PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Feasibility of a prehabilitation programme dedicated to older cancer patients before complex medical-surgical procedures: the PROADAPT pilot study protocol
AUTHORS	Roche, Mélanie; Ravot, Christine; Malapert, Amélie; Paget-Bailly, Sophie; Garandeau, Charlène; Pitiot, Virginie; Tomatis, Mélanie; Riche, Benjamin; Galamand, Béatrice; Granger, Marion; Barbavara, Claire; Bourgeois, Chrystelle; Genest, Evelyne; Stefani, Laetitia; Haïne, Max; Castel-Kremer, Elisabeth; Morel-Soldner, Isabelle; Collange, Vincent; Le Saux, Olivia; Dayde, David; Falandry, Claire

VERSION 1 – REVIEW

REVIEWER	Maas H. MD PhD Elisabeth-Tweesteden hospital Tilburg
REVIEW RETURNED	14-Aug-2020

GENERAL COMMENTS	-line 338 patient's satisfaction with the program is evaluated. In the present draft this issue is not explicitly described. - Why monitoring satisfaction only at the end: you will probably lack valuable information once you will not question patients who want to discontinue their participation earlier on. - as the study include elderly (70 yr and older) or multimorbid patients over 60 yrs the number of questionnaires, tests and assessments is rather extensive. Especially in the oldest old this may lead to selection bias to participate in the study. Please compare the average + SD age of the study participants compared to relevant patient groups in the same centres. Thus, generalizability of data on feasibility will be put into (clinical) perspective

REVIEWER	Cynthia Olotu, MD University Medical Centre Hamburg Department of Anaesthesiology Geriatric Anaesthesiology Research Group Martinistrasse 52 22051 Hamburg Germany
REVIEW RETURNED	03-Oct-2020

GENERAL COMMENTS	The authors describe an ambitious, well designed project to improve elder patients care. The chosen study design, a multidimensional and complex intervention is appropriate to archive this goal in a pragmatic approach. It can be trusted that many patients will profit from such a prehabilitation program. Despite this project deserves enthusiasm, some aspects still need to be adressed in the manuscript. 72: it can not be concluded that "71 percent" of all surgeons support

	prehabilitation in general just because this was the number detected in one study. This should be more generalized, eg "it can be estimated that a majority of surgeons.." Introduction: terms like "iatrogenic event" or "iatrogenic prevention" are not revealing, it should be described what exactly is meant instead 110: what is meant by "appreciate longitudinal evolution" - this is not clear in this context and should be rewritten 113: NCI-CTC version 4: a reference should be added 129: check wording/language: "the human person" 138: CSS / ADL score: a reference should be added 169: what is meant by "artificial nutrition"? Probably oral nutrition supplements? Please explain or re-write. 189: Please describe in detail how "psycho cognitive context" shall be assessed. 199: please refer the described recommendations 203: as the physical training is a key element of the prehabilitation process it should be described in more detail: how is it to be performed? Always by a physiotherapist? In an offpatient setting, at a gym, or via home visitis? Can the training be individualized to the patients need? How is this done, especially as the patient is not seen by a physiotherapist at inclusion but only by a nurse?sihT applies to assessment of nutrition: Concerning nutrition: how is the nutritional state of the patient assessed? Which instrument is used? 249: and 302: please specify "WHO score" (there are many scores developed by the WHO) and refer accordingly 257: reference error needs to be corrected 338: reference error needs to be corrected 342: how shall "kinetics" be assessed / recorded? Please specify. Discussion: it should be discussed why the bar defining feasibility was set so low (one intervention for at least 50% of all patients). It should be further mentioned how the nurse coaching the patients was trained and how much training efforts (nurses, physicians, ward teams) were needed for the intervention to work, respectively. Concerning dissemination, it should be discussed how the intervention could work in other hospital settings and how the authors would estimate the potential for that. Does the intervention requires a special "nurse coach" in all cases or can this function be taken by the regular team if trained accordingly? As the study started in 2018, it can be assumed that the Covid-19 situation had grave impact on the ongoing trial. How was the protocol adapted? Which implications occured? And how can such an intervention be realized in the future concerning the new

