interventions was mainly "not feeling well",

Table 2
Intervention characteristics.

Authors (year)	Timing	Duration	Setting	Level of supervision	Frequency	Physical exercise training intervention details	Exercise intensity
Alejo et al. (2019)	During NACRT	6 weeks	In-hospital and outdoor (park)	Supervised by fitness or exercise professional	6 sessions: 1 theoretical introduction 4 practical session 1 completing practical session	Aerobic, resistance, and flexibility exercises	*Aerobic exercises*: <95% of maximal heart rate *Resistance exercises*: based on rating of perceived exertion (0-10 Borg scale) 6-10
Bruns et al. (2019)	Before surgery	Maximum 32 days	Home-based	Television-guided	Once daily	7-min resistance workout	No measurements reported
Dronkers et al. (2009)	Before surgery	Maximum 4 weeks	Outpatient clinic physical therapy + home-based	Supervised by physical therapist (in-hospital) + unsupervised (home-based)	2 days/week	*Intervention*: Supervised: 60-min resistance training, inspiratory muscle training, aerobic training, and functional exercise training Unsupervised: prescribed walking or training for a minimum of 30 min/day *Control*: Unsupervised home-based exercise advice to be active for minimally 30 min/day in the period prior to surgery	*Resistance exercises*: at 60–80% of the one-repetition maximum *Inspiratory muscle exercises*: at 10–60% of the maximal inspiratory pressure *Aerobic exercises*: moderate intensity (55–75% of maximal heart rate) or rating of perceived exertion (6-20 Borg scale) 11-13 *Functional exercises*: to the patient's capabilities and interest
Heldens et al. (2016)	During NACRT	Maximum 17 weeks	Outpatient clinic physical therapy	Supervised by physical therapist	2 days/week	45-60-min endurance training and resistance exercises	*Endurance and resistance exercises*: moderate intensity based on rating of perceived exertion (6-20 Borg scale) 13-14
Karlsson et al. (2019)	Before surgery	Minimum of 6 sessions before surgery	Home-based	Supervised by physical therapist	2–3 days/week	*Intervention*: Supervised: 1-h sessions including inspiratory muscle training, high intensity functional strength exercises, and endurance training Unsupervised: recommendation of 150 min/week of moderate-intensity physical activity *Control*: Advice to follow the recommendation of 150 min/week of unsupervised home-based moderate-intensity physical activity	*Inspiratory muscle exercises*: rating of perceived exertion (0-10 Borg scale) 5-7 *Functional strength exercises*: high intensity based on rating of perceived exertion (0-10 Borg scale) 7-8 *Endurance exercises*: high intensity based on rating of perceived exertion (0-10 Borg scale) 7-8
Loughney et al. (2019)	Before surgery with or without NACRT	Maximum 4 weeks	Leisure centre	Supervised by trained personnel	3–5 days/week	Moderate-to-high intensity exercise program including aerobic and resistance exercises, as well as encouragement to be physically active outside of the program	*Aerobic interval exercises*: moderate-to-high intensity based on rating of perceived exertion (B 6-20 Borg scale) 13-15 *Aerobic exercises*: high intensity based on rating of perceived exertion (6-20 Borg scale) 16 *Resistance exercises*: based on individual ability (e.g. at 12-repetition maximum)
Morielli et al. (2016)	During and	12–14 weeks: 6 weeks during NACRT	Fitness centre near the hospital	Supervised (during NACRT) + unsupervised (before surgery)	Supervised: 3 days/week	Supervised: moderate-intensity aerobic exercises	*Aerobic exercises*: 40–60% of estimated peak oxygen uptake

(*continued on next page*)

Table 2 (*continued*)

