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► To cite this version:

Cecile Charles, Aurelie Bardet, Nusaibah Ibrahim, Olivier Aromataro, Linda Cambon, et al.. Delivering adapted physical activity by videoconference to patients with fatigue under immune checkpoint inhibitors: Lessons learned from the PACTIME-FEAS feasibility study. *Journal of Telemedicine and Telecare*, 2021, 10.1177/1357633x211021743 . hal-03287175

HAL Id: hal-03287175

<https://hal.science/hal-03287175>

Submitted on 3 Jun 2024

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Title: Delivering adapted physical activity by videoconference to patients with fatigue under immune checkpoint inhibitors: Lessons learned from the PACTIME-FEAS feasibility study

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Ethical approval information: N°ID-RCB 2019-A00947-50 (National Ethical Committee)

Funding statements: With the support of Bristol-Myers Squibb Foundation for Research in Immuno-Oncology

Acknowledgements: The authors thank the sponsorship and the regulatory teams of Gustave Roussy for their support, all exercise physiologists from Mooven for their contribution to the intervention.

Conflict of Interest statement for all authors:

Cécile Charles, Nusaibah Ibrahim, Olivier Aromatario, Linda Cambon, Alexis Imbert, Magali Pons, Bruno Raynard, Dominique Sauveplane, Camille Pouchepadass, and Sarah Dauchy have no conflicts of interest to declare.

Aurélie Bardet reports consultancy fees from Roche France, outside the submitted work.

Cédric Baudinet is an employee of Mooven SAS.

Dr Aurélien Marabelle reports sponsored research at Gustave Roussy Cancer Center with: Abbvie, Aduro, Agios, Amgen, Argen-x, Astex, AstraZeneca, Aveo pharmaceuticals, Bayer, Beigene, Blueprint, BMS, Boeringer Ingelheim, Celgene, Chugai, Clovis, Daiichi Sankyo, Debiopharm, Eisai, Eos, Exelixis, Forma, Gamamabs, Genentech, Gortec, GSK, H3 Biomedecine, Incyte, Innate Pharma, Janssen, Kura Oncology, Kyowa, Lilly, Loxo, Lysarc, Lytix Biopharma, Medimmune, Menarini, Merus, MSD, Nanobiotix, Nektar Therapeutics, Novartis, Octimet, Oncoethix, Oncopeptides AB, Orion, Pfizer, Pharmamar, Pierre Fabre, Roche, Sanofi, Servier, Sierra Oncology, Taiho, Takeda, Tesaro, and Xencor, outside the submitted work.

Pr Olivier Lambotte reports expert testimony and consultancy fees from BMS France, outside the submitted work.

Abstract

Introduction. Fatigue is one of the most frequent symptoms under anti-cancer immune therapy. Physical activity (PA) has been proven effective in reducing fatigue, but unmet needs remain regarding the provision and access to adapted programs which efficiently addresses the main barriers to PA.

Methods. The PACTIME-FEAS study aimed primarily to evaluate the feasibility and the acceptability of a videoconference-based 6-month program promoting PA, and secondarily to assess its potential post-immediate and short-term effectiveness in reducing fatigue in cancer patients under immune therapy. Numeric self-reported questionnaires (VAS-fatigue, MFI-20, IPAQ, EMAPS, SF36, HADS, ISI) were completed by participants through an online secure platform at 3 time points: just before (T1), and after (T2) the program, and 3 months later (T3).

Results. Sixteen participants (50% male, 50% female, mean age 54 years, 69% melanoma, 31% overweight), with moderate to severe fatigue, entered the internet-delivered intervention; 14 completed it, with an average completion rate of PA supervised sessions of 75%. Satisfaction was high, confirming a demand for group format, personalized approach, professional guidance, and home-based device, to support the practice of regular PA. A decrease in fatigue was observed at the end of the program.

Discussion. Recruitment process did prove to be challenging, with a relatively small eligible population, and will need to be reconsidered to envision a larger scale trial. But here and now, this feasibility study provides first promising foundations to develop further research on the effectiveness of an original remote program.

