Impact of virtual case management of multimorbidity on hospital use over a 2 year period: a randomized controlled trial nested in a cohort of patients with chronic conditions

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Summary

Context

Multimorbidity, the occurrence of multiple chronic conditions in a same patient has become a common situation. Multimorbidity raises multiple problems to manage these patients. Use of new technologies could help empowering patients to discuss and find solutions with their physicians.

Virtual case management of multimorbidity involves use of an "intelligent" internet platform that automatically analyzes patients' data on medication and conditions and answers to valid and reliable instruments. It could provide patients and physicians accurate summaries of potential problems to tackle.

Objective

We aim to assess the efficacy of a virtual case management of multimorbidity, on hospital use, care fragmentation, burden of treatment, quality of life and patients' primary care experience for patients with multiple chronic conditions.

Study design

Large pragmatic randomized controlled trial nested in the COMPARE e-cohort of patients with chronic conditions using a Cohort multiple randomized controlled trial (cmRCT) design.

Trial population

Patients participating in the COMPARE cohort with ≥ 3 chronic conditions and moderate or high burden of treatment (defined as having a Treatment Burden Questionnaire Score > 15) will be eligible for the trial.

Intervention

The intervention will be developed with the help of patients and experts of multimorbidity management in order to ensure its relevance. Patients in the intervention arm will be offered a virtual case manager that: 1) will regularly analyses patients' data on conditions, treatments and answers to questionnaires; 2) automatically detects potential problems of burden of treatment, adherence to medication, potential inappropriate prescriptions and potential

overtreatment; and 3) sends written summaries to both patients and physicians, inciting them to discuss problems and suggesting potential solutions.

Comparator

Usual care

Outcomes

Primary outcome:

- Hospital use (number of days hospitalized) over the 2 year period

Secondary outcomes:

- Number of hospital admissions over the 2 year period
- Burden of treatment (using the TBQ) every 4 months
- Adherence to treatment (using the Sidorkiewicz adherence questionnaire) every 4 months
- Symptoms and function (using the MYMOP questionnaire) every 4 months
- Quality of life (using the SF-36 questionnaire) every 4 months
- Index of care fragmentation using data from the last 2 years
- Patients' primary care experiences after 2 years of intervention

Statistical analyses

Both intention-to-treat (ITT) and Complier Average Causal Effect (CACE) analyses will be performed.

Conclusion

Our project is a simple large pragmatic trial aiming to test an intervention based on ne technologies to tackle problems of management of multimorbidity. If the intervention proves its efficacy, it could be easily replicated and generalized, at low costs.

1. Context

Chronic diseases are the leading cause of mortality in the world, representing more than 36 million deaths in 2008 [1]. A recent cross sectional study of 1,751,841 patients registered in 314 medical practices in Scotland showed that 42% of patients had at least one chronic condition [2]. Prevalence of chronic conditions should rise in the future. It has been estimated that, in 2020, approximately 50% of the population will have one chronic condition [3].

Most people with a chronic condition have in fact several, which is called multimorbidity [4]. In the Scottish study presented earlier, it is estimated that 23.2% (IC 95% [23.1 – 23.2]) of patients were multimorbid [2]. More importantly 65% of patients older than 65 years old are multimorbid. Multimorbidity is not only a problem associated with older patients: in absolute terms, there are more multimorbid patients aged <65 years old than >65 years old.

It is no surprise that considerable efforts has been directed to develop treatments to control conditions such as diabetes, high blood pressure, stroke, chronic obstructive pulmonary disease (COPD) etc. Treatments are then synthesized and organized into clinical practice guidelines, which guide the physician through the course of diagnosis, treatment and follow-up. One major limitation of these guidelines is that they focus on a single chronic condition and do not address multimorbidity.

It may be tempting for physicians to consider multimorbid patients as the sum of their different conditions and apply each clinical guideline. However, there is evidence that such approach may lead to overtreatment [5], avoidable burden of treatment [6] and/or drug interactions [7]. As an example, a physician following extant guidelines could prescribe up to 12 medications for a 79 years old patient with osteoporosis, osteoarthritis, type 2 diabetes mellitus, hypertension and chronic obstructive pulmonary disease[5]. Approximately 20% of

patients with two conditions were prescribed four to nine drugs and 1% were prescribed 10 or more drugs [8].

Focusing on single diseases instead of patients is not only present in guidelines but also in practice where patients often receive care from several different physicians who only care about one specific condition. This results in specialists consultants frequently complaining about the poor quality of information sent by referring clinicians and the inappropriateness of referrals [9]. Similarly, primary care physicians often receiving no information back from consultants [10] and/or not notified when their patients are admitted to the hospital. These failures in communication and care coordination may lead to ineffectiveness due to repeated exams and duplication of care, depersonalization and increased burden of treatment for patients. There is evidence that multimorbidity impacts disability [11], hospitalization rates [3] and quality of life [12] beyond the multiplicative effects of diseases taken independently.

Thus, there is a need to develop specific care for multimorbid patients that is both integrated at the level of decision making (guidelines level), at the level of coordination between physicians to take into account complex interactions (disease-disease interactions; disease-drug interactions and drug-drug interactions) [13] and at the level of implementation in patients' everyday life, taking into account their burden of treatment [6, 14]. This care should focus on realistic goals: physicians and patients should define what is most important and/or what should be done first according to clinical, prognostic and contextual factors.

There is some research on the impact of different care management models on patients' outcomes but those experiments had mitigated results. In the present study, we will move from existing trials to develop and assess new care management model for patients with chronic conditions.

2. Previous experimentations on management of multimorbidity

Some interventional studies have assessed organizational interventions for the management of multimorbid patients in ambulatory care. We updated the systematic review of trials aiming at management of multimorbidity in primary care and community settings [15] up to June 2015 and found 11 published randomized controlled trials and 3 ongoing projects (**Table 1**) which represents a low number of studies as compared to the importance of the problem.