Authors (year)	Timing	Duration	Setting	Level of supervision	Frequency	Physical exercise training intervention details	Exercise intensity
	after NACRT	+ 6–8 weeks before surgery			+ unsupervised: 150 min/week	Unsupervised: aerobic exercise program	
Moug et al. (2018)	During NACRT	Maximum 17 weeks: 8 weeks of graduated step count goals + maintaining/ increasing step count over the remaining weeks before surgery	Home-based	1 exercise counselling session + telephone-guidance	3–5 days/week	*Intervention:* Walking program based on targeted stepping counts (1500–3000 extra steps/day in approximately 30 min) *Control*: Standard care	No measurements reported
Northgraves et al. (2019)	Before surgery	Maximum 31 days	University Sport Science Laboratory	Supervised by certified instructor	3 days/week	*Intervention:* Individualized 60-min sessions on a one-to-one basis including moderate-intensity aerobic exercises and functional resistance exercises *Control:* Standard care with instructions to maintain their normal exercise levels	*Aerobic exercises*: moderate intensity at 40–60% of heart rate reserve and/or rating of perceived exertion (6-20 Borg scale) 11-13 *Resistance exercises*: based on individual ability
Singh et al. (2017)	Before surgery	Maximum 16 weeks	University exercise clinic + home-based	Supervised (in hospital) + unsupervised (home-based)	2 days/week	60-min aerobic and resistance exercises combined with home-based aerobic exercise at least twice or more per week for 15 min each	*Aerobic exercises*: 60–80% of estimated maximal heart rate *Resistance exercises*: at 6- to 12-repetition maximum
Singh et al. (2018)	During NACRT	10 weeks	University exercise clinic + home-based	Supervised by exercise physiologist (in-hospital) + unsupervised (home-based)	Supervised: 2 days/ week + unsupervised: minimum of 2 days/ week	Supervised: 60-min aerobic and resistance exercises combined Unsupervised: aerobic exercises for 15 min each	*Aerobic exercises*: 60–80% of estimated maximal heart rate *Resistance exercises*: at 6- to 12-repetition maximum
Van Rooijen et al. (2019)	Before surgery	4 weeks	In-hospital	Supervised by sports physician and physical therapist	3 days/week	*Intervention*: High-intensity endurance (interval) training including aerobic endurance exercises and resistance training combined, as well as encouragement to walk *Control*: Usual perioperative care according to ERAS guidelines	*Aerobic endurance exercises*: high intensity based on 85–100% of VO_{2peak} (or rating of perceived exertion (6-20 Borg scale) 15–17) *Resistance* exercises: 65–75% of one-repetition maximum

"side effects of NACRT", "being too busy", having "personal issues (such as work commitments)", "fatigue", and "transportation issues".

Compared to retention and adherence rates, eligibility and recruitment rates were considered primary feasibility outcomes in two [34,35] and four studies [32,34,35,37], respectively (Table 1). Eligibility rates were (partially) calculable in six studies [29,32,34–36,38], and ranged from 11.0% to 89.5% (Table 3; Fig. 3). When calculable, recruitment rates ranged from 19.3% to 100%. The reasons of patients to not participate in the programs were "being too busy", "being overwhelmed by the diagnosis", having "too much going on", and "travel distance" (Table 3).

Adverse events were reported as an outcome measure by all authors [28–39]. Eleven studies (92%) provided a statement concluding their prehabilitation intervention to be safe [28,30–32,34–40]. All studies reported baseline and post-intervention results. Preoperative physical fitness was assessed in various ways, including measures of aerobic fitness, functional performance, muscle strength, and muscle endurance (Table 1). Estimations of the treatment effects within studies and the variance of the treatment effects between studies implicate an effect of exercise prehabilitation towards an improvement of preoperative physical fitness and/or maintaining physical fitness in case of NACRT (Supplementary Table 4).

4. Discussion

This systematic review assessed the reporting quality of feasibility outcomes in feasibility studies addressing exercise prehabilitation in CRC surgery, as well as critically appraised the methodological quality of the feasibility assessments and its potential impact on clinical generalizability. Whereas most authors conclude exercise prehabilitation to be feasible, the results of this study indicate largely inadequate reporting of methodologies and participation rates. These inadequacies included insufficient attention to the feasibility of study participation, and insufficient clarity towards representativeness of the study samples for the intended target populations. There was a lack of lessons learned on how to solve patient-reported issues hampering feasibility to participate and how to improve clinical generalizability of the study results. Furthermore, an imbalance existed between reporting of feasibility and preliminary effectiveness outcomes, with too much focus on preliminary effectiveness. Therefore, current evidence is insufficient to solidly conclude on feasibility of exercise prehabilitation in patients with CRC, as well as to guide clinicians on how to improve clinical feasibility of exercise prehabilitation.

