Secondary Prevention of unfavorable evolution in Patients with non-specific chronic low BACK Pain (BACK-4P): from Prediction to intervention

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Keywords: Chronic low back pain; digital interventions; disability; rehabilitation; randomized controlled trial.

1. Scientific background

Non-specific low back pain (LBP) is the leading cause of years lived with disability in the world[1] and its burden is growing alongside the increasing and ageing population. LBP was included in the World Health Organization list of 12 priority diseases in 2013. In France, it is the most lifetime prevalent rheumatic and musculoskeletal disease and affects 12.5% of the adult population[2]. LBP is usually treated according to symptoms duration, presence of concomitant radicular pain and of consistent anatomical abnormalities and is defined according to symptoms duration: acute (< 6 weeks), subacute (6 to 12 weeks) and chronic (> 12 weeks)[3]. The prognosis of acute LBP is excellent[4], but in 5 to 15% of patients, LBP becomes chronic[5]. At 6 months, about 10% of patients with chronic LBP are on sick leave, and at 12 months, 20% report persistent disability[6]. **These cases account for up to 80% of direct and indirect costs of LBP**. **In France, they represent 2.7 billion € a year and 1.5% of all medical expenses**[7]. Unfavorable evolution of chronic LBP is characterized by onset and persistence of spine-specific disability in all patients and work absenteeism in working age individuals[8]. The probability of returning to work is only 20% after 1 year of sick leave and 0% after 2 years[9]. Multidisciplinary rehabilitation that combines education, physical therapy, cognitive behavioral therapy and rehabilitation is usually offered. However, lack of personalization of these programs could affect their efficacy and systematic evaluation suggests their low cost-effectiveness.

In order to prevent onset and persistence of disability associated with LBP, a first challenge is to develop a deep understanding of patients' phenotypes and trajectories[10]. A second challenge is to be able to identify patients at risk of unfavorable evolution. This early detection would allow designing interventions specifically targeting these patients to change their beliefs and behaviors. A third challenge is to prevent unnecessary exposure of these patients to healthcare and the use of practices that are harmful or wasteful while ensuring equitable access to effective, affordable, minimally

disruptive and minimally burdensome healthcare for those who need it, on a community basis. These challenges have been recently highlighted in The Lancet Series published on March 21st, 2018 and have been summarized in a Call for Action authored by 30 key opinion world leaders with a specific focus on the challenge of providing adequate resources taking into account social inequalities of access to care in patients with non-specific LBP[11].

To tackle these 3 important challenges in the field of LBP research, we specifically designed the 3-year BACK-4P research program. Substantial changes have been made to the project since the letter of intention in order to address the reviewers' specific comments and to comply with selection criteria. **General aims of the BACK-4P research program will be: 1/ to develop a reliable prediction tool aimed at being used in primary care and at enabling early identification of patients with chronic LBP at risk for persistent pain and disability and 2/ to develop and assess a personalized digital behavioral change intervention to prevent unfavorable evolution in patients with chronic LBP, taking advantage of a large e-cohort of people with chronic LBP.**

Our program will combine the expertise of a multidisciplinary consortium of physicians, methodologists, biostatisticians, care providers, engineers, and bioinformaticians and will empower patients with chronic LBP from the earliest stages of the project development to implementation of its findings in the community. Digital tools, conceived in collaboration with patients, and accounting for personal factors, will allow the large-scale diffusion of remote and continuous behavioral change interventions, at low cost, personalized at initiation and adapted over the course of treatment, on the basis of context, timing and prior response[12].

2. Scientific and medical specific aims

Specific aims will be addressed in 4 scientific work packages (WP) and will be to:
(i) Set up a large e-cohort of French patients with non-specific chronic LBP,
(ii) Develop a tool to predict the risk for persistent disability in patients with chronic LBP,
(iii) Develop a personalized automated coaching intervention to support patients' engagement in positive behavioral changes in partnership with patients,
(iv) Evaluate this intervention in a pragmatic randomized controlled trial embedded in the e-cohort.

3. Importance of the collaboration of the teams for the completion of the project

The 3 partners of the project will have strong collaborations in all WPs. Multicentric clinical recruitment will be led by Partner 1, methodological and biostatistical expertise by Partner 2 and the development of an innovative digital intervention by Partner 3. Partners 1 and 2 have successfully collaborated in previously funded academic projects in the field of chronic LBP[13-15] and other musculoskeletal disorders[16-18].