Table 1: Randomized controlled trials aiming at management of multimorbidity in primary care and community settings

Author	Year	Population	Intervention	Results
Bogner[16]	2008	Hypertension and depression Age>50 (n=64)	Intervention focused on the integrated care manager's unique role as an intermediary or liaison between the physician and the elderly depressed patient with hypertension. The integrated care manager collaborated with physicians to help participating patients recognize depression in the context of hypertension, offered the patients guideline-based treatment recommendations, monitored the patients' treatment adherence and clinical status, and provided appropriate follow-up. The key components of this integrated care intervention were (1) providing the patient with an individualized program that is congruent with patients' social and cultural context; and (2) integrating depression treatment with hypertension management. The integrated care manager worked individually with patients. Through in-person sessions and telephone conversations, the integrated care manager provided education about depression and hypertension, emphasizing the importance of controlling depression to manage hypertension; offered encouragement and relief from stigma; helped to identify target symptoms for both conditions; explained the rationale for antidepressant and antihypertensive medication usage; assessed for side-effects and assisted in their management; assessed progress (e.g. reduction in depressive symptoms); assisted with referrals; and monitored and responded to life-threatening symptoms (e.g. chest pain, suicidality). The intervention was offered to patients as a supplement to, rather than a replacement for, existing primary care treatment.	Decrease in depression scores Decrease in blood pressure Improvement of medication adherence
Boult[17, 18]	2011	High risk of using health services estimated using a predictive model Age>65	Registered nurses who had completed a course in guided care nursing joined their assigned primary care teams. Each guided care nurse was integrated into the practice and established a caseload of 50 to 60 guided care patients. For each patient, the guided care nurse (1) performs a comprehensive assessment at home, (2) creates an	No change in hospital admissions/emergency department visits/primary care visits

		(n=904)	evidence-based care guide and a patient-friendly version called an action plan, (3) monitors the patient on a monthly basis, (4) smoothes the patient's transitions among sites of care, (5) coordinates the efforts of all the patient's providers of care, (6) uses motivational interviewing to promote patient self-management, (7) educates and supports family caregivers, and (8) facilitates access to appropriate community resources.	
Hogg[19]	2008	At least 2 conditions and at risk of experiencing an adverse outcome Age>50 (n=241)	The intervention was delivered by nurses (facilitators) with training in business or health administration. Nurses who were not facilitators assessed the practices performances using standardized questionnaires. Facilitators then shared with each practice its performance scores. With the facilitator's assistance, they identified areas of high preventive performance as well as areas with room for improvement. The group reflected on the reasons underlying their performance and through consensus set practice targets (goal setting) for the areas of preventive care they perceived change was feasible and necessary. The facilitator explored with the practice ways of integrating preventive care into routine/episodic care visits and shared tools used for improving the quality of preventive care delivery. Based on the practice's care goals and their choice of tools, a plan or strategy was agreed upon with the facilitator for reaching the proposed goals. Practice and facilitator worked together to tailor (adapt) the tools and the facilitation services to the needs and characteristics of the practices. Every 3–6 weeks up to the intervention's end, facilitators would visit the practice to follow-up on their progress and needs for improving preventive care. This could include reviewing their use of tools and of practice goals (i.e. decision to address a preventive issue formerly deemed as not feasible) and responding to previous practice requests. If necessary, facilitators would share with a practice lessons learned from other sites (dissemination/networking) and would provide educational materials for clinicians and advice on patient-mediated activities	Improvement of a chronic management score
Katon[20]	2010	Depression, diabetes and coronary heart disease (N=214)	The intervention combined support for self-care with pharmacotherapy to control depression, hyperglycemia, hypertension, and hyperlipidemia. Patients worked collaboratively with nurses and primary care physicians to establish individualized clinical and self-care goals. In structured visits in each patient's primary care clinic, nurses monitored the patient's progress with respect to management of depression, control of medical disease, and self-care activities. Treatment protocols guided adjustments of commonly used medicines in patients who did not achieve specific goals Nurses followed patients proactively to provide support for medication adherence. Using motivational and encouraging coaching, nurses helped patients solve problems and set goals for improved medication adherence and self-care Patients received self-care materials, including a video compact disk on depression care, a booklet and other materials on chronic disease	Decrease in depression scores Improvement of HbA1C Improvement of systolic blood pressure Improvement of LDL cholesterol

			management, and self-monitoring devices appropriate to their condition.	
Krska[21]	2001	At least 2 conditions Age>50 (n=332)	Pharmacists completed pharmaceutical plan for each patient using medical notes and computer records. The plan listed all potential pharmaceutical care issues (past and actual). It was then sent to the GPs. When GPs and pharmacist agreed on issues, they implemented actions.	Improvement of number of pharmaceutical care issues
Sommers[22]	2000	At least 2 conditions Age>65 (n=543)	The intervention focused on a set of defined activities for each intervention patient. First, the nurse or social worker visited the patient in the home, listened to health concerns, took vital signs and health histories, and completed a patient functional assessment and a home safety check. Second, using these data and the physician's prior knowledge of the patient, the team discussed the patient's health status and generated frailty and health risk scores. They drafted a risk reduction plan for discussion with the patient and family to set target objectives and plan treatment by means of chronic disease self-management strategies. Third, the nurse and social worker monitored the patient's health status between office visits through contacts by telephone, home visit, small-group session, or office or hospital visit at least once every 6 weeks. During contacts, the nurse or social worker inquired about new problems, checked chronic disease status, coached patients in self-management skills, and promoted use of community-based services. Finally, the physician, nurse, and social worker met at least monthly to review each patient's status and revise care plans.	Improvement in number of admissions/patient/year and 60days readmissions.
Coventry[23]	2015	Diabetes and/or coronary heart disease with depressive symptoms (n=387)	Face-to-face sessions of brief psychological therapy delivered by a case manager who were “psychological wellbeing practitioners” The psychological wellbeing practitioner gathered information about the nature of the patient’s key problems, including their experience of the autonomic, behavioral, and cognitive symptoms associated with low mood and anxiety (the ABC model), any modifying factors, and the impact of these symptoms, including level of risk. The link between the patient’s mood and management of their diabetes and/or heart disease was explored. They developed a main problem statement and personalized goals. Participants in the collaborative care arm chose to engage in behavioral activation, graded exposure, cognitive restructuring, and/or lifestyle changes. To better achieve integrated care, a collaborative meeting (by telephone or in person) between the patient and the psychological wellbeing practitioner and a practice nurse from the patient’s general practice was scheduled to take place at the end of the second and eighth sessions. These collaborative meetings focused on ensuring that psychological treatments did not complicate management of physical health and patient safety, reviewing patients’ progress with their problem statement and goals, reviewing relevant physical and mental health outcomes (such as depression, anxiety, diet, exercise), and planning future care.	Decrease in depression score