Key words: Cancer, immune therapy, fatigue, physical activity, videoconferencing

Context

The exponential development of immune checkpoint blockade therapies has radically changed the therapeutic area in oncology by opening up strong hopes in terms of long term responses for a number of patients, with survival curves already significantly prolonged in a growing list of cancers.^{1,2} By acting on the immune system, immune therapies generate specific side-effects, which can concern all organs and are different from those classically observed with conventional therapies.^{1,3} Among the most common but not lethal side-effects, fatigue could affect up to 40% of patients regardless of grade of severity and 10% for the most severe grades.⁴ The risk of developing severe fatigue is not the same depending on the mechanisms of action and doses of the immune therapies, and whether they are used alone or in combination (e.g., with chemotherapy or another immune therapy), but causal pathways and underpinning mechanisms are still unclear.³⁻⁵

Among the non-pharmacological treatments of fatigue, physical activity (PA) has the strongest evidence of efficacy.⁶ However, many barriers to PA persist, related to environmental and organizational conditions (climatic and temporal constraints, distances from appropriate structures, isolation...), but also to psychological aspects (lack of self-confidence and/or motivation, negative representations towards PA...)⁷ Fatigue itself is a major obstacle, as is pain.⁸ Motivational support, which takes into account the individual specificities and needs (own limitations, preferences, etc.), social support (through group format) and the use of new technologies are currently promising levers that can be activated in the oncological context.⁷ Though very few adapted PA programs combining these aspects have been developed in French-speaking language, particularly with the aim of reducing immune therapy-related fatigue.⁹ The PACTIME videoconference-based program (“Physical

ACTivity during Treatment of Immune Therapy, e-health program”) was built to address this gap.

This article describes the results of the PACTIME-FEAS feasibility trial, and highlights the lessons learned from a mixed picture. This study firstly aimed to examine the feasibility, and the acceptability of the PACTIME program, and secondly aimed to explore its potential post-immediate and short term effectiveness in reducing fatigue. With reference to Banck-Petersen¹⁰, we hypothesized that the feasibility and the acceptability of the PACTIME program would be confirmed if the following criteria were met: a recruitment time below 4 months, a minimum of 40 inclusions, an attrition rate below 20%, an adherence rate above 75%, and a satisfaction rate above 80%.

Methods

Study design and population

The PACTIME-FEAS feasibility trial was a monocentric before-after single-arm study. The inclusion criteria were: a) 18-75 years old cancer outpatients, b) with a WHO Performance status¹¹ of 0-2, c) to be starting or undergoing an immune checkpoint blockade therapy, d) reporting a level of fatigue ≥ 4 on a 10-point visual analogous scale (optimal cut-off for identifying clinically significant fatigue),¹² e) for whom an organic assessment for fatigue had been realized, g) having an Internet access from home and a webcam. The exclusion criteria were: a) any formal contraindication to the practice of PA, b) surgery scheduled within six months from inclusion, c) simultaneous participation in a clinical trial with drugs, d) known severe cognitive impairments or psychiatric disorders which were incompatible with the study.

Study procedure

The study protocol was approved by the National Ethic Committee. From the end of June 2019 to January 2020, eligible patients were systematically met by the investigator at the day hospital of a French cancer center, after consultation of the appointment list and the medical records. All of them received oral information, and all included patients signed an informed consent. The absence of contraindications to the practice of PA was assessed by their referring physician, who provided a certificate.

Intervention

The PACTIME 6-month program was designed to reduce fatigue with the perspective to promote long-standing change in health behaviors, and notably “*making physical activity a part of each day*”.¹³ Therefore, this program targeted the achievement of the international recommendations, at least 150 minutes of moderate intensity PA per week.^{8,14} It followed a fixed timeframe (Supplementary 1) which was based on a model of progressive 1) modulation of the duration and of the intensity of adapted PA, 2) empowerment towards autonomy and sustainable change.