Large-scale trials are often undermined by problems in participation, such as difficulties in recruiting and retaining participants, and delivering the intervention. Feasibility studies aim to detect

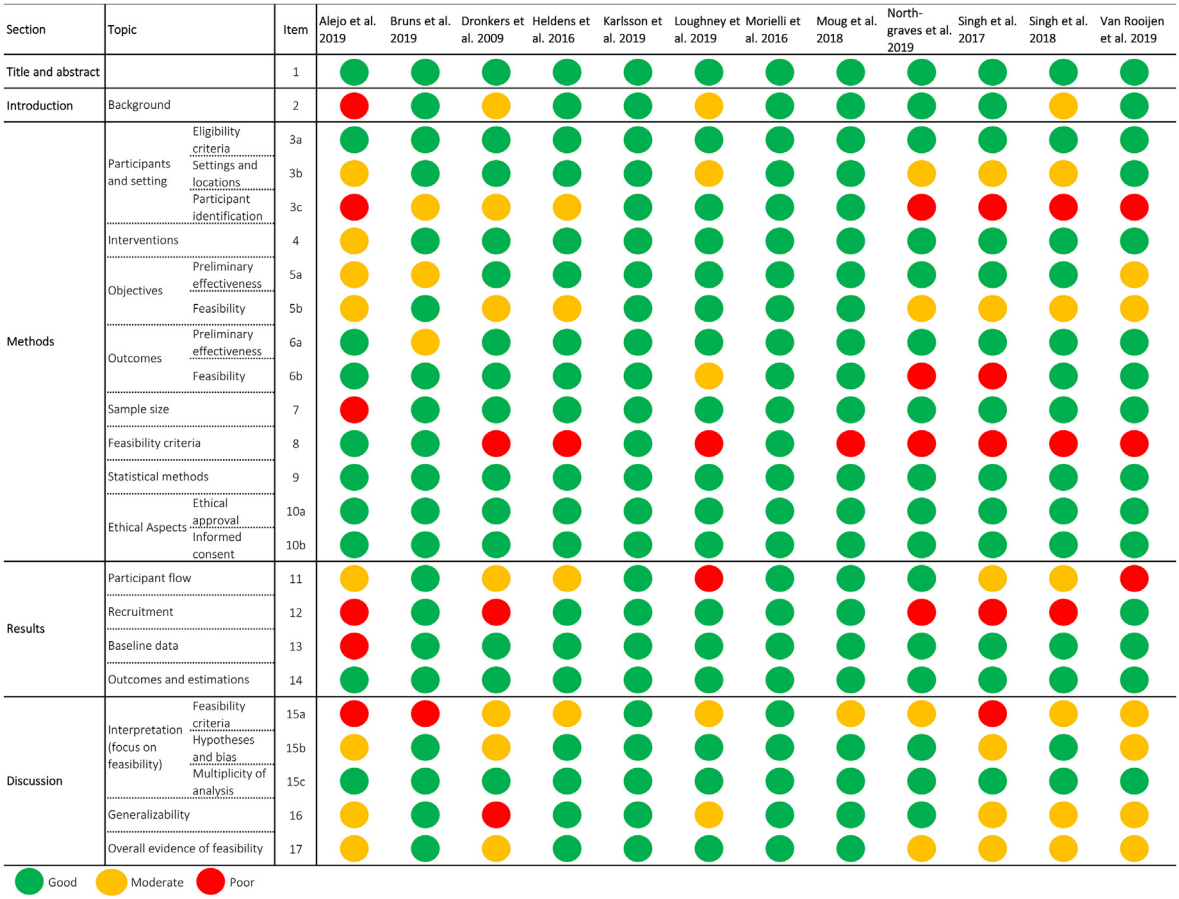

Fig. 2. Assessment of reporting quality according to Eldridge et al. [19] and Thabane et al. [23]. (Colour figure).

and overcome these problems by answering the questions whether the study can be performed, whether the intervention is feasible for the intended target population, and how researchers should proceed towards clinical implementation or towards a methodologically correct and fully powered study that is suitable for all patients of the target population [13,14,19,23]. Using feasibility studies regarding exercise prehabilitation before CRC surgery as an example, high retention and adherence rates indicate that exercise prehabilitation is feasible for the study sample included in the feasibility studies. However, this does not necessarily mean that the intervention is feasible for the entire target population. When evaluating participation rates in the included feasibility studies from start of the study to completion of the intervention, one can conclude that many authors do not report or fall short on addressing (potential) eligibility and recruitment numbers. Studies reporting all participation details demonstrate retention rates up to a maximum of 58.2% (Table 3). Shortcomings in recruitment and retention make studies susceptible for selection bias, because 1) it is unclear which part of the target population participated in the study, 2) the feasibility of the intervention is unknown in the non-recruited patients, and 3) reasons why patients did not participate or did not complete the study are largely unaddressed.