			Psychological wellbeing practitioners also worked collaboratively with the patient and practice nurse to check that patients adhered to antidepressants as prescribed, dealt with concerns about side effects, and helped to arrange drug reviews with the general practitioner if necessary.	
Eakin[24]	2007	At least 2 conditions (n=175)	The intervention was conducted by an experienced, bilingual, health educator, and involved two face-to-face visits 3 months apart, three follow-up phone calls, and three newsletters tailored to the behavioral goals of each participant. The face-to face visits took place either at the clinic or in the participant's home, based on participant preference. The use of visual aids was emphasized throughout the intervention Participants received education on national physical activity and dietary recommendations along with feedback from their baseline assessment. Participants then chose a self-management goal related to physical activity or healthy eating, and—key to the emphasis on external resources—identified one or two types of social environmental resources they could use to help them reach their goal (e.g., family and friends, health care team, neighborhood resources). At 2 and 6 weeks after the initial visit, the health educator made a brief follow-up phone call to reinforce progress toward goal attainment and to problem-solve barriers. During the second face-to-face visit, participants were encouraged to consider setting a goal for the second target behavior. A third follow-up phone call, the last point of contact, occurred 2 weeks after this visit to address the goals and barriers again, and to discuss strategies for maintenance of behavior change, with an emphasis on use of multilevel support resources. To reinforce behavior change goals, three tailored newsletters were mailed to participants over the course of the 6-month intervention. The newsletters reminded participants of their physical activity or diet goals, addressed participant-reported barriers and suggested examples of multilevel support resources that could be used.	Improvement in dietary behavior Improvement in score of healthy living Change in minutes/walking per week
Gitlin [25]	2006	At least 2 conditions Age>70 (n=319)	The intervention goal was to compensate for declining abilities by training in the use of control-enhancing strategies including cognitive (problem-solving, reframing), behavioral (pace self, sit instead of stand to perform tasks), and environmental (grab bars) modifications. The 6-month intervention consisted of five occupational therapy contacts and one physical therapy visit. Occupational therapists (OTs) met with participants and conducted a clinical interview to identify and prioritize problem areas. For each targeted area, an OT observed the participant's performance for safety, efficiency, and difficulty and presence of environmental barriers. In subsequent sessions, the OT engaged the participant in problem solving to identify behavioral and environmental contributors to performance difficulties. Specific strategies were derived and equipment options provided. In the fourth session, the physical therapist (PT) provided balance and muscle strengthening and fall-recovery	Improvement in ADL and IADL No difference in mortality at 4 years

			techniques. In the fifth session (telephone), the OT reinforced strategy use, and in the sixth session, the OT reviewed problem solving, refined strategy use, and provided education and resources to address future needs for environmental adjustments. Before the sixth contact, the area agency on aging ordered and installed home modifications (grab bars, rails, raised toilet seats), which were paid for through grant funds. Over the following 6 months, OTs conducted three telephone calls to reinforce the use of intervention-derived strategies and generalize these strategies to new problem areas. Interventionists served as consultants, helped participants solve problems, and offered strategy choices, whereas home care is more directive and prescriptive.	
Hochhalter[26]	2010	At least 2 conditions Age >65 (n=79)	The intervention offered tools and taught skills to (a) prepare for healthcare appointments, (b) communicate effectively and gather information and support during healthcare appointments, and (c) follow through on plans of care. Intervention contacts included a 2-h workshop and two telephone calls individualized to the patient's pre- and post-healthcare appointment needs. During the workshop, a group of participants and one leader (''coach'') discussed how to talk with their doctor. Following the workshop, coaches monitored participants' upcoming healthcare appointments using electronic records available in the integrated healthcare system in which the intervention was implemented. Coaches and participants took part in a brief coaching phone call within a week before a scheduled appointment and another call within a week after that appointment. They discussed the workshop content in the context of each participant's unique circumstances during these calls.	No difference in patient activation measure or HRQOL
Lorig [27]	1999	Subgroup with comorbidities: At least 2 conditions (n=536)	The Chronic Disease Self-Management Program (CDSMP) is a community-based patient self-management education course. Three principal assumptions underlie the CDSMP: (1) patients with different chronic diseases have similar self-management problems and disease-related tasks; (2) patients can learn to take responsibility for the day-to-day management of their disease(s); and (3) confident, knowledgeable patients practicing self-management will experience improved health status and will utilize fewer health care resources. The Chronic Disease Self-Management Program covered : exercise; use of cognitive symptom management techniques; nutrition; fatigue and sleep management; use of community resources; use of medications; dealing with the emotions of fear, anger, and depression; communication with others including health professionals; problem-solving; and decision-making. It promotes weekly action planning and feedback, modeling of behaviors and problem-solving by participants for one another, reinterpretation of symptoms by giving many possible causes for each symptom as well as several different management techniques, group problem-solving, and individual decision-making. The leaders act more as facilitators than as lecturers.	No difference in hospital admissions No difference in physician visits

Loffler [28]	2014	Patients taking >5 prescribed long-term drugs Age> 65	A pharmacist specially trained in communication skills performs a narrative-based medication review with both face-to-face clinical "brown bag" medication review and narrative medicine. Apart from detecting potentially inadequate medication, aim was to identify patient preferences and to include them into a hierarchically structured list of evidence-based medication recommendations. Thus, priorities for medication modification were based on both objective pharmaceutical considerations as well as on subjective patient preferences. The pharmacist then prepares a list of possible drugs to be stopped. The list will be discussed with the hospital physician in charge and will be submitted for adjustment with the patient's individual GP.	Ongoing
Altiner [29]	2012	>3 chronic conditions Age >65 and <84	GPs will be trained into performing a narrative doctor-patient-dialogue reflecting treatment targets and priorities of the patient. During the one year intervention GPs will have three conversations with the enrolled patients instead of routine consultations. Each conversation is scheduled for about 30 minutes. The first conversation will focus on treatment targets and priorities of the patient, the second will focus on the medication taken by the patient and the third will combine the elements of both previous conversations. The idea behind the approach of installing a structured framework of regular consultations is that this will eventually reduce the high number of (often unscheduled) consultations. The concept of narrative medicine shall facilitate the development of the patient's own agenda.	Ongoing
Jager [30]	2013	>4 different drugs >3 chronic conditions Age>64	Implementing into practice the three core recommendations as well as a set of strategies addressing these determinants. GPs and healthcare assistants will receive training in: (1) medication counseling; (2) medication management, (3) pharmacological issues; and (4) organizational study issues. Each PCP team will create an individual concept which describes how they plan to implement the recommendations into their practice and present it in quality circle meetings. A tablet PC with an interactive educational tool for the three core recommendations for patients will be provided (one tablet PC per PCP). All patients in the target group should complete the educational tool at least once. The aim of the tool is to increase patients' interest in and awareness of medication-related topics and thus introduce a behavior change that results in a higher proportion of patients carrying a medication list with them and reporting medication changes and problems proactively to GPs.	Ongoing

2.1. Studied populations

Study populations related to either specific groups of conditions (e.g. diabetes and depression, etc.) or more general populations with multimorbidity (e.g. all patients with > 2 chronic conditions). In the review of Smith et al., studies focusing on specific groups of conditions showed more significant effects than those for people with a broad range of conditions. However, improvements found in these studies were likely to be related to the strong focus in interventions targeted at specific conditions [15]. In the study of Boult et al. [17], investigators found no effect of implementation of nurses in general practices on health services use. One of the reasons was the broad inclusion criteria used which may have selected patients not likely to benefit from the team care.