WP1: Launching and maintaining the ComPaRe Chronic LBP e-cohort

Leaders: C Nguyen, VT Tran. Members: I Boutron, P Ravaud, F Rannou, MM Lefèvre-Colau, A Dupeyron, E Coudeyre

The aim of WP1 is to set up an e-cohort of 5,000 patients with chronic LBP aimed at describing patients' functioning, phenotypes and healthcare. This e-cohort will be part of the ComPaRe (Community of Patients for Research) project (https://compare.aphp.fr/) and will benefit from an existing IT platform allowing the online inclusion and follow-up of patients using patient-reported outcome and experience measures. Participants will be adults with non-specific chronic LBP, who have a valid e-mail address and who read and write French language. Our recruitment strategy will rely on several approaches. Participants will be recruited by advertising in general media (TV, radio, newspapers, health magazines), social networks (Facebook, Twitter, LinkedIn), scientific conferences and through patients' associations. In addition, we will use the snowball sampling principle where the pool of initial participants can advertise the study through their social networks and inform other participants who could potentially be enrolled. Information about the e-cohort will also be broadly disseminated among care providers of the main investigating centers' network using the snowball sampling principle. We expect to recruit 5,000 participants (1,700 participants per year over 3 years).

Participants to the e-cohort will have to complete an initial questionnaire (38 questions, 15 minutes) to collect self-reported baseline demographical, clinical, socio-professional characteristics, imaging report, co-interventions and relevant patient-reported outcomes. Then, they will have to record every 6 months (approximately 1h a year) core outcome criteria that are recommended in randomized controlled trials of LBP[19], such as mean pain intensity in the previous 48 hours using a self-administered numerical rating scale, LBP-specific activity limitation using the self-administered Roland Morris Disability Questionnaire (24 items) and quality of life using the self-administered 12-item Short Form Survey. In addition, in working age patients, we will assess absenteeism using self-reported number of sick leave days because of LBP since last contact. This e-cohort will serve as the foundation of our research program by enabling: (i) the precise description of the evolution of pain and disability in a large sample of participants characterized by their individual markers; and (ii) the recruitment of a population of patients eager to participate in the development of new interventions to improve their health.

An e-cohort has some advantages compared to traditional cohorts as it facilitates and accelerates the collection of data for a large population of geographically distant patients, despite the external validity of its results may be challenged by selecting patients who are younger and more educated. In the literature, e-cohorts have shown that the systematic differences between their population and the target population could be addressed using statistical weighting methods[20]. In addition, there is evidence that the recruitment methods used in our e-cohort will permit the inclusion

of participants with diverse sociodemographic backgrounds, including socioeconomically disadvantaged individuals who are usually difficult to reach and retain in long-term epidemiologic studies[21]. Finally, the objective our e-cohort is not to recruit a population of participants representative of those with LBP in the French population, but a population sufficiently diverse to ensure that the tools and interventions developed can be generalized to all types of participants. Selection criteria of participants in the e-cohort are very large. Consequently, the population included will be heterogeneous. This heterogeneity is important to be able to identify and describe different patients' phenotypes and trajectories. From this heterogeneous e-cohort, we will select homogeneous subgroups of patients to develop a prediction tool and to evaluate the impact of an innovative intervention.

WP2: Creating a prediction tool of the risk for persistent disability in patients with chronic LBP

Leader: R Porcher. Members: I Boutron, VT Tran, P Ravaud, C Nguyen, F Rannou, MM Lefèvre-Colau, A Dupeyron, E Coudeyre