Feasibility studies must focus on obtaining externally valid results by ensuring that study participants accurately reflect the intended target population to whom the intervention will ultimately be offered [18,19,23,41–43]. Not assessing all potentially eligible patients for inclusion, not reporting the size of the intended target population, or using too strict eligibility criteria might exclude selected parts of the target population from participation. High-risk patients are often excluded from exercise intervention studies because of (non-proven) safety reasons or ethical considerations [44]. As shown in the included studies, patients with contraindications or comorbidities impeding exercise were often excluded. In the case of feasibility studies in exercise prehabilitation however, precisely these patients should be considered for inclusion because they might benefit most from prehabilitation, and because safety is a feasibility outcome. As shown in the review of Thomas et al. that includes the majority of the exercise prehabilitation trials, most studies included low-risk surgical patients and showed no significant improvements in clinically relevant postoperative outcome measures (e.g., postoperative complications) [10]. This might be a potential effect of the used eligibility criteria or the intervention not being feasible for the entire target population.

The reported recruitment difficulties, low recruitment rates, and low retention rates up to a maximum of 58.2% further hamper target population representativeness of the study samples. Instead of solving patient-reported reasons for non-participation or drop-out which hamper clinical feasibility, authors often seem to overestimate the possibilities and/or willingness of patients to participate, and draw their conclusions based on only those patients who entered the study and took part in the intervention. Consequently, interpretation of the feasibility outcomes might not be generalizable, also affecting the effectiveness results of future larger follow-up trials [14,15,18–23,45]. Feasibility studies should assess external validity by evaluating whether the intervention is feasible in

Table 3
Process feasibility outcomes.

Authors (year)	Potentially eligible patients	Eligibility criteria	Eligible patients (Eligibility rate)	Recruited patients (Recruitment rate)	Retained patients (Retention rate)	Adherence (Adherence rate)
Alejo et al. (2019)	NR	*Inclusion*: age ≥18 yrs, Eastern Cooperative Oncology Group performance status <3	23 (Rate incalculable)	12 (12/23: 52.2%)	12 (12/12: 100%)[a] (12/23: 52.2%)[b]	64 out of 72 sessions (89%)
		Exclusion: in need of transfusion, psychoactive drug use	*Reasons for exclusion*: NR	*Reasons for refusal:* NR		*Reasons for non-adherence*: Disease progression, side effects NACRT
Bruns et al. (2019)	104[c]	*Inclusion*: age ≥70 yrs, frail (as defined by as Safety Management System score ≥1 or Identification of Seniors at Risk Hospitalized Patients score ≥2)	24 (24/104: 23.1%)	14 (14/24: 58.2%)	14 (14/14: 100%)[a] (14/24: 58.2%)[b]	Mean 6 out of 7 exercises per week (86%)
		Exclusion: severe cognitive (e.g., dementia) or physical (e.g., bedridden) inability to join the program, being scheduled for surgery within 2 weeks of program start	*Reasons for exclusion:* Patients not considered frail	*Reasons for refusal:* Preference for surgery as soon as possible, surgery <14 days, personal reasons		*Reasons for non-adherence:* Too tired, busy with other things, forgotten
Dronkers et al. (2009)	NR[d]	*Inclusion*: age ≥60 yrs, elective colon surgery in >2 weeks, adequate cognitive functioning	42 (Rate incalculable)	42 Intervention: 22 Control: 20 (42/42: 100%)	38 Intervention: 19 Control: 19 (38/42: 90.5%)[a,b]	Attendance at training sessions: 97% in the intervention group (mean number of sessions 5.1 (SD 1.9)
		Exclusion: heart disease that prohibits or impedes exercise, severe systemic illness, recent embolism, thrombophlebitis, uncontrolled diabetes, severe orthopaedic conditions that prohibit or impede exercise, wheelchair dependence	*Reasons for exclusion:* NR		*Reasons for drop-out:* Death of a spouse, unable to combine with daily work, personal reasons	*Reasons for non-adherence*: NR
Heldens et al. (2016)	NR [e]	*Inclusion*: age >18 yrs, diagnosed with locally advanced resectable rectal cancer, undergoing NACRT	20 (Rate incalculable)	15 (15/20: 75%)	9 (9/15: 60%)[a] (9/20: 45%)[b]	198 out of 207 sessions (95.7%)
		Exclusion: contraindications for exercise in medical status, not able to cooperate with training and/or testing procedures	*Reasons for exclusion:* NR	*Reasons for refusal:* Too busy, no need for participation, disease impact	*Reasons for drop-out:* Side effects NACRT, knee problems, increase in fatigue, cardiovascular comorbidity, disease impact	*Reasons for non-adherence:* Feeling too ill, other medical intervention, too busy
Karlsson et al. (2019)	602	*Inclusion*: age ≥70 yrs, able to understand and speak Swedish, scheduled for surgery due to colorectal cancer	66 (66/602: 11.0%)	23 Intervention: 11 Control: 12 (23/66: 34.8%)	21 Intervention: 10 Control 11 (21/23: 91.3%)[a] (21/66: 31.8%)[b]	58 out of 60 sessions (97%)
		Exclusion: health status that prohibits physical exercise (e.g., unstable heart disease, severe systemic illness, severe orthopaedic conditions), if prolonging surgery with ≥2 weeks was a medical risk of if participants lived outside the catchment area of the primary care units	*Reasons for exclusion:* Living out of catchment area, <70 years of age, non-surgical treatment, surgery at other hospital acute surgery, or already undergone surgery, no colorectal cancer, medical reasons (deemed by surgeon), physical functioning prohibiting exercise, severe cognitive impairment, or unable to speak Swedish	*Reasons for refusal:* Not willing to delay surgery, too much going on/feeling stressed, additional hospital visit for baseline assessment, already exercising (self-reported), no reasons given, could not be reached for inclusion	*Reasons for drop-out:* Medical reason, declined due to long travel	*Reasons for non-adherence*: Physical therapist unable to conduct a session, medical reason
Loughney et al. (2019)	NR	*Inclusion*: age ≥18 yrs, diagnosis of prostate cancer or CRC being scheduled for surgery (with or without NACRT)	NR (Rate incalculable)	17 (Rate incalculable)	10 (10/17: 58.8%)[a] (Rate incalculable)[b]	Adherence exercise program: 81% (SD 21) Median (IQR) number of exercise sessions attended: 6 (4–11)
		Exclusion: contraindications to exercise including uncontrolled	*Reasons for exclusion:* NR	*Reasons for refusal:* NR	*Reasons for drop-out*: Due to date of surgery, work commitments,	*Reasons for non-adherence*: NR