	pandemic situation and its rules, especially in the health care sector, when dealing with patients very much belonging to the "risk population"? This important aspects should be precisely described and discussed by the authors. Literature: the literature needs to be extended and updated urgently, especially in the field of prehabilitation - there have been quite some new data reported in recent years. Table 1: fluid intake 2 hours before induction of anaesthesia: why is this considered a "shortened" fluid fasting while it is in fact current guideline recommendation and state of the art? Please explain. Table 2: references need to be assigned to all instruments / scores that have not been invented by the authors. What is meant by "Pain scale"? NRS? And "nutrition scale"? Are these validated instruments? Please specify. Figure 1: should be either simplified or removed, as there is no additional value compared to the information given in the text. The term "kinesitherapy" is not used in the body of the manuscript elsewhere, this should be unified. The different colours indicating the training program seemed to be mixed up (green = gray?) Supp 1 seems to be a duplicate.

REVIEWER	Virginia Sun City of Hope, Duarte, CA, United States of America
REVIEW RETURNED	06-Oct-2020

GENERAL COMMENTS	Thank you for the opportunity to review this study protocol on the PROADAPT intervention to improve the outcomes for older adults with cancer undergoing complex surgical procedures for treatment. Overall the protocol paper is very comprehensive. I have the following suggestions for the authors to consider in their revisions: 1. Inclusion criteria (pg. 9): what types of complex medico-surgical procedures for curative intent are included? All procedures for solid tumors? Are the procedures both minimally invasive (laparoscopic, robotic) and open? 2. The intervention includes self-management coaching for both patients and caregivers. Will caregiver outcomes be assessed? If not this is fine, but might be worthwhile to include in the next study. 3. 7 day pre-op immune-nutrition: what types? oral drinks with special formulations (i.e. higher protein, etc)? 4. Rehabilitation was described to be at the discretion of the rehab team. The personalized approach is based on geriatric assessment and other factors?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Maas H. MD PhD
Institution and Country: Elisabeth-Tweesteden hospital Tilburg, Netherlands Please state any competing interests or state ‘None declared’: none

-line 338 patient's satisfaction with the program is evaluated. In the present draft this issue is not explicitly described.
The sentence was modified as follow :
“- To estimate patients’ satisfaction with the overall program at the end of the study (end of follow-up or study discontinuation) using a questionnaire (supplemental table 1).” L. 365-366
The patient satisfactory questionnaire was added as an appendix.

- Why monitoring satisfaction only at the end: you will probably lack valuable information once you will not question patients who want to discontinue their participation earlier on.
Thank you for this remark. The sentence has been modified and the questionnaire will be completed at end of the study for each patient (end of follow-up or study discontinuation). The sentence was modified (see previous answer).

- as the study include elderly (70 yr and older) or multimorbid patients over 60 yrs the number of questionnaires, tests and assessments is rather extensive. Especially in the oldest old this may lead to selection bias to participate in the study. Please compare the average + SD age of the study participants compared to relevant patient groups in the same centres. Thus, generalizability of data on feasibility will be put into (clinical) perspective
To our experience, the patients oriented towards PROADAPT-pilot study are identified and suggested to attend geriatric assessment by their cancer specialist (in particular cancer surgeons). This is particularly true for older patients thought to be at high risk of post-operative deconditioning or for whom the decision for surgery depends on the geriatric assessment. For that reason, the population expected to be enrolled in the study is far older and more comorbid than the general population treated by the same cancer specialists. However, a screening of older patients will be systematically performed and described in the final analysis of the study.
The following sentence was added in the manuscript “, a screening of older patients will be systematically performed during multidisciplinary meetings and described in the CONSORT diagram of the study” l.159-160