The program was entirely run remotely thanks to the use of a simple and secure web platform (VisioMoov®, Mooven, France). After inclusion, a videoconference appointment was scheduled with each participant with a trained exercise physiologist for the first motivational interview and fitness assessment. The program weekly combined supervised and autonomous PA sessions. The videoconference-based PA sessions were supervised by the referring exercise physiologist, in small groups (4-5 participants), lasted 45-60 minutes, and included articular mobilization, aerobic and resistance exercises, relaxation or stretching. A time was also reserved for an overall group feedback on the session experience and on the autonomous practice during the past week. The autonomous practice time was supposed to increase month after month and could be divided into as many sessions as the participants wished, respecting

a minimum duration of 15 minutes to be significant. These sessions, performed outdoors or indoors, consisted of moderate intensity activities chosen in accordance with each patient's habits and preferences, and potentially based on some of the movement sequences proposed during supervised sessions. The self-monitoring of the autonomous practice was based on the weekly completion of a logbook. An individual telephone follow-up was scheduled with the exercise physiologist in the middle of the 2nd and the 4th months to re-visit progress or difficulties during the program.

The program included also a progressive path of 4 videoconference-based workshops which intended to help patients in the daily self-management of fatigue, and to empower them for long term behavior change.¹⁵ Two of them were conducted by a psychologist, trained in behavioral change techniques and health education, one by an exercise physiologist and one by a dietician. During the last month, at least two half hours of the weekly supervised PA sessions were devoted to developing in group an individual action plan to support the sustainable integration of PA in everyday life. A final individual fitness assessment marked the end of the program.

Measures

Patients were evaluated before starting the program (Time 1), just after ending the program (Time 2), and three months later (Time 3). Measures and time points are summarized in Table 1. All questionnaires were completed by patients through the study secure web platform. Demographic and medical data were collected at T1 with an ad-hoc questionnaire, including: age; gender; marital status; children; education level, employment status; cancer type; immune treatment type and duration; body mass index; pain.

Primary outcomes. The feasibility metrics were recruitment process (duration and number of inclusions) and attrition rate (number of drop out participants before the end of the program). The acceptability metrics were adherence and satisfaction. Adherence was based on two

parameters, the total number of supervised sessions performed, and the cumulated time spent physically active without supervision. Satisfaction was globally assessed with an ad hoc questionnaire at T2.

Secondary outcomes. The potential post-immediate, and short term, effectiveness of the program on reducing fatigue was based on the evolution of the level of fatigue, measured by a visual analogous scale at each time point. The Multidimensional Fatigue Inventory (MFI) was also used to better capture the different aspects of fatigue.¹⁶ As exploratory effectiveness outcome measures were considered physical condition (endurance, 2-minute Step Test; balance, Unipedal Stance Test; flexibility, Sit and Reach Test; lower-limb strength, 30-second Chair Stand Test),¹⁷⁻²⁰ PA and sedentariness (International Physical Activity Questionnaire short form, IPAQ),²¹ motivation (Scale of motivation towards health-oriented physical activity, ÉMAPS),²² and quality of life (Medical Outcomes Study 36-item Short Form Health Survey, SF-36).²³ Pretrial exercise behavior (5-item ad hoc questionnaire), anxiety and depression (Hospital Anxiety and Depression scale, HADS),²⁴ sleep disorders (Insomnia Severity Index, ISI),²⁵ were investigated as control variables.

Statistical analyses

The expected minimal number of patients included in PACTIME-FEAS study was 40, which met the empirical criteria usually defined for pilot studies.²⁶ Analyses were performed on all patients who entered the program, and were only exploratory given the final small sample size. Descriptive statistics were used to describe the participants' characteristics, the feasibility and acceptability metrics, and the secondary outcomes. The difference in the level of fatigue between pre- and post-program was estimated, with 95% confidence intervals [CI], and a test of nullity was performed using the Wilcoxon Signed-Rank test. All analyses were performed using SAS 9.4 software (SAS® France).