It was to be noted that no study took place in France. It is likely that organizational interventions for management of multimorbidity are affected by the healthcare system and/or cultural differences; thus, there is a need for studies conducted in our context.

2.2. Studied interventions

All interventions evaluated in these studies included multiple components. Interventions could be divided into: 1) predominantly organizational interventions and 2) predominantly patient oriented interventions. Organizational interventions involved case management, coordination of care and/or enhancement of skill in multidisciplinary teams. Patient oriented interventions were focused on changing patients' health behaviors through educational programs.

A recent study published in the JAMA assessed the efficacy of a "virtual ward", that is the implementation of elements of hospital care (e.g. multidisciplinary teams, daily meetings, single point of contact for patients, etc.) into community-based care [31]. Although this study did not specifically focus on multimorbid patients, the study population of patients at high risk of readmission (as determined by length of stay, acuity of the admission, co-morbidities, and

emergency department visits in the previous 6 months) had similarities with our study population. This randomized trial found no reduction in the composite outcome of readmission or death at 30 days after discharge from the hospital. Among the potential reasons for which the virtual ward did not reduce readmissions was the difficulty for virtual ward team members to communicate with the patients' primary care physicians and/or personal support workers providing care to a patient. We hypothesize that an intervention centered on the patient and his primary caregiver might have better results.

2.3. Studied outcomes

With the exception of two trials, outcomes were disease specific outcomes (e.g. depression score, change in mean blood pressure, etc.) or management scores (such as number of potential pharmacological issues detected). In our review, we found only two studies using objective, patient-centered outcomes (hospitalization rates and number of physicians' visits) [17, 27].

2.4. Specificities of our research

The present study is original because of the following reasons:

- **Its settings.** None of the studies examined took place in France. It is likely that organizational interventions for management of multimorbidity are affected by the healthcare system and/or cultural differences.
- **Its population and outcomes.** On the contrary to the studies presented, we will focus on both: 1) complex multimorbid patients which are more likely to benefit from the intervention; and 2) important patient outcomes (hospital use, quality of life and burden of treatment).

- **Its intervention.** In all selected studies, interventions were either complex and expensive (e.g. nurses joining each general practitioner's clinic, etc.) or limited to specific settings (e.g. Single study site, Veteran Affairs clinics, etc.). In the present study, we want to take advantage of new technologies to empower patients and improve patient physician discussion. This intervention would involve use of a Virtual case manager, an "intelligent" internet platform that automatically analyzes patients' data to help patients and physicians tackle problems associated with management of multimorbidity. This approach would result in a highly standardized and generalizable intervention, with low costs.

3. How to improve management of multimorbidity

Many medical decisions, especially for care of complex multimorbid patients, are not clearly cut and patients and clinicians need to discuss the options using the best available evidence to make decisions that take into account patients' contexts, values and preferences [32]. As mentioned in the introduction, such discussions should take place at three levels of the patient care: 1) at the level of decision making (i.e. which intervention to start), 2) at the level of coordination between physicians and; 3) at the level of implementation in patients' everyday lives (i.e. how to implement the interventions in daily lives of patients).

3.1. Cornerstones of care of multimorbid patients

At each level, care may be optimized by taking into consideration new concepts, not fully accounted in previous studies: 1) deprescribing of inappropriate treatment; 2) limitation of overtreatment; 3) limitation of care fragmentation and 4) adaptation of care to the patient's burden of treatment.

Levels	**Possible action**
Decision making level	Management of medicines (deprescribing) Limitation of overtreatment
Physician coordination level	Minimizing the impact of care fragmentation
Care implementation level	Minimizing the burden of treatment

3.1.1. At decision making level

Deprescribing

Deprescribing is defined as the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within

the context of an individual patient's care goals, current level of functioning, life expectancy, values and preferences [33]. Deprescribing can reduce the workload of patients and may avoid drug interactions [34].

Limitation of overtreatment

Overtreatment relates to provision of treatment, by clinicians, with no net benefit to patients. It is generally driven by defensive practice, guideline driven care and tendency to treat rather than to watch and wait [35]. Better prioritization of care as a function of the patient's context, co-morbidities and other treatments might help reduce the workload of patients, avoid drug interactions and improve patients' quality of life.

3.1.2. At physician coordination level

Minimizing the impact of care fragmentation

Patients often receive care from several different physicians, who only care about one disease that the patient has. Coordination of care is often lacking due to the following facts: 1) most practices are independent; 2) physicians are not rewarded for their efforts to coordinate care; and 3) there is a separation between primary care and specialist care. These failures in communication and care coordination may lead to ineffectiveness due to repeated exams and duplication of care, depersonalization and increased burden of treatment for patients.

3.1.3. At care implementation level

Minimizing of the burden of treatment

In addition to the burden of illness, patients are affected by the burden of treatment, defined as the impact of the "work of being a patient" on functioning and well-being. This work includes medication management, self-monitoring, visits to the doctor, laboratory tests, lifestyle changes, etc. Burden of treatment is a factor of intentional and non intentional adherence and

is associated with poor quality of life [36]. Optimal care of multimorbid patients should seek to adapt healthcare to patients' contexts in order to have effective treatment strategies which minimize this burden of treatment.

3.2. Improving doctors' knowledge of these cornerstones

All these concepts are not well taken into account by physicians in their usual consultations [37] because: 1) they are not prepared during their studies to take into account these elements [38] and 2) they lack the time to do so during short consultations [39].

In the present study, we want to improve physicians' knowledge of patients' capacities, burden of treatment and contexts by complementing what is already done by the physician with assessments of the cornerstones of multimorbidity before consultations.

Previous studies have explored similar interventions, but they often involved costly implementations of new healthcare providers. In the present study, we want to take the opportunity of the development of new technologies and online patient communities to develop a "virtual patient case manager", similarly to the "virtual wards" that are emerging to follow up patients after hospital discharge [31]. This virtual case manager would use an internet platform for collection, analysis and synthesis of structured data relative to patients' problems not usually discussed during consultations. Thus, this may help in beginning discussions about management of multimorbidity and may lead to finding solutions tailored to each patient.

3.3. Making the most of doctors' appointments for patients

Most patients consider that their physicians have poor knowledge of their values and beliefs [40]. This may be related to a mismatch during discussions between patients and doctors, the latter focusing on disease objectives while often neglecting the impact of conditions and

treatments on patients' personal, social and professional lives. We expect that use of a virtual case manager, preparing patients before consultations and structuring points of interests could help patients and physicians focus on what matters the most to patients.