The aim of WP2 is to describe individual-derived trajectories of patients with chronic LBP in order to develop a tool to predict the risk for persistent disability. Owing to the heterogeneity of the population included, dynamic prediction models will be restricted to patients with LBP for less than 5 years. Two types of prediction models will be derived. First, we will develop dynamic prediction models of a high level of spine-specific disability (i.e. reference standard Roland Morris Disability Questionnaire score ≥ 7/24, as proposed by Hill and colleagues[22]) and/or absenteeism in working age patients (i.e. at least 1 day of sick leave because of LBP since last contact), assessed at 6 and 12 months using clinical data of patients collected at repeated time points. Model derivation will be based on machine-learning techniques such as random forests, or artificial neural networks. Internal model validation will use numerical resampling approaches (bootstrap). We do not plan split-sampling for model development/model testing, because this corresponds to internal (and not external) validation and split-sampling is dominated by bootstrapping for internal validation. Second, we will cluster patients' trajectories of the spine-specific disability score. Identified groups or clusters of trajectories identified will be reviewed by the clinical experts (Partner 1) to assess their clinical relevance. Then a prediction model to classify patients into the relevant groups of trajectories will be derived using baseline features of patients. Ultimately, we will design an algorithm using both static (baseline) trajectory-based and dynamic prediction models to predict the risk of disability of patients, the Unfavorable Evolution Risk Assessment tool (UE-RAX). UE-RAX predictive performance will be further assessed in a random sample of the e-cohort. Outside a formal framework for statistical testing, sample size calculations have unclear validity. However, it is necessary to insure a "sufficient number of patients (and events) for meaningful analysis. We expect to include in this analysis 30% of the 5,000 patients (~1,700 patients) and that about 300 of these will experience the

event of interest during the study accounting for differential follow-up. Such number of events should prevent overfitting of the models and sparse data bias.

WP3: Development of a personalized automated coaching intervention to support patients' engagement in positive behavioral changes

Leaders: JC Martin, C Nguyen. Members: I Boutron, P Ravaud, VT Tran, F Rannou, MM Lefèvre-Colau, A Dupeyron, E Coudeyre, A Roren

As previously stated, intensive multidisciplinary rehabilitation is usually offered in disabled patients with chronic LBP. However, systematic evaluation suggests its low cost-effectiveness. Further, these programs are usually provided in specific centers and are not easily available to all patients, particularly those with lower socio-economic status.

The aim of WP3 is to create, in collaboration with patients, a personalized automated coaching intervention to support patients' engagement in positive behavioral changes, as recently prompted by authors of the Call for Action published in the Lancet Series[11]. The intervention will be designed to be easily implemented in a primary care setting, accessible to all patients, cost-effective and minimally disruptive. It will rely on recent research developed in affective computing which enables to design personalized motivational interventions to support emotional regulation and increase patients' self confidence in terms of physical activity and behavioral changes. It will be based on state of the art knowledge about motivational technologies for behavioral changes, as well as theories and models from psychology and affective computing (i.e. emotion regulation, motivation, individual differences, self-determination, self-confidence). The goal of the intervention will be: 1) to overcome widespread misconceptions about LBP, 2) to promote the concept of "living well" and "positive health" defined as the ability to adapt and to self-manage in the face of social, physical and emotional challenges with LBP[11]: e.g. advices to increase comfort during certain movements and postures (heavy lifting, position at the desk, housekeeping etc…); methods for coping with pain (e.g. relaxation strategies) and 3) to increase physical activities through a set of 3 personalized core exercises recommended and monitored.

The theoretical framework of the intervention will rely on theories and models from exercise psychology and emotion regulation. The automated coaching intervention[23] will be personalized according to the patients' personality, believes, behaviors and socio-economic context. We will also rely on the "storytelling" or "narrative communication" conceptual model which has demonstrated being a powerful tool for health promotion and behavioral change. According to this model, stories drawn and told by patients in patients' natural voices could be used to inform and inspire positive health behavior change if the listeners identify themselves with the storyteller[24]. We will develop short videos of 1-3 minutes of patients sharing their experience with LBP and promoting appropriate management of LBP as well as coping strategies.

To develop the intervention, we will use our previous findings from a qualitative study of patients with chronic LBP regarding new technologies[25]. Complementary user-centered design methods will be conducted to collect additional patients' expectations, perception, preferences and experiences about psychological support for emotion and pain regulation, self-efficacy, customized prescription of exercise therapy and physical activities and sharing of decision making[26]. A steering committee including patients' representatives from and outside the ComPaRe e-cohort, specialists in physical and rehabilitation medicine, physiotherapists, occupational therapists, instructors specialized in physical training and psychologists will be responsible for developing an algorithm for personalizing reassuring motivational messages and user interactions according to a) patients' personality measured with the Regulatory Focus Questionnaire (18-item inventory)[27] and the brief Big Five Inventory (10 items)[28], b) main activity limitations, c) environmental factors including socio-economic and professional context, and d) personal factors including coping strategies, fear-avoidance beliefs and usual level of physical activity. Personalized graded exercise therapy and physical activity will be delivered as a user-friendly mobile application guided self-help, with dose (number of sessions a week, duration) and content of program self-determined by patients' preference and willingness and finely adjusted overtime according to patients' individual needs and capabilities, and self-reported difficulties and progresses, with the guidance of the automated tool.