Results

Participants' characteristics

Participants were 8 women and 8 men (mean age = 54 years, Standard Deviation [SD] = 12.2, range 34-72). More than two thirds were treated for metastatic melanoma, and received first line treatment (mean duration = 8 months, SD = 8.2, 0-21). Nearly half of the patients were overweight or obese, a quarter reported significant pain, and three quarters had moderate to severe fatigue at baseline. In terms of physical abilities, if about one third of the patients stood out with performance well above the mean, another third had performance below the mean. Detailed participants' characteristics are described in Table 2.

Primary outcomes

Recruitment process. Two hundred and ninety-one patients were treated with immune therapy at the day hospital during the 7-month inclusion period. After consultation of all medical records, 94 (32%) were selected for pre-screening. Of those, only 34 (11.7%) were confirmed eligible after the meeting with the investigator, and 24 (8.2%) consented to the study.

Attrition rate. Of 24 patients included, 8 never started the program: 2 withdrew their consent, 5 had a rapid alteration of their general condition, and one was lost to follow-up. Sixteen patients entered the program, and 14 completed it; discontinuations at 10 days, and 4 months, were due to disease progression. The disease progressed for one patient, and one patient died, shortly after completing the 6-month program. Finally, nine out of 16 patients (56.3%) completed the 3-month follow-up assessment.

Adherence. On average, patients participated to 18.7 supervised PA sessions (SD = 6.7, range 1-24), which corresponded to 78% of the planned sessions. Among those who completed the 6-month program (n=14), the average number of supervised PA sessions was 20.8 (SD = 4.8, range 15-24), which corresponded to 87% of the planned sessions. Only 4 out of 16 patients

filled in their logbook on the study web platform, for 1, 8, 14, and 24 weeks, respectively. Thus, the assessment of the patients' adherence to the recommended weekly autonomous practice was not feasible.

Satisfaction. Overall, patients expressed a high level of satisfaction with the program, and all would recommend it. Patients particularly appreciated the group format (peer support, sharing experience), the quality of supervision by the trained exercise physiologists, the personalized approach, and not having to travel to undertake physical exercise.

Secondary outcomes

Among the 13 patients who completed the pre- and post-immediate-program assessments, it was globally observed (Table 3 and Figure 2): a significant 2.1 point mean decrease in fatigue ($p = 0.0161$; IC: [-3.61; -0.55]), an increase in moderate physical activity time, an increase in intrinsic motivation to practice PA, an improvement in endurance, balance, and lower limb strength, as well as an overall improvement in perceived physical and mental health.

Discussion

The primary aim of this study was to assess the feasibility and the acceptability of a videoconference-based PA program addressing fatigue under anti-cancer immune therapy. Firstly, the results showed that only a very small proportion of patients (11.7%) were eligible for the study. It is noteworthy that during the recruitment period, 12.7% of the patients treated by immune therapy had poor performance status (≥ 3), and 27.5% had a contraindication to PA. Afterwards, some of the study criteria appeared restrictive (age limited to 75 years, not being included in a clinical trial). The problem of inadequate access to digital technology, which is known to prevent the implementation of internet-delivered interventions, was also identified as a barrier for some patients.^{27,28} Unfortunately, the provision of tablets would have only solved part of the access issue.

Despite the challenging recruitment process, the results also showed a good uptake of the program among confirmed eligible patients with: 1) a substantially lower attrition rate than that reported in studies on internet-delivered interventions (43-99%);²⁹ 2) an average completion rate of PA supervised sessions of more than 75%. An unstable physical condition was after inclusion the main reason for not participating in the program or for leaving early the program. While the progression-free survival associated with immune therapies is increasing in non-small cell lung cancer and melanoma, a proportion of metastatic patients will not respond or will respond only for a very limited time.^{30,31} In this context, regular participation in a PA program lasting several months can be a challenge.