Reviewer: 2
Reviewer Name: Cynthia Olotu, MD
Institution and Country: University Medical Centre Hamburg, Department of Anaesthesiology Geriatric Anaesthesiology Research Group, Hamburg, Germany Please state any competing interests or state ‘None declared’: none declared

The authors describe an ambitious, well designed project to improve elder patients care. The chosen study design, a multidimensional and complex intervention is appropriate to archive this goal in a pragmatic approach. It can be trusted that many patients will profit from such a prehabilitation program.
Despite this project deserves enthusiasm, some aspects still need to be adressed in the manuscript.
72: it can not be concluded that "71 percent" of all surgeons support prehabilitation in general just because this was the number detected in one study. This should be more generalized, eg "it can be estimated that a majority of surgeons.."
The sentence was modified as indicated.

Introduction: terms like "iatrogenic event" or "iatrogenic prevention" are not revealing, it should be described what exactly is meant instead
“The deconditioning of older patients, not anticipated, can thus lead to prolonged and iatrogenic hospitalizations such as immobilization syndrom, acute confusion, undernutrition, falls, de novo urinary incontinence and adverse drug events, generating frustration, appeals by patients and their families and additional hospital costs.” l. 78-81

110: what is meant by "appreciate longitudinal evolution" - this is not clear in this context and should be rewritten
We will appreciate the concept of resilience. For this, we will analyze the functional recovery time of patients after surgery. By analyzing the RAPA, QoL etc. criteria at 3, 6 and 12 months of the patients we will have a kinetics of their recovery. I give you a reference explaining this concept.

113: NCI-CTC version 4: a reference should be added
The reference below was added at the end of the manuscript
(http://www.cepd.fr/CUSTOM/CEPD_toxicite.pdf)

129: check wording/language: "the human person"
I would like to let the Human Person, this is how Jardé's law was defined.

138: CSS / ADL score: a reference should be added
The following references were added in the corresponding
CIRS-G Linn BS, Linn MW, Gurel L. Cumulative Illness Rating Scale. J Am Geriatr Soc 1968; 16:622-6.
ADL Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of the illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963; 21: 914-9

169: what is meant by "artificial nutrition"? Probably oral nutrition supplements? Please explain or re-write.
The following sentence was completed and the reference below was added:
« artificial nutrition (ie enteral or parenteral nutrition) » l. 184
Arends 2016 ESPEN guidelines on nutrition in cancer patients:
“Artificial nutrition is the non-volitional application of nutrients via enteral tubes (enteral nutrition) or parenteral infusions (parenteral nutrition).”

189: Please describe in detail how "psycho cognitive context" shall be assessed.
The corresponding questionnaires were added in the following sentence.
“- Evaluation of psycho-cognitive context using questionnaires (GDS4/GDS15, MNA, MINI-COG)” l. 208-209

199: please refer the described recommendations
These following references were added in the manuscript.
ARENDS 2006 - ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology
WEIMANN 2006 - ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation
et ARENDS 2016 - ESPEN guidelines on nutrition in cancer patients

203: as the physical training is a key element of the prehabilitation process it should be described in more detail: how is it to be performed? Always by a physiotherapist? In an offpatient setting, at a gym, or via home visitis? Can the training be individualized to the patients need? How is this done, especially as the patient is not seen by a physiotherapist at inclusion but only by a nurse?sihT applies to assessment of nutrition:
The breathing exercises are presented by the coaching nurse and an appointment with a physiotherapist is prescribed who will explain the exercises presented in PROADAPT bookmet if the practitioner is available.

Concerning nutrition: how is the nutritional state of the patient assessed? Which instrument is used?
As mentioned, the coaching nurse asked for the patient weight and nutritional intake during phone calls.