The mobile application will be available free of charge on tablet and mobile phone with a companion web site. The utilization of web-based technology is particularly important to enable dissemination of the intervention and to make it accessible at low-cost to a large number of patients. This approach will be made possible thanks to the significant increase in the use of the Internet in the world. In France, in 2018, the proportion of the population using the Internet is 85%, which may allow to better taking into account social inequalities of access to care. Digital tools and applications dedicated to patients with chronic LBP currently available mainly offer standardized reassuring messages and one-size-fits-all home-based exercise therapy program without personalized coaching or attempt to enhance adherence to treatment. Further, their impact has never been assessed in clinical trials. In contrast, our personalized automated coaching intervention will involve patients in all stages of the development of the tool from its earliest steps, will derive from clearly defined theoretical framework, will be personalized, flexible and evolving overtime and will be assessed in a randomized controlled trial.

WP4: Assessing the personalized automated coaching intervention in a pragmatic randomized controlled trial

Leaders: P Ravaud, I Boutron, VT Tran. Members: R Porcher, C Nguyen, F Rannou, MM Lefèvre-Colau, A Dupeyron, E Coudeyre, A Roren, JC Martin

The aim of WP4 is to assess the impact of the intervention developed in WP3 compared to usual care. We hypothesized that the personalized automated coaching intervention could reduce disability and absenteeism in patients with chronic LBP compared to usual care. We will conduct a pragmatic randomized controlled trial embedded in the ComPaRe LBP e-cohort using « the cohort multiple randomized controlled trial » design[29]. This innovative design aims to take advantage of the patients and data available in large observational e-cohorts. A sample of participants eligible for an intervention is randomly selected and these persons are offered the intervention. Outcome criteria are routinely collected as part of the e-cohort. The group randomly selected to receive the intervention is then compared with the rest of the e-cohort eligible for the intervention but not selected to receive it. This innovative design reduces the costs and time needed to conduct a randomized controlled trial and prevents resentful demoralization in the control group and consequently performance and detection bias.

Eligibility criteria will be patients included in the ComPaRe chronic LBP e-cohort with regular follow-up data for at least 6 months. We will exclude patients who are unemployed, retired or had a total sick leave duration longer than 3 months because of their LBP in the previous year. Randomization will be centralized and stratified according to the level of disability and job dissatisfaction. Participants randomized to the intervention arm will have access to the personalized automated coaching intervention developed in WP3. Patients in the control group will receive usual care. Primary endpoints will be the mean changes in disability assessed by the self-administered Roland Morris Disability Questionnaire (24 items) at 6 months. Secondary endpoints will be mean changes in disability at 12 months, mean changes in LBP intensity assessed by a self-administered numeric rating scale at 6 months, the self-reported number of sick leave days at 6 months after randomization, mean changes in work-related fears and beliefs assessed by the self-administered fear-avoidance beliefs questionnaire at 6 months. Co-interventions will be allowed and systematically recorded. Adherence to the intervention will be systematically web-based recorded. Quantitative and qualitative feedbacks from participants will also be recorded in order to understand patients' and care providers' perception and views on strengths and shortcomings of the intervention and potential lack of uptake. These data will be analyzed in a second time and will help optimizing and consolidating our innovative intervention. Finally, if possible, we will consolidate the patients' self-reported data about the number of sick leave days by chaining ComPaRe database to the *Système National des Données de Santé* medical-administrative database.

A sample size of 125 patients per group is necessary to detect an improvement of 2 points (SD 5.6) on the Roland Morris Disability Questionnaire (24 items) at 6 months with a two-sided 5% significant level and a power of 80%. With an expected 20% lost to follow-up, 312 patients will be recruited and randomized. The statistical analysis will be performed by the Center of Clinical Epidemiology, Hôtel-Dieu Hospital, AP-HP, Paris Descartes University. All analyses will be on intent-to-treat. Sensitivity analysis will be performed according to the adherence to the intervention.