In addition, the overall satisfaction at the end of the program was high, confirming a demand for this type of remote intervention, combining group format and personalized support, as well as its attractiveness and quality. A lack of adherence to the completion of the online logbook was nevertheless observed, as it was judged by patients as time-consuming. In this context, it was not possible to assess whether or not autonomous practice goals had been met. This issue has already been documented by pilot studies in PA.³² An alternative would have been the automatic monitoring of patients' daily PA by means of connected tools, such as pedometers, which however have also limitations as they cannot capture all forms of activity (e.g. resistance exercise, cycling, swimming...).³² But the remote format of the program would have been hardly compatible with the maintenance of connected tools. Besides, some patients might have perceived them as intrusive or constraining (need for continuous wearing).

In terms of clinical changes, encouraging signs were observed, especially a decrease of the level of fatigue, an increase of the overall level of physical activity, and a global improvement of the physical conditions, among the participants who completed the program.

The two main limitations of this study are the small sample size, which explains why only descriptive and exploratory statistical analyses were performed, while remaining comparable

to that of other pilot studies testing videoconference-based interventions; the absence of a control group, to provide stronger preliminary elements on the effectiveness of the PACTIME program. Without financial cover or equipment loan, a number of patients, who may be in need, remain excluded from internet-delivered interventions. The issue of social health inequalities has not been addressed in this study, but is one of the points being considered in the development of future remote interventions.

Implementing interventions for a vulnerable group of patients and being in condition to test them remains a challenge in oncology.³³ Based on a priori evaluation criteria, the PACTIME-FEAS study has achieved its main goals, by enabling to determine how many patients may be eligible, what would be the potential barriers to the patients' participation to the program (mainly impaired or unstable physical condition, and inadequate access to digital technology), and thus by providing a realistic recruitment ratio and recruitment duration in the population of interest.³² Given the limited number of studies on PA programs delivered by videoconference, this study also adds knowledge about the feasibility of proposing adapted PA to patients with fatigue during immune therapy, with good adherence, whether the patients were initially physically active or not, and overweight or not.

Conclusion

Promoting physical activity to cancer patients with fatigue is both an issue and a challenge. The PACTIME program has been designed to overcome key barriers. The PACTIME-FEAS study provided preliminary evidence for the feasibility and the acceptability of this videoconference-based program with patients with various profiles, within a physical vulnerability context. Optimization of the recruitment process will be a prerequisite for a future large-scale trial. An ongoing qualitative study will provide further information on the conditions for adherence to the program. The use of videoconferencing is today one of the

solutions to be more extensively considered to support regular physical activity as close as possible to patients' living conditions.

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Table 1. PACTIME-FEAS study: Measures and time points

Measures	Data collection process and format	Instruments	Before program (T1)	During program ↔	Post-immediate (T2)	+ 3 months follow-up (T3)
Demographic/Medical data	Research e-space (Patient)	Ad hoc questionnaire	+	-	-	-
Adherence <i>Supervised APA sessions</i> <i>Autonomous practice time</i>	Logbook (Patient)	Logbook	- -	+ +	- -	- -
Fatigue	Research e-space (Patient)	VAS-fatigue MFI-20	+ +	+ -	+ +	+ +
Physical condition <i>Endurance</i> <i>Balance</i> <i>Flexibility</i> <i>Lower-body strength</i> <i>Pain</i>	Fitness assessment e-report (APA professional)	2-minute Step Test Unipedal Stance Test Sit and Reach Test 30-Second Chair Stand Test VAS-pain	+ + + + +	- - - - -	+ + + + +	- - - - -
Physical activity / sedentariness	Research e-space (Patient)	IPAQ	+	-	+	+
Exploratory outcomes <i>Motivation</i> <i>Anxiety/Depression</i> <i>Insomnia</i> <i>Quality of life</i>	Research e-space (Patient)	ÉMAPS HADS ISI SF-36	+ + + +	- - - -	+ + + +	+ + + +
Satisfaction	Research e-space (Patient)	Ad hoc questionnaire	-	+	+	-

T1, Time 1; T2, Time 2; T3, Time 3; MFI-20, Multidimensional Fatigue Inventory;¹⁶ IPAQ, International Physical Activity Questionnaire;²¹ ÉMAPS, Échelle de Motivation envers l'Activité Physique en contexte de Santé;²² SF-36, Medical Outcomes Study 36-item Short Form Health Survey;²³ Hospital Anxiety and Depression Scale;²⁴ Insomnia Severity Index;²⁵ 2-minute Step Test;¹⁷ Unipedal Stance Test;¹⁸ Sit and Reach Test;¹⁹ 30-Second Chair Stand Test;²⁰ APA, adapted physical activity.