Table 3 (*continued*)

Authors (year)	Potentially eligible patients	Eligibility criteria	Eligible patients (Eligibility rate)	Recruited patients (Recruitment rate)	Retained patients (Retention rate)	Adherence (Adherence rate)
		cardiovascular conditions, significant skeletal muscle/orthopaedic/neurological conditions, cognitive decline, significant mental illness or intellectual disability that prevented participations in a physical training program, as per physician discretion			holidays, medical issue, disease progression	
Morielli et al. (2016)	45	*Inclusion*: aged 18–80 yrs, scheduled to receive long-course NACRT followed by definitive surgery, no uncontrolled medical or psychiatric conditions, cleared to participate in exercise as determined by PAR-Q+ and able to understand English	32 (32/45: 71.1%)	18 (18/32: 56.3%)	14 (14/18: 77.8%)[a] (14/32: 43.8%)[b]	Mean 13.3 out of 18 supervised sessions 10 out of 14 patients reached unsupervised training goal of 150/min or more per week
		Exclusion: NR	*Reasons for exclusion:* Medical contraindications, treatment decision too late, >80 years of age, did not understand English, palliative care without surgery	*Reasons for refusal*: Afraid participation will be too much/fatigue, overwhelmed, working, living out of town, not interested	*Reasons for drop-out:* Heart attack, emergency surgery, too stressful, not feeling well	*Reasons for non-adherence:* Side effects NACRT (hand-foot syndrome, not feeling well, poor sleep, diarrhoea, nausea, enteritis), fatigue, too difficult to keep up adherence next to medical appointments
Moug et al. (2018)	296	*Inclusion*: age ≥18 yrs, newly diagnosed rectal cancer between August 2014 and March 2015, no metastatic disease, recommended for NACRT by the multidisciplinary team	78 (78/296: 26.4%)	48 Intervention: 24 Control: 24 (48/78: 61.5%)	40 Intervention: 18 Control: 22 (40/48: 83.3%)[a] (40/78: 51.3%)[b]	93 out of 116 phone call assessments (80%)
		Exclusion: metastatic disease, mobility preventing them from performing a walking intervention, already achieving the recommended government guidelines for physical activity per week, any physical, mental of psychological impairment that prevented signing informed consent	*Reasons for exclusion:* Not put forward for NACRT	*Reasons for refusal*: Too busy/too much going on, overwhelmed by diagnosis, DNA test, too unwell, interfere with job, family/friends advised against, unknown reasons	*Reasons for drop-out*: Emigrated prior to NACRT, withdrew consent for unknown reason, medical complications secondary to NACRT, fatigue/tiredness during NACRT, emergency surgery, DNA test	*Reasons for non-adherence:* NR
Northgraves et al. (2019)	198	Inclusion: age ≥18 yrs, scheduled for elective surgery *(after 9 months of recruitment, also patients with benign disease were included due to poor recruitment)*	114 (114/198: 57.6%)	22 (22/114: 19.3%)	21 Intervention: 11 Control: 11 (21/22: 95.5%)[a] (21/114: 18.4%)[b]	Individual adherence range: 75–100%, with 5 patients attending all sessions.
		Exclusion: cardiac or uncontrolled metabolic or respiratory conditions precluding exercise, hypertension (SBP >180 mm Hg and/or DBP >110 mm Hg), any pre-existing severe physical disability preventing participations in all components of the prehabilitation program (inability to perform specific exercises wat no reason for exclusion)	*Reasons for exclusion:* Less than 2 weeks prior to surgery (insufficient time)	*Reasons for refusal*: Unwilling to travel, inadequate time, other commitments, already physically active	*Reasons for drop-out*: Adverse event not caused by intervention, unknown reasons	*Reasons for non-adherence*: Holiday, family events, work commitments, transport issues