WP5: Management, dissemination and communication

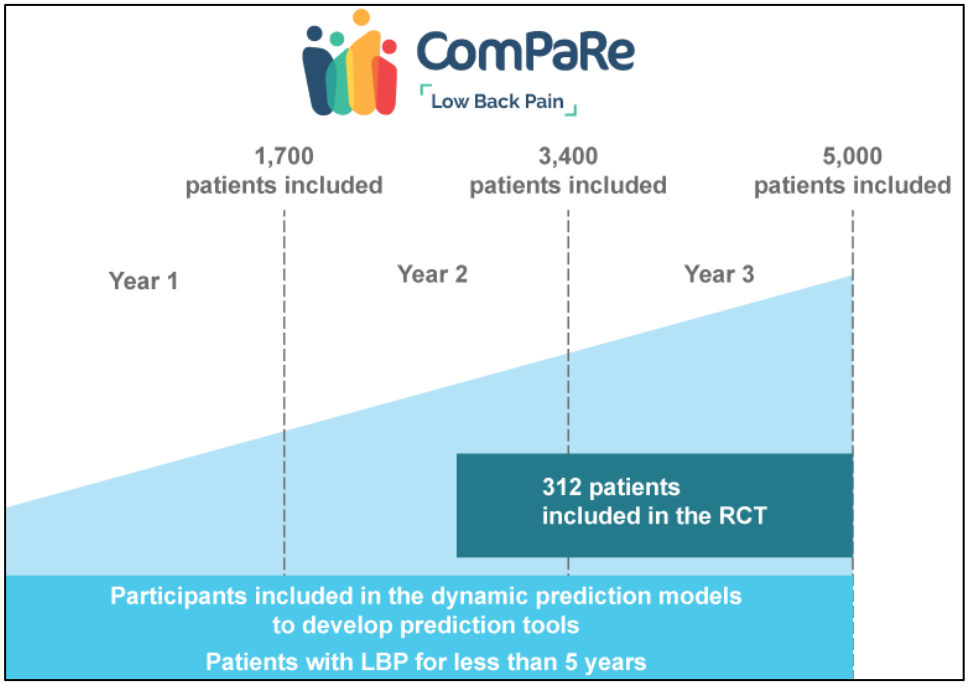
Leaders: C Nguyen, F Rannou, P Ravaud, I Boutron, VT Tran.

The BACK-4P research program will be managed and coordinated by a scientific committee composed of clinicians, scientists, methodologists, researchers and patients. The aim of WP5 is to ensure that the project reaches its objectives in a given contractual timeframe and budget by managing and monitoring project resources. Strategies to promote the study and disseminate its results to researchers and to a general audience will be implemented and will include core dissemination tools (logo, public website, video, poster, e-newsletters and project brochure). Operating procedures will include a kick-off meeting planned in June 2018, semestrial meetings and an end of research meeting planned in June 2021.

4. Measurable and easy to vulgarize deliverables consistent with the project and its timetable

Deliverables	
Year 1	WP1: Launch of the ComPaRe LBP e-cohort
Year 2	WP3: Development and assessment of the digital intervention WP4: Launch of the randomized controlled trial
Year 3	WP2: Prediction tool WP4: Dissemination of the results of the randomized controlled trial

General overview of the BACK-4P research program



5. Feasibility of the project

The 3 partners have complementary expertises necessary to carry out this project. Partner 1 has a clinical expertise in assessing musculoskeletal disorders and in patients' care and will participate in the development of the intervention as well as in the recruitment of patients with chronic LBP. Partner 2 has a methodological and biostatistical expertise in designing non-pharmacological trials[30 31] and e-cohort embedded randomized controlled trials and in developing and validating prediction tools from large and complex dataset[32] and will provide methodological and biostatistical support. Further, Prof Philippe Ravaud (partner 2) has created the ComPaRe e-cohort. Partner 3 has an expertise in computer science with a specific focus on affective multimodal interaction in humans and in machines and several application areas related to social skills training and will lead the development of the innovative digital intervention. Partners 1 and 2 have successfully collaborated in previously funded academic projects in the field of chronic LBP[13-15] and other musculoskeletal disorders[16-18].