Table 2. Characteristics of the participants

Characteristics	N=16
	n (%)
Age, years	
Mean (SD)	54,2 (12.2)
Range	[34-72]
Gender	
Female	8 (50)
Male	8 (50)
Familial status	
Living with partner	15 (93.8)
Having children	14 (87.5)
Professional status	
Working	5 (31.25)
Disabled	4 (25)
Retired	6 (37.5)
Unemployed	1 (6.25)
Education level	
≤ High school level	6 (37.5)
> High school level	10 (62.5)
Cancer type	
Melanoma	11 (68.75)
Lung	3 (18.75)
Other	2 (12.5)
Current therapy	
Nivolumab	9 (56.25)
Pembrolizumab	7 (43.75)
Time since the beginning of therapy	
Mean (SD), years	8 (8.2)
Range	[0-21]
Line of treatment	
1 st	11 (68.75)
2 nd -3 rd	3 (18.75)
> 3 rd	2 (12.5)
Body Mass Index	
Normal	9 (56.25)
Overweight	5 (31.25)
Obesity	2 (12.5)
Level of pain (Visual analogous scale, 0-10)	
≥4	5 (31.25)

Table 3a. Evolution of the physical parameters during the PACTIME program

Physical parameters	Time points			Difference between T1 and T2 (n=13)	
	T1 (n=14) Mean (SD)	T2 (n=13) Mean (SD)	T3 (n=9) Mean (SD)	Mean (SD)	Range
Fatigue	(n=15)				
VAS	4.5 (2.3)	2.0 (2.2)	2.3 (3.5)	-2.1 (2.5)*	[-5; 3]
MFI-20			(n=7)		
General fatigue	10.7 (3.1)	10.8 (1.7)	13.1 (1.7)	0.3 (2.5)	[-5; 5]
Physical fatigue	8.9 (2.0)	10.3 (2.5)	11.9 (3.0)	1.6 (2.4)	[-1; 8]
Mental fatigue	11.5 (1.9)	11.3 (1.9)	11.9 (2.5)	-0.1 (2.3)	[-4; 4]
Reduction of activities	8.8 (1.8)	10.4 (2.4)	11.3 (4.2)	1.6 (2.7)	[-3; 7]
Reduction of motivation	10.8 (2.4)	10.9 (2.2)	12.0 (3.7)	0.2 (2.8)	[-5; 6]
Physical activity (IPAQ) (minutes per week)		(n=10)	N.A.	(n=10)	
Low	44.7 (35)	66 (56.2)		24 (75.5)	[-140; 120]
Moderate	136 (220.7)	175 (171.9)		76 (109.4)	[-30; 330]
High	38.3 (95.2)	68.5 (88.9)		11 (114.5)	[-240; 150]
Sedentariness	331.9 (162.3)	339 (158)		-46 (224.5)	[-380; 300]
Physical condition (Fitness assessment)	(n=16)	(n=14)	N.A.	(n=14)	
Endurance (2-minute Step Test)	88.2 (28.5)	105.6 (32.0)		13.9 (15.5)	[-15; 39]
Balance (Unipedal Stance Test)	36.5 (22.2)	40.7 (19.9)		5.9 (16.5)	[-25; 35]
Flexibility (Sit and Reach Test)	2.8 (9.2)	-0.4 (10)		-3.3 (10.1)	[-38; 0]
Lower-limb strength (30-second Chair Stand Test)	13.9 (3.7)	16.1 (5.3)		1.7 (2.9)	[-3; 5]
Sleep (ISI)				N.A.	N.A.
Absence of insomnia [0-7], n (%)	6 (42.9)	7 (53.8)	5 (55.6)		
Moderate insomnia [8-14], n (%)	4 (28.6)	3 (23.1)	.		
Severe insomnia [15-28], n (%)	4 (28.6)	3 (23.1)	4 (44.4)		