The following sentence was added:
“If the coaching nurse identifies an unfavorable nutritional trend, she reports it to the referring physician and nutritionist.” L. 222-223

249: and 302: please specify "WHO score" (there are many scores developed by the WHO) and refer accordingly
The WHO score was modified by “ECOG scale” in the 2 locations and the corresponding reference (below) was added.
Oken MM, Creech RH, Tormey DC, Horton J, Carbone PP et al., « Toxicity and response criteria of the Eastern Cooperative Oncology Group », Am J Clin Oncol, vol. 5, no 6, 1982, p. 649-55. (PMID 7165009, DOI 10.1097/00000421-198212000-00014)

257: reference error needs to be corrected
The name and the corresponding references for each questionnaire were added in the text as follow:
A standardized geriatric assessment using validated questionnaires with a particular attention on physical activity and nutrition (ADL(15)/iADL(24), G8 (25), RAPA (26), AIPVQ (27), QLQ-C30 (28), QLQ-ED14 (29), EQ-5D-3L (30), SF-36 (31), SPPB (32), FSS (33), MNA (34), GDS4/GDS15 (35), MINI-COG (36), Tinetti test (37), Borg scale (38), Pain scale (39), Nutrition scale (40)) (tables 2 and 3) .

338: reference error needs to be corrected
The patients’ satisfaction questionnaire was implemented in the supplementary files.

342: how shall "kinetics" be assessed / recorded? Please specify.
Actually, we know that the “kinetics” of physical activity will be difficult to exploit because it is subjective. The pre-operative visit, which normally evaluates the "objective" improvement in performance, is not always achieved/achievable. The use of tablet will palliate a little bit this difficulty.

Discussion: it should be discussed why the bar defining feasibility was set so low (one intervention for at least 50% of all patients). It should be further mentioned how the nurse coaching the patients was trained and how much training efforts (nurses, physicians, ward teams) were needed for the intervention to work, respectively.
Boereboom et al. mentioned that studies dedicated to the elderly have an adherence that varies from 16% to 95% and we have set an intermediate target. The following sentence below was added:
“It has been shown that compliance in studies dedicated to the elderly varies between 16 and 95%, so an intermediate value of 50% has been chosen.(44,45) Indeed, this feasibility study is very ambitious, tailored for the elderly but with a high risk of low adherence due to its complexity.” L. 396-399
The nurses have been trained internally and only 2 or 3 people are responsible for coaching all patients. The following sentence was added:
“In practice, only 2 or 3 people from the coordination team are in charge of coaching for all patients. In the future, a “special nurse coach will be trained in each center and responsible of patients’ coaching.” L. 194-196

Concerning dissemination, it should be discussed how the intervention could work in other hospital settings and how the authors would estimate the potential for that. Does the intervention requires a special "nurse coach" in all cases or can this function be taken by the regular team if trained accordingly?
We have identified the risk of bias related to the training of such nurses, explaining the centralized coaching in the first instance (see previous answer). The use of ID-PROADAPT will also reduce this bias.

As the study started in 2018, it can be assumed that the Covid-19 situation had grave impact on the ongoing trial. How was the protocol adapted? Which implications occured? And how can such an intervention be realized in the future concerning the new pandemic situation and its rules, especially in the health care sector, when dealing with patients very much belonging to the "risk population"? This important aspects should be precisely described and discussed by the authors.
PROADAPT program has been developed as an outpatient-based program, hospital admission in rehabilitation unit before surgery being proposed only in patient with a high level of sarcopenia. Phone coaching and physiotherapists interventions at home, applying the PROADAPT program using PROADAPT booklet complete the device. In that context, PRODAPT pilot study could be pursued as long as surgical procedures were maintained. Since France has stopped programmed major surgical surgeries for a while (6 weeks), some new PROADAPT-patients are included in the prehabilitation program without any definitive operative date, and chemotherapy courses may be prolonged as far as planned surgery is forbidden.