(*continued on next page*)

Table 3 (*continued*)

Authors (year)	Potentially eligible patients	Eligibility criteria	Eligible patients (Eligibility rate)	Recruited patients (Recruitment rate)	Retained patients (Retention rate)	Adherence (Adherence rate)
Singh et al. (2017)	19[f]	*Inclusion*: scheduled surgery for localized rectal cancer, absence of any musculoskeletal, cardiovascular, or neurologic disorder that could inhibit the ability to walk 400 m unassisted and undertake upper- and lower-body exercise and having obtained medical clearance from their general practitioner	17 (17/19: 89.5%)	12 (12/17: 70.6%)	10 (10/12: 83.3%)[a] (10/17: 58.8%)[b]	8 out of 10 patients (80%) completed at least 60% of the sessions.
		Exclusion: NR	*Reasons for exclusion:* NR	*Reasons for refusal*: NR	*Reasons for drop-out*: Recovered from cancer, feeling unwell, pain	*Reasons for non-adherence*: Feeling unwell
Singh et al. (2018)	NR	*Inclusion*: scheduled for surgery for localized rectal cancer, absence of any acute illness or any musculoskeletal, cardiovascular, or neurological disorder that could inhibit the ability to walk 400 m unassisted and undertake upper and lower body exercise, and obtained medical clearance from their general practitioner	15 (Rate incalculable)	10 (10/15: 66.7%)	10 (10/10: 100%)[a] (10/15: 66.7%)[b]	Overall attendance: 77% 5 patients completed 17 sessions or more out of the possible 20 (85%)
		Exclusion: NR	*Reasons for exclusion:* NR	*Reasons for refusal:* Travel distance, no transport to testing site, wanting to focus on medical treatment only	*Reasons for drop-out*: Feeling unwell	*Reasons for non-adherence*: Feeling unwell
Van Rooijen et al. (2019)	NR	Inclusion: age ≥18 yrs, scheduled for elective resection for CRC without NACRT	NR (Rate incalculable)	50 Intervention: 20 Control: 30 (Rate incalculable)	47 Intervention: 17 Control: 30 (47/50: 94.0%)[a] (Rate incalculable)[b]	"All patients who enrolled attended at least 9 of 12 training sessions (88%)"
		Exclusion: ASA score 4–5, metastatic disease, conditions interfering with the ability to perform the exercises such as paraplegia or orthopaedic impairments and patients unable to provide informed consent	*Reasons for exclusion:* NR	*Reasons for refusal:* NR	*Reasons for drop-out*: No time, surgery rescheduled	*Reasons for non-adherence*: NR

Abbreviations: ASA: American Society of Anesthesiologists, CRC; colorectal cancer, DBP: diastolic blood pressure, NACRT: neoadjuvant chemoradiotherapy, NR: not reported, PAR-Q: physical activity readiness questionnaire, SBP: systolic blood pressure, SD: standard deviation.