4. Study hypotheses and objectives

4.1. Hypotheses

Multimorbidity, the co-occurrence of multiple chronic conditions in an individual, is a health issue mostly dealt by general practitioners [41]. However, physicians may feel overwhelmed by multimorbidity, specifically for encompassing the inter-dependence between current and continuing problems, managing multiple changing conditions, and the interplay between psychosocial (including professional), economic and therapeutic issues [42]. As a result, there is a potential mismatch between patients' and doctors' preferences and priorities.

We hypothesize that the use of reliable pre-consultations assessments of problems encountered by patients could help physicians adapt care to patients' contexts. To obtain these pre-consultation assessments, we want to develop a virtual case management of multimorbidity. It would involve an "intelligent" internet platform that automatically analyzes patients' data on medication and conditions and answers to valid and reliable instruments in order to provide patients and physicians accurate summaries of potential problems to tackle.

4.2. Primary objective

The primary objective of the study is to compare efficacy of a virtual case manager intervention with usual care on number of days hospitalized during a 2 year period, for complex multimorbid patients.

4.3. Secondary objectives

Secondary objectives are to compare efficacy of a virtual case manager intervention with usual care on: 1) number of hospital admissions at 2 years; 2) Care fragmentation, assessed using a Herfindahl-Hirschmann index of visits across care providers at 2 years; 3) quality of life assessed every 4 months over a 2 year period; 4) medical outcome profile assessed every

4 months over a 2 year period ; 5) Burden of treatment every 4 months over a 2 year period ; 6) Adherence to medication every 4 months over a 2 year period and 7) patients primary care experiences at 2 years .

5. Methods

We will conduct a large pragmatic simple trial nested in a e-cohort of patients with chronic conditions to assess the efficacy of a case manager intervention in a population of complex multimorbid patients.

5.1. Study design

This study will use an innovative design: "*the cohort multiple randomized controlled trial*" (cmRCT) [43].

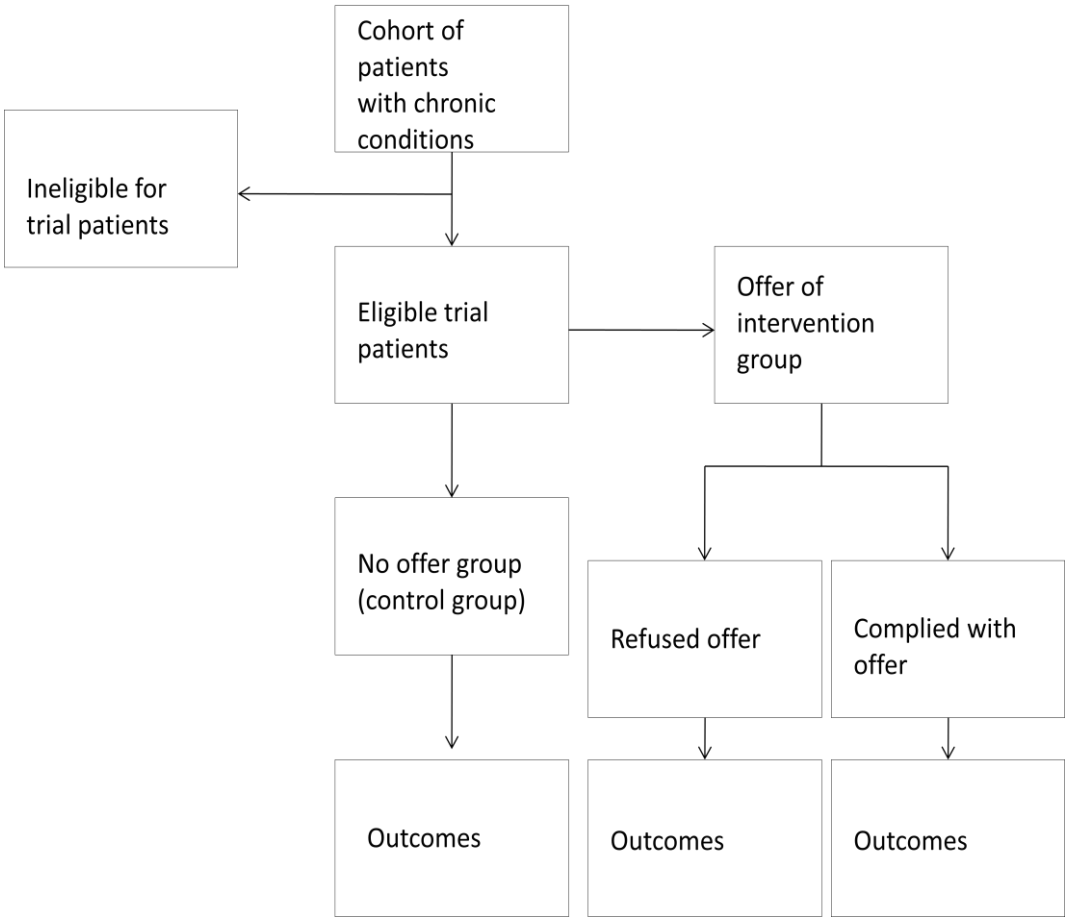


Figure 1: cmRCT design, from [44]

This design involves use of a large observational cohort of patients with the condition(s) of interest and with the outcomes of interest measured regularly. All patients in the cohort consent at the outset to provide data to be used to scrutinize the benefit of treatments for the condition(s) of interest. First, we identify all eligible patients in the whole cohort. Second, we randomly select some patients from all eligible patients in the cohort and offer them the trial intervention. Third, we compare the outcomes in randomly selected patients with the outcomes in eligible patients not randomly selected; that is, those receiving usual care. Informed consent is patient centered and aims to replicate "real world" routine health care.

This design is intended to address shortcomings of "classic" randomized controlled trial: 1) difficulties in recruiting sufficient number of participants [45]; 2) trial population not representative of the population "with need"; 3) randomization of patients in a usual care arm which may disappoint patients and lead to withdrawal (attrition bias).

5.2. Description of the E-Cohort

The trial will be nested in the COMPARE cohort, a web-based prospective cohort study involving adult patients with one or more chronic disease(s). The cohort is an institutional project funded by the Assistance Publique Hôpitaux de Paris (AP-HP), a network of 39 hospitals around and in Paris which manages 5 millions of outpatients and 1.2 millions of inpatients yearly, and the Communautés d'Universités et d'Etablissements (COMUE) of Sorbonne Paris Cité.

This e-cohort uses an online platform with multiple functionalities, based on the model of NUTRINET Santé [46], an e-cohort to evaluate associations between nutrition and health. The online platform will enable the registration and follow-up of patients though regular sending of questionnaires and is also able to identify patients with specific characteristics. The platform can evolve over time to add « *A la carte* » questionnaires for additional projects.