Literature: the literature needs to be extended and updated urgently, especially in the field of prehabilitation - there have been quite some new data reported in recent years.
Some literature was added as references into the text (l. 85)

Table 1: fluid intake 2 hours before induction of anaesthesia: why is this considered a "shortened" fluid fasting while it is in fact current guideline recommendation and state of the art? Please explain.
The recommendations written by ESPEN Weimann et al 2006 : « 1. Is preoperative fasting necessary? could explain this sentence and was added.
Preoperative fasting from midnight is unnecessary in most patients. Patients undergoing surgery, who are considered to have no specific risk of aspiration, may drink clear fluids until 2 h before anaesthesia. Solids are allowed until 6 h before anaesthesia (A) – Level A recommendation

Table 2: references need to be assigned to all instruments / scores that have not been invented by the authors. What is meant by "Pain scale"? NRS? And "nutrition scale"? Are these validated instruments? Please specify.
The following references were added for each questionnaire.
ADL Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of the illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963; 21: 914-9
iADL Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9:179-86)
G8 CA Bellera, M Rainfray, S Mathoulin-Pélissier. Screening older cancer patients: First evaluation of the G-8 geriatric screening tool. Ann Oncol. 2012; 23: 2166– 2172.
RAPA Topolski TD, LoGerfo J, Patrick DL, Williams B, Walwick J, Patrick MB. The Rapid Assessment of Physical Activity (RAPA) among older adults. Prev Chronic Dis. 2006;3(4):A118
AIPVQ Gill TM, Baker DI, Gottschalk M, et al., 2004, A Prehabilitation Program for the Prevention of Functional Decline: Effect on Higher-Level Physical Function, Arch Phys Med Rehabil, 85: 1043-1049
QLQ-C30 Chantal Quinten, Corneel Coens,, Irina Ghislain , Efstathios Zikos, Mirjam A.G. Sprangers, Jolie Ringash, Francesca Martinelli, Divine E. Ediebah, John Maringwa, Bryce B. Reeve, Eva Greimel, Madeleine T. King, Kristin Bjordal, Hans-Henning Flechtner, Joseph Schmucker-Von Koch, Martin J.B. Taphoorn, Joachim Weis, Hans Wildiers, … Andrew Bottomley The effects of age on health-related quality of life in cancer populations: A pooled analysis of randomized controlled trials using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 involving 6024 cancer patients. Eur. J. of Can. 2015; 51; 18; 2808-2819
QLQ-ED14 Wheelwright S, Darlington AS, Fitzsimmons D, Fayers P, Arraras JI, Bonnetain F, Brain E, Bredart A, Chie WC, Giesinger J, Hammerlid E, O'Connor SJ, Oerlemans S, Pallis A, Reed M, Singhal N, Vassiliou V, Young T, Johnson C. International validation of the EORTC QLQ-ELD14 questionnaire for assessment of health-related quality of life elderly patients with cancer. Br J Cancer. 2013 Aug 20;109(4):852-8.

EQ-5D-3L Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, Swinburn P, Busschbach J. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res. 2013 Sep;22(7):1717-27.