[a] Retention rate calculated as the percentage of recruited (included) patients who completed the study.

[b] Retention rate calculated as the percentage of eligible patients who completed the study.

[c] *"104 patients ≥70 years with colorectal cancer scheduled for surgery"*.

[d] *"All patients referred for preoperative physical therapy by the gastroenterologist or the surgeon went to the outpatient department of physical therapy, as part of the multidisciplinary preoperative work-up"*.

[e] *"The medical oncologist and colorectal nurse referred patients receiving NACRT to the physical therapy department for participation in a physical exercise training program"*.

[f] *"19 patients with localized rectal cancer scheduled for rectal resection were referred by their attending specialist to the chief investigator for potential inclusion in the study"*.

varying conditions that could occur in large-scale trials or clinical practice. Therefore, assuring clinical generalizability should actually be the primary aim, as well as ensuring that all patients who are likely to benefit from prehabilitation are willing and able to participate. When focussing on the feasibility of exercise prehabilitation in particular, more attention should be given to patient-centred aspects related to clinical feasibility of exercise prehabilitation. Clinical feasibility might be improved by offering supervised home- and/or community-based exercise prehabilitation interventions that are tailored to the physical and mental abilities, as well as preferences of the individual when awaiting surgery or during the course of NACRT. It is also important to realise that working with patients who undergo NACRT is different compared to delivering exercise prehabilitation to patients who go straight to surgery. Where fatigue, several physical complaints, and the burden of multiple hospital visits might hamper clinical feasibility in patients undergoing NACRT, time constraints due to the short period between diagnosis and surgery, work commitments, and prehabilitation being mentally "too much", might hamper feasibility in patients going straight to surgery. Exercise prehabilitation interventions should not be predetermined, but need to be adaptable to each individual patient. In such design, also high-risk patients become eligible for participation. Participation might be further improved by increasing the patient's understanding of the importance of exercise prehabilitation and why it might be beneficial for them [11,46].

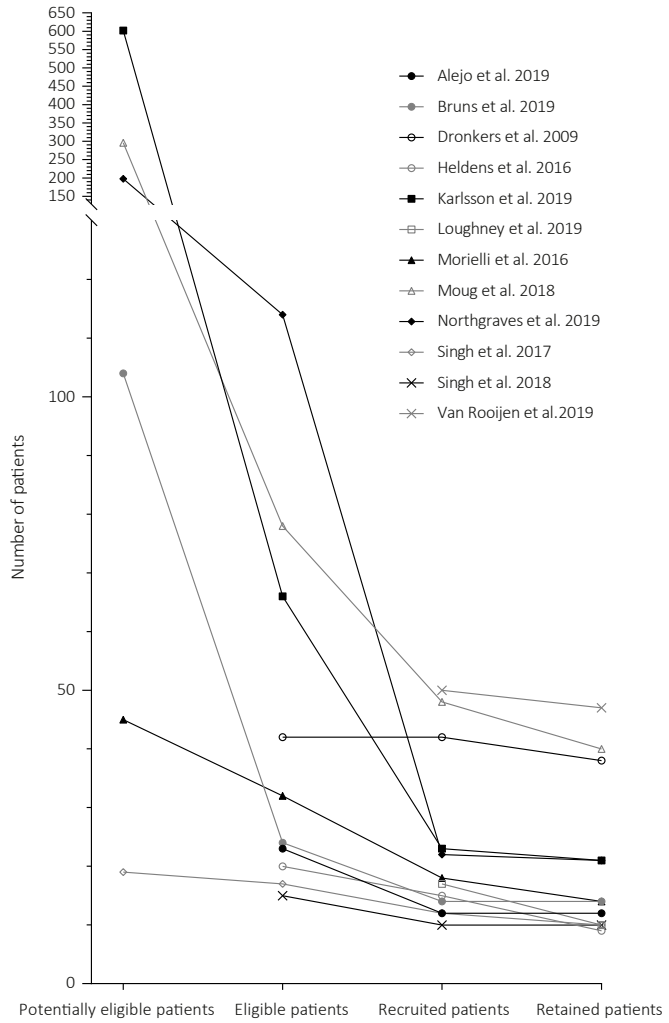

Fig. 3. The number of potentially eligible patients up until the number of retained patients completing each of the included feasibility studies (participation flow).