5.2.1. Patients included in the cohort

Patients included in the COMPARE cohort are: 1) adult; 2) with at least 1 chronic condition in a list of conditions adapted from lists of conditions used in other multimorbidity cohorts [2]; and 3) with a functional individual e-mail address.

All willing patients who fulfill eligibility criteria may be enrolled in the cohort. Recruitment will be supported by physicians managing patients with chronic diseases at the APHP hospitals' network and from other hospitals, patient associations and an extensive media campaign (e.g. television, radio, newspapers, posters, internet, etc.). Participants enrolled in the COMPARE cohort will also have the possibility to invite other eligible patients to get enrolled in the e-cohort using a snowball sampling technique [47].

All patients in the COMPARE cohort have to sign an electronic consent form: 1) for participation in the e-cohort and 2) allowing invitation in trials using the cohort population.

It is expected to recruit 200 000 patients in the COMPARE project.

5.2.2. Outcomes assessed regularly in the cohort

Three types of data are available in the cohort: 1) data about conditions and treatments through the Medical chart; 2) specific data about quality of life, burden of treatment and through regular mail questionnaires; and 3) data on mortality and healthcare use through linkage to the SNIIR-AM databases.

Medical chart

All patients in the cohort will enter the following data in their "Medical chart". This medical chart may be updated at the patient's convenience. Patients will be prompted by email to

update their medical chart every 3 months. It contains precise data on conditions and treatments.

Demographic data	Familial data (e.g. marital status) Profession Level of education Level of income
Lifestyle data	Alcohol and tobacco Anthropometric data
Medical history	Diseases (nature, date of diagnosis, date of recovery) Treatments (nature, start date/stop date) Health events (including hospitalizations) Health exams (nature, date, results)

Regular questionnaires

Patients in the cohort will also be regularly invited to answer specific questionnaires, in function of their diseases and/or treatment.

Multimorbid patients will regularly complete validated tools which are used as outcomes in this trial:

1) Patient reported quality of life using both the SF-36 scale [48] and the PROQOL [49]. The SF-36 is a self administered questionnaire containing 36 items which takes about five minutes to complete. It measures health on eight multi-item dimensions, covering functional status, well being, and overall evaluation of health. It is the most used questionnaire for evaluation of quality of life in trials [50]. It has been validated in primary care settings [48]. The PROQOL is an innovative tool, designed to be answered online and taking advantages of new technologies with branching questions, comparison of the patient score and the population's average scores. It assesses patients concerns in 9 areas: 1) personal relationships; 2) monitoring; 3) emotional

health; 4) money; 5) health behaviors; 6) medicine; 7) getting healthcare; 8) work; 9) physical health.

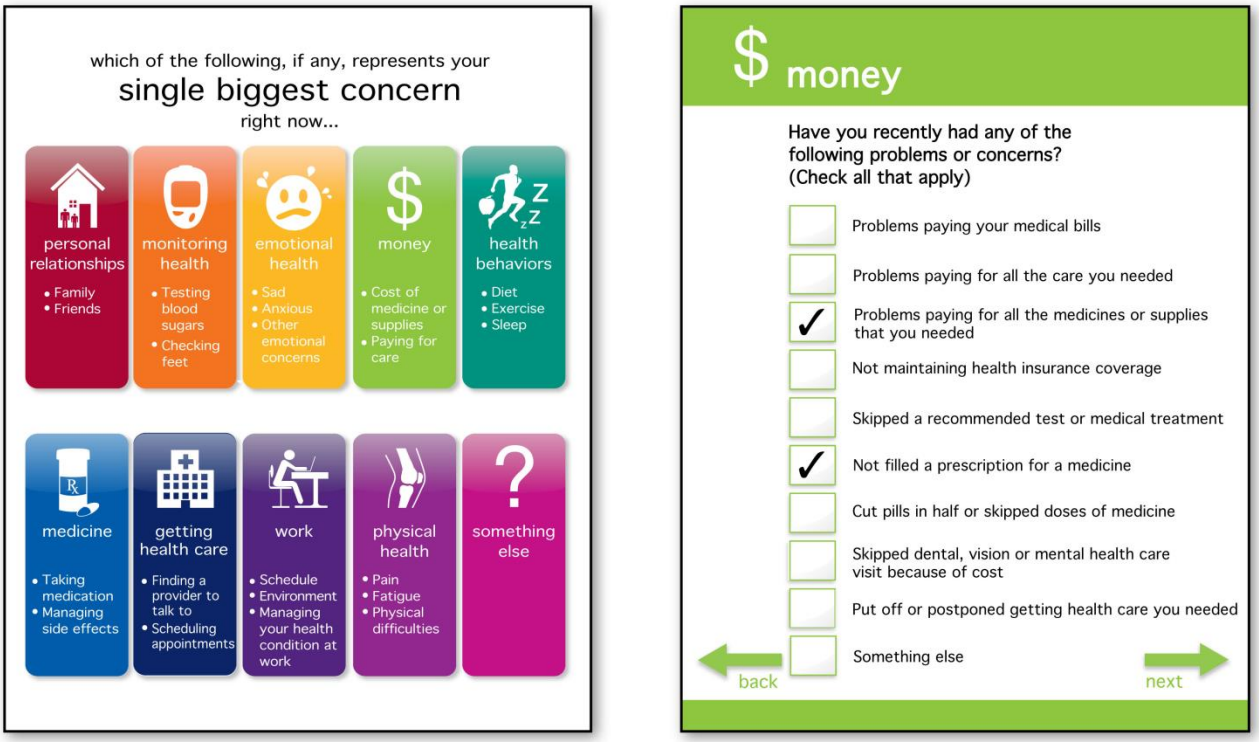


Figure 2 : PROQOL, adapted from [49]

2) Symptoms and function using the MYMOP scale [51]. It is a self administered questionnaire which aims to measure the outcomes that the patient considers the most important which takes about five minutes to complete. The patient chooses one or two symptoms that they consider to be the most important. They also choose an activity of daily living that is limited. These choices are written down in the patient's own words and the patient scores them for severity over the past week on a seven-point scale. Lastly wellbeing is scored on a similar scale. On follow-up questionnaires the wording of the previously chosen items is unchanged. The MYMOP is practical, reliable and sensitive to change. It has been tested and validated in primary care settings [51].

3) Burden of treatment using the TBQ scale [14]. It is a self administered questionnaire containing thirteen items which takes about ten minutes to complete. It evaluates the burden of treatment associated with their treatments, follow-up, administrative tasks and change of life style. It has been developed and validated in primary care settings.
4) Adherence to medication using the Sidorkiewicz questionnaire for adherence [52]. It is a self administered questionnaire asking for medication taking behaviors for each drug taken by a patient. It consists of 5 questions per drug. Responses are analyzed at either the drug level or the patient level.