T1, Time 1, pre-program; T2, Time 2, post-immediate program; Time 3, 3-month follow-up; SD, standard deviation; VAS, Visual Analogic Scale; MFI-20, Multidimensional Fatigue Inventory;¹⁶ IPAQ, International Physical Activity Questionnaire;²¹ Insomnia Severity Index;²⁴ N.A., non applicable; *p = 0.0161, Confidence Interval = [-3.61; -0.55], Wilcoxon Signed-Rank Test

Table 3b. Evolution of the psychological parameters during the PACTIME program

Psychological parameters	Time points			Difference between T1 and T2 (n=13)	
	T1 (n=14) Mean (SD)	T2 (n=13) Mean (SD)	T3 (n=9) Mean (SD)	Mean (SD)	Range
Motivation towards PA (ÉMAPS)			(n=6)		
Intrinsic	12.6 (5.1)	14.4 (3.9)	12.5 (5.0)	2.1 (4.2)	[-4 ; 9]
Extrinsic - integrated	12.2 (6.3)	11.7 (6.3)	8.5 (5.7)	-0.2 (4.8)	[-13 ; 6]
Extrinsic - Identified	15.4 (4.6)	16.4 (3.6)	15.2 (5.2)	1.3 (3.9)	[-6 ; 8]
Extrinsic - Introjected	10.6 (3.8)	12.5 (4.5)	10.7 (3.5)	2.4 (3.9)	[-5 ; 8]
Extrinsic – Regulated	5.2 (2.9)	4.5 (2.0)	4.8 (2.2)	-0.8 (3.1)	[-7 ; 5]
No motivation	4.4 (2.1)	5.8 (4.3)	5 (2.5)	1.4 (3.2)	[-3 ; 9]
Emotional state (HADS)				N.A.	N.A.
Depression (≥ 11), n (%)	4 (28.6)	3 (23.1)	2 (22.2)		
Anxiety (≥ 11), n (%)	2 (14.3)	2 (15.4)	1 (11.1)		
Quality of life (SF-36)					
Physical total score	55.2 (18.3)	63.8 (23.5)	70.2 (27.8)	7.9 (18.4)	[-16 ; 38]
Physical functioning	75.4 (18.5)	78.1 (26.4)	81.1 (30.6)	2.7 (25.1)	[-60 ; 40]
Physical limitation	26.8 (30.2)	50.0 (42.5)	55.6 (41.0)	15.0 (47.4)	[-50 ; 75]
Pain	63.6 (32.2)	65.0 (31.0)	79.4 (34.5)	1.5 (25.6)	[-43 ; 43]
Overall Health	55.1 (21.3)	57.1 (21.6)	64.8 (30.3)	1.3 (13.2)	[-29 ; 21]
Mental total score	65.5 (19.0)	73.7 (23.1)	69.2 (32.2)	5.2 (17.1)	[-18 ; 32]
Vitality	43.2 (21.7)	61.9 (23.4)	53.9 (27.9)	16.9 (26.3)	[-40 ; 60]
Social functioning	70.5 (23.8)	81.7 (24.8)	73.6 (36.7)	7.7 (24.2)	[-38 ; 63]
Emotional limitation	73.8 (37.4)	70.0 (39.9)	74.1 (40.1)	-3.3 (36.7)	[-67 ; 67]
Mental Health	74.3 (18.5)	79.4 (20.7)	75.1 (31.2)	4.0 (10.6)	[-12 ; 24]

T1, Time 1, pre-program; T2, Time 2, post-immediate program; Time 3, 3-month follow-up; SD, Standard Deviation; PA, Physical Activity; ÉMAPS, Échelle de Motivation envers l'Activité Physique en contexte de Santé;²² Hospital Anxiety and Depression Scale;²⁴ SF-36, Medical Outcomes Study 36-item Short Form Health Survey;²³ N.A., non applicable.