The umbrella ComPaRe e-cohort and the ComPaRe LBP e-cohort (https://compare.aphp.fr/les-cohortes/cohorte-lombalgie-chronique.html) already exist in their pilot versions since October 2016 and March 2018, respectively, and benefit from a functional IT and flexible platform which structure and tools have been optimized and consolidated during the pilot phase of the project. Before the official launching of the full ComPaRe e-cohort scheduled on June 2018, 4,800 patients with at least one chronic disease and more than 100 of patients with non-specific chronic LBP have already been enrolled. More than 11,000 questionnaires have already been completed online. Recruitment in the ComPaRe LBP e-cohort will be secured by regular advertising on national TV and media by Prof François Rannou and Mrs Sylvie Bouchard (President from the LBP patients' association) who are regularly invited on TV shows and interviewed in journals, an information letter about the study systematically attached to medical report of patients followed-up for chronic LBP in the clinical investigating centers and a large promotional campaign supported by AP-HP and Paris Descartes University starting from June 2018.

6. Expected results and clinical impact for patients

The BACK-4P research program will allow describing individual markers in a large e-cohort of French patients with chronic LBP and implementing a personalized, cost-effective, minimally disruptive and easy-to-disseminate intervention to prevent unfavorable evolution in patients with chronic LBP in primary care taking into account social inequalities of access to care. The BACK-4P research program will meet some important healthcare needs recently highlighted in the Call for Action published in the Lancet Series on LBP, such as developing and implementing strategies designed to early identify and adequately educate patients with LBP at risk for persistence of pain and disability and promoting the notion of "positive health" and broader strategies for preventing other

chronic conditions (physical activity and behavioral changes)[11]. More specifically, the BACK-4P research program will:

- in the short and mid-terms: produce deliverables easily implementable in primary care, namely a web-based prediction tool of risk for persistence of disability and a personalized automated coaching intervention designed to prevent persistent pain and disability in patients with chronic LBP,
- in the long term: set up a large e-cohort of French patients with chronic LBP that will be a unique source of data to explore original research questions and to accelerate research in the field of LBP. For example, it could be used for validating patient-reported outcomes, understanding the effect of co-occurring non-communicable diseases or assessing innovative interventions by conducting randomized controlled trials embedded in the e-cohort.

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BUDGET
Project: BACK-4P
Principal investigator: Assoc Prof Christelle Nguyen

Partner 1		
TYPE	**DESCRIPTION**	**COSTS (€)**
Staff	physicians (1.5 years)	97 500
	physiotherapists (0.5 year)	13 500
	occupational therapists (0.5 year)	13 500
	instructors specialized in physical training (0.5 year)	13 500
	psychologists (0.5 year)	13 500
Consumables	printing of documents, stationary items, miscellaneous	5 000
	publication fees	5 000
	communication	10 000
Equipment	hardware, software	2 500
Mission expenses	travel expenses	2 500
Other direct costs	ComPaRe platforrm	80 000
	management fees	28 500
TOTAL		**285 000**

Partner 2		
TYPE	**DESCRIPTION**	**COSTS (€)**
Staff	epidemiologist (3 years)	195 000
	senior statistician (2 years)	114 000
	data manager (3 years)	98 000
Consumables	printing of documents, stationary items, miscellaneous	6 000
Equipment	hardware, software	3 000
Mission expenses	travel expenses	2 500
Other direct costs	management fees	46 500
TOTAL		**465 000**

Partner 3		
TYPE	**DESCRIPTION**	**COSTS (€)**
Staff	project engineer (3 years)	116 400
Consumables	operating costs	14 000
Equipment		
Mission expenses	travel expenses	9 000
Other direct costs	management fees	10 600
TOTAL		**150 000**

Arthritis R&D		
TYPE	**DESCRIPTION**	**COSTS (€)**
PhD	overall management of the project	100 000
TOTAL		**100 000**

SUMMARY	**COSTS (€)**
Partner 1	285 000
Partner 2	465 000
Partner 3	150 000
Arthritis R&D	100 000
TOTAL	**1 000 000**