Healthcare use, mortality using administrative claims

Data on healthcare use and mortality will be obtained by several ways.

- First, participating patients will have the possibility to declare health-related events on their medical chart online using the COMPARE platform whenever they want.
- Second, they will receive by email regular questionnaires to ask them news about their health (in particular the questionnaires will include questions about any hospitalizations or any events that happened).
- Finally, it is planned to match individual data from patients in the cohort with data from with the SNIIR-AM and Cepi-DC databases. The SNIIR-AM databases are the centralized databases of the French universal health insurance system which manages all reimbursements of healthcare to people affiliated to a health insurance scheme in France. It is one the largest database of medical in the general population, covering nearly 65 million persons [53]. This will allow us to obtain reliable information on health events (including hospitalizations) and prescriptions of patients. The Cepi-DC database provides data on vital status and causes of death in France. Connection with

these databases requires specific authorizations. It has already been done in other French e-cohorts such as NUTRINET [46] or CONSTANCE.

5.2.3. Progress of the e-cohort

The COMPARE project is ongoing. The platform, allowing patient recruitment and follow-up, is currently being developed and will become fully operational in October 2016. Pre-recruitment of patients will begin in November 2015 using a simplified version of the platform allowing for registration only.

5.3. Trial population

Following the cmRCT design, we will select all eligible participants in the COMPARE cohort. Besides criteria from the cohort, we will select:

- Multimorbid patients, defined as patients who have ≥ 3 chronic conditions. Indeed, although multimorbidity is defined as patients with more than two chronic conditions, this definition may lack specificity because of the high proportion of patients involved [54]. Some authors argued that using more than three disease entities would likely identify patients with greater health needs and would therefore be more useful to clinicians [55]. Chronic conditions are self reported by patients and defined by conditions requiring healthcare for at least 6 months.
- With moderate or high burden of treatment, as defined by a Treatment Burden Questionnaire (TBQ) score > 15. As stated earlier, the TBQ is a valid and reliable instrument assessing the burden of treatment globally [14]. Cut-off was determined in a previous study involving 502 French patients with chronic conditions, using

hierarchical ascendant classification. This cut-off allowed identification of patients who had no problems and didn't require specific help with their care.

5.4. Randomization and allocation concealment

A randomization list will be generated by the statistician not involved in the conduct of the trial, using a block randomization procedure with randomly permuted block size. Use of a block randomization ensures similar numbers of patients in the treatment groups. Randomization will be centralized using the COMPARE platform and thus will be completely separate from patients and physicians participating in the study ensuring allocation concealment.

5.5. Blinding

Due to the nature of the intervention, patients and physicians cannot be blinded from the study intervention. Blinding of participants is intended to minimize demoralization bias and ascertainment bias. Demoralization bias is avoided in this trial by using the cmRCT design [43, 56]. It is not possible to avoid ascertainment bias in this trial. However, this would not strongly impact the trial's primary outcome results (number of days of hospitalization) because it is unlikely that patients or physicians avoid hospitalization and/or reduce the number of hospitalization days, by simply knowing the intervention and randomization. Although the outcome could be influenced by the patient and/or physician, it is objectively measured.

5.6. Intervention

Our objective is to develop an intervention that is generalizable. In order to do that, we will focus on:

- Its *costs*. Stakeholders are making decisions among alternative care approaches based on the cost of interventions as well as on clinical effectiveness. There is no use to develop complex and costly interventions if they are not fundable afterwards. We want to create an effective intervention as "low cost" as possible.
- Its *standardization*. We want clinicians and patients to be able to reliably implement the intervention if it is effective, and other researchers to replicate or build on our research findings.
- Its *specificity to certain population or settings*. We want to create an intervention that may be applied to broad populations, to maximize its relevance.

5.6.1. Conception of the intervention

As presented earlier, we plan to create an intelligent internet platform to promote communication between patients and physicians around problems arising with management of multimorbidity (i.e. burden of treatment, adherence to treatment, etc.). This would be called the "virtual case manager intervention".

The intervention will be developed by a group of experts from different areas: general practitioners, hospital specialists caring chronic conditions (e.g. diabetes, arthritis, etc.), IT specialists and patients that can be considered as experts of their disease and methodologists with experience in patient reported outcome measures and elaboration of decision aids.

Conception of the intervention will be based on: 1) identification of mismatch between patients and physicians views in management of multimorbidity and; 2) creation of a behavioral change intervention for physicians and patients to tackle the identified mismatch.

Identification of mismatch between patients' and physicians' views in the management of multimorbidity

In order to build an intervention to optimize patient- and physician- discussions, it is necessary that key mismatches in their views of management of multimorbidity are considered. In order to achieve this goal, we will analyze how patients and physicians experience the management of multimorbidity using the "Walk Through" method. The Walk Through method has been developed in the industry to understand how processes work or do not work [57]. It involves: 1) the development of a character based on the process under; 2) completion of each step of the process as though one were the character created; and 3) think about what the experience feels like from that character's perspective.

We will perform Walk Through experiments to identify problems encountered by patients with >3 chronic conditions with their routine healthcare (i.e. during regular follow-up, outside of exacerbation). A working group of patients, methodologists and clinicians will analyze data from the Walk Through experiments in the light of the taxonomy of the burden of treatment [6] to the gaps between patients and physicians' views of patients and physicians.

Creation of a behavioral change intervention for physicians and patients

We want design an intervention to empower patients and modify how they and their physicians manage multimorbidity. According the behavior system, a behavior change intervention may only be effective if it provides capability, opportunity and motivation for change [58]. We can safely hypothesize that both physicians and patients are *motivated* to improve care management.

For physicians:

- *Capability* and *opportunity* to change management of multimorbidity are mainly limited by time during consultations (consultations' mean duration is approximately 16-18 minutes [39]) and lack of training to discuss about burden of treatment and/or adherence to treatment in a reliable fashion during consultations.

For patients:

- *Capability* is mainly limited by their skills to talk to their physicians about their problems. When informing patients about their disease or treatment, doctors usually define medical information objectively (type of disease, its stage, type of treatment) while patients usually define it in terms of personal relevance (will I fully recover? how much pain will I have?). As a result, the physician may feel he has given precise and relevant information, the patient on the other hand may feel unsatisfied [59].
- *Opportunity* may be limited by the fact that patients may often be unaware that most medical decisions in medicine are not clearly cut [60] and that optimal solutions are found by shared decision between patients and physicians. Patients may not initiate discussions with their physicians about problems they could have with their care because of fear of judgment.

We want to develop an intervention that may tackle the aforementioned problems while saving the physician's time.

The intervention will be designed from: 1) the Walk Through experiments presented before, 2) our experience on the burden of treatment [6, 14, 36] and; 3) participation in several meetings with patients and clinicians.