SF-36 Ware JE, Jr., Sherbourne CD. The MOS 36 ItemShort Form Health Survey (SF 36). 1. Conceptual framework and item selection. Medical Care 1992; 30:473-483.
Time up and Go Beauchet, O., Fantino, B., Allali, G., Muir, S., Montero-Odasso, M. et Annweiler, C. (2011). Timed up and go test and risk of falls in older adults: A systematic review. The Journal of Nutrition, Health & Aging, 15(10), 933-938.
SPPB Fish J. (2011) Short Physical Performance Battery. In: Kreutzer J.S., DeLuca J., Caplan B. (eds) Encyclopedia of Clinical Neuropsychology. Springer, New York, NY. https://doi.org/10.1007/978-0-387-79948-3_1832
FSS Goo AJ, Song YM, Shin J, Ko H. Factors Associated with Depression Assessed by the Patient Health Questionnaire-2 in Long-Term Cancer Survivors. Korean J Fam Med. 2016 Jul;37(4):228-34.
MNA Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. Nutr Rev 1996;54:S59-S65
GDS4/GDS15 Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey MB, Leirer VO: Development and validation of a geriatric depression screening scale: A preliminary report. J Psychiatric Res 1983; 17: 37-49
MINI-COG McCarten J, Anderson P et al. Screening for cognitive impairment in an elderly veteran population: Acceptability and results using different versions of the Mini-Cog. J Am Geriatr Soc 2011; 59: 309-213.
Tinetti test Tinetti M. E., Baker D.I., Mc Avay G., Claus E.B., Garrett P., Gottschalk M., Koch M.L., Trainor K., Horwitz R.I. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med 1994; 331 : 821-827
Borg scale Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med. 1970;2(2):92-8.
Pain scale :
Agence Nationale d'Accréditation et d'Évaluation en Santé (ANAES) - Service des Recommandations et Références Professionnelles. "Évaluation et suivi de la douleur chronique chez l'adulte en médecine ambulatoire ". Février 1999
Nutrition scale:
Société Francophone Nutrition Clinique et Métabolisme (SFNCM) – « Evaluation de la prise alimentaire ».

Figure 1: should be either simplified or removed, as there is no additional value compared to the information given in the text. The term "kinesitherapy" is not used in the body of the manuscript elsewhere, this should be unified. The different colours indicating the training program seemed to be mixed up (green = gray?)
As the figure does not add any additional elements to the text it has been removed.

Supp 1 seems to be a duplicate.
The supplementary table was deleted.

Reviewer: 3
Reviewer Name: Virginia Sun
Institution and Country: City of Hope, Duarte, CA, United States of America Please state any competing interests or state 'None declared': None declared.

Thank you for the opportunity to review this study protocol on the PROADAPT intervention to improve the outcomes for older adults with cancer undergoing complex surgical procedures for treatment.

Overall the protocol paper is very comprehensive. I have the following suggestions for the authors to consider in their revisions:

 Inclusion criteria (pg. 9): what types of complex medico-surgical procedures for curative intent are included? All procedures for solid tumors? Are the procedures both minimally invasive (laparoscopic, robotic) and open?
The complex medico-surgical procedure in a curative intent (breast excluded) could be included. No restriction on surgical methods (minimally invasive and open) has performed.
The sentence was modified as below:
« complex medico-surgical procedure in a curative intent (major abdominal surgery (breast excluded...) etc.; no restriction on surgical methods (minimally invasive and open))." l. 152-153

1. The intervention includes self-management coaching for both patients and caregivers. Will caregiver outcomes be assessed? If not this is fine, but might be worthwhile to include in the next study.
"this is not the case but we agree that an evaluation of the caregivers could be interesting and planned in a future study"

2. 7 day pre-op immune-nutrition: what types? oral drinks with special formulations (i.e. higher protein, etc)?
We follow Weimann recommendations, ESPEN 2006, because elderly population is at higher nutritional risk.
"Use EN preferably with immuno-modulating substrates (arginine,o-3 fatty acids and nucleotides) perioperatively independent of the nutritional risk for those patients undergoing major neck surgery for cancer (laryngectomy, pharyngectomy), undergoing major abdominal cancer surgery (oesophagectomy, gastrectomy, and pancreatoduodenectomy) after severe trauma.
Whenever possible start these formulae 5–7 days before surgery and continue postoperatively for 5 to 7 days after uncomplicated surgery."

3. Rehabilitation was described to be at the discretion of the rehab team. The personalized approach is based on geriatric assessment and other factors?
You're right. The following sentence was added:
"The rehabilitation program is left at the discretion of the rehabilitation team (standard care and local habits)." L.251-252

Pr Claire Falandry and Mélanie Roche

VERSION 2 – REVIEW

REVIEWER	Virginia Sun City of Hope, USA
REVIEW RETURNED	23-Nov-2020

GENERAL COMMENTS	The authors have addressed this reviewer's comments sufficiently.