Instead of focussing on clinical generalizability, most studies mainly emphasised the potential effectiveness of the exercise prehabilitation itself, despite feasibility being the primary aim in 92% of the articles. Even when recruitment problems such as "the intervention being too much", "long travel distance", "side effects of NACRT", and "fatigue" were encountered and reported, most of these studies still concluded exercise prehabilitation to be feasible and did not describe how these patient-related problems could be overcome. These results are in line with previous literature and show that the reporting of feasibility studies requires improvement by focussing primarily on feasibility, addressing and trying to solve patients-reported problems which hamper clinical feasibility, and avoiding formal effectiveness testing without adequate sample size calculations [15,24,26]. Hypotheses regarding the potential effectiveness of exercise prehabilitation should be of secondary importance [18,19,23,47] in feasibility studies. In addition, feasibility studies often insufficiently discuss the intention to proceed to a large scale trial [24]. This was also observed in the current review, in which only 42% of the included studies mentioned plans for a follow-up study [32,34–36,39], and only three registered follow up trials could be identified (Supplementary Table 5) [34,35,39]. Authors should be more explicit about their purpose and the criteria used to decide if and how to proceed with a large-scale trial or clinical implementation [24].

This systematic review has several limitations. The presented evidence was based on a single patient population, namely patients undergoing CRC surgery. However, it is expected that the suggestion that the reporting quality and clinical generalizability of feasibility studies needs improvement is generalizable towards exercise prehabilitation in surgical patients with other abdominal cancer types. Furthermore, other components of prehabilitation, such as nutritional and psychological interventions, were not addressed. Physical exercise interventions are the cornerstone of most prehabilitation programs and are believed to be the most demanding for patients, because they often have to be performed in a short period of time, all while coming to terms with their cancer diagnosis, or during intensive neoadjuvant treatment. As such, performing a proper feasibility assessment for these exercise interventions is believed to be most vital. Therefore, this study merely focussed on exercise prehabilitation. Another limitation is the fact that articles that used the term "pilot" or "feasibility" study to justify a small sample size and that only assessed effectiveness without showing any evidence of assessing feasibility were excluded. Not including these articles may have led to an overestimation of the reporting quality.

To conclude, exercise prehabilitation programs are complex interventions, in which all patients who would likely benefit from the intervention should be eligible to participate, and both willing and able to complete the program. True feasibility and thereby effectiveness and clinical usefulness of, in this case, exercise prehabilitation remains questionable when aspects as reporting quality, representativeness of the study sample for the entire target population, attention for patient-reported reasons for non-participation, drop-out and non-adherence, and the ability to assess the generalizability of the results will not be profoundly improved. Future feasibility studies should focus on patient-reported participation difficulties to guarantee external validity of the feasibility outcomes and the future effectiveness results. In case of exercise prehabilitation, feasibility might be improved by offering supervised community- or home-based interventions tailored to the physical and mental abilities of the patient.

Data sharing and data accessibility

Data and analysis methods of this study are available on reasonable request.

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CRediT authorship contribution statement

Anne C.M. Cuijpers: contributed to the conceptualization and design of the study. contributed to the acquisition of the data, contributed to the analysis and interpretation of the data. wrote the draft of the manuscript, which was critically revised for important intellectual content by BB, LS, TL and NvM, All authors read and approved the final version of the manuscript. **Fieke G. Linskens:** contributed to the conceptualization and design of the study, contributed to the acquisition of the data. contributed to the analysis and interpretation of the data, wrote the draft of the manuscript, which was critically revised for important intellectual content by BB, LS, TL, and NvM, All authors read and approved the final version of the manuscript. **Bart C. Bongers:** contributed to the conceptualization and design of the study. contributed to the acquisition of the data, contributed to the analysis and

interpretation of the data, All authors read and approved the final version of the manuscript. **Laurents P.S. Stassen:** contributed to the conceptualization and design of the study, contributed to the analysis and interpretation of the data, All authors read and approved the final version of the manuscript. **Tim Lubbers:** contributed to the conceptualization and design of the study, contributed to the analysis and interpretation of the data, All authors read and approved the final version of the manuscript. **Nico L.U. van Meeteren:** contributed to the conceptualization and design of the study, contributed to the analysis and interpretation of the data. All authors read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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