One solution could be the use of pre-consultation assessments of multimorbidity management using reliable and reproducible tools allowing physicians to use their consultation time to focus on finding solutions.

Component of behavior change	Why it could be limited for physicians	Why it could be limited for patients	What our intervention offers
Capability	Time Training in assessing multimorbidity management problems in a reliable fashion during consultations	Skills to talk with their physicians	Preconsultation assessements will save physicians' time Tips for patients to discuss with their physicians
Opportunity	Patients usually consult physicians for one or multiple other problems: physicians do not have the opportunity to focus on management of multimorbidity	Patients may ignore that medical decisions are not clearly cut and do not focus on management of multimorbidity during consultations	Create the opportunity by inviting patients to visit physicians for specific management of multimorbidity

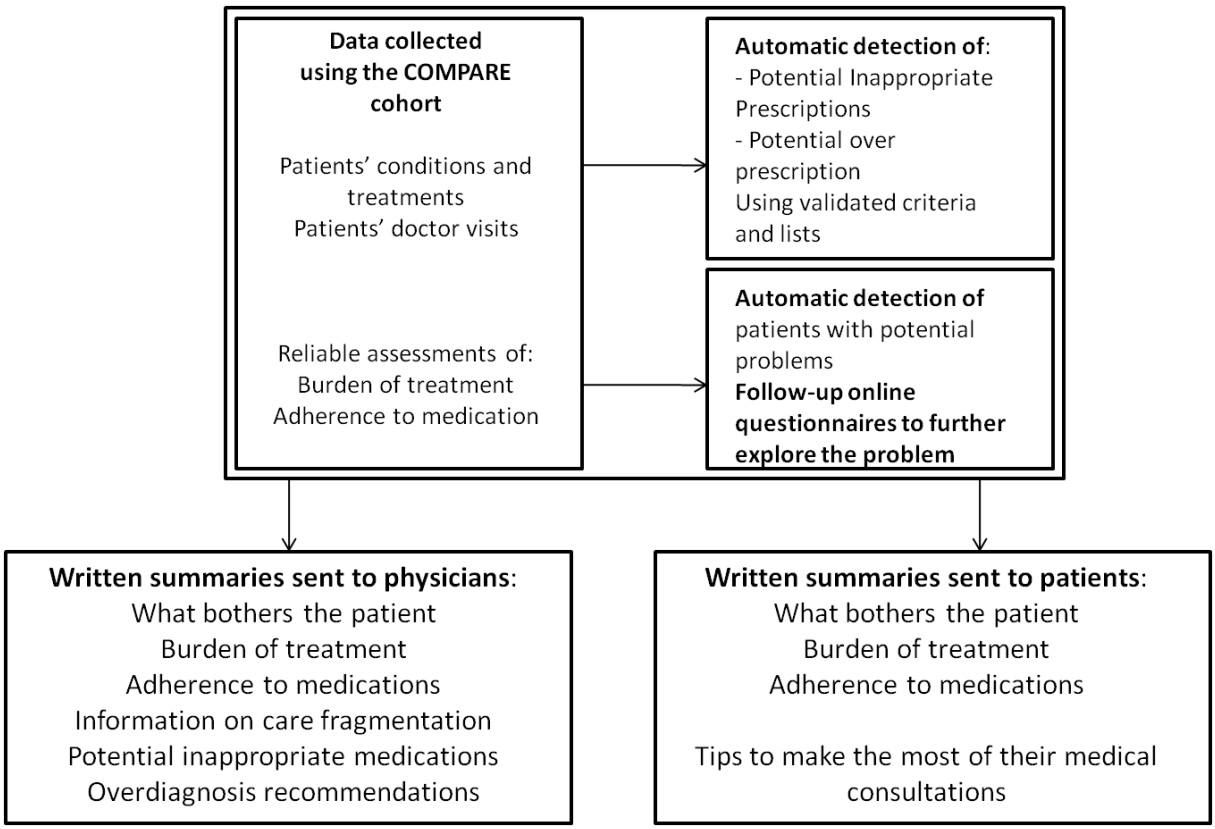
5.6.2. Draft of the intervention

We draft here a tentative for the intervention providing the main principles for the virtual case manager intervention. Final intervention will be refined during the first phase of the trial with the help of patients and experts. We want to develop an "intelligent" internet platform that:

1) Uses data entered by patients on the COMPARE cohort about cornerstones of multimorbidity (burden of treatment, adherence to medication, detection potential inappropriate medications and avoidable overtreatment prescriptions).
2) Automatically analyses the data to detect patients with potential problems

3) Automatically provides patients and physicians reliable pre-consultations assessments of the management of multimorbidity

We think that this may result in a change in physicians' management of multimorbidity with a more individualized approach for patients and lead to deprescribing, reduced workload and burden of treatment.



Data collected using the COMPARE cohort

The virtual case manager will analyze data collected on the COMPARE cohort platform and use reliable validated criteria to automatically identify problems. It will especially collect information on:

- Burden of treatment using the Treatment Burden Questionnaire (TBQ)
- Conditions and medications taken by patients using structured forms
- Adherence to these medication using the Sidorkiewicz questionnaire (SQ)

- Healthcare resources (doctor visits, tests, exams, etc.) using structured forms

Automatic detection of potential problems

The virtual case manager will automatically detect patients with potential problems regarding their:

- Burden of treatment. The virtual case manager will automatically identify patients with an overall burden of treatment > 15 or a specific burden of treatment (defined as the answer to a given item) >5. These patients will receive a follow-up questionnaire using open-ended questions, elaborated and tested in a previous study [6], to further explore their problems. These questions will detect barriers of care (e.g. problems in transportation and distance from healthcare, insurance, literacy, informal care (children, elder), family support, financial problems, beliefs about treatment or condition, problems in scheduling care, interaction with professional or social life, etc. [6]).
- Adherence to medication. The virtual case manager will automatically identify patients with an adherence level for a given medication equal or lower than "Poor drug adherence" (as defined by drug holidays during 2-3 days and/or missing doses ≥ once a week) [52]. These patients will receive a follow-up questionnaire to detect reasons for non adherence (intentional/non intentional).
- Potential inappropriate medications. The virtual case manager will review treatments entered by patients on the online platform and consider potentially inappropriate medications (PIP) using either the PRescribing Optimally in Middle-aged People's Treatments(PROMPT) tool [61] or the START/STOPP version 2 tool [62], depending on the patient's age. The PROMPT tool consists of 22 criteria for potential

inappropriate use of medication which may be used for patients aged 45 to 64 years old. We will extend its use for patients younger than 45 years old. The START/STOPP tool consists of 114 criteria which may be used for patients > 64 years old.

- Potential overtreatment. The virtual case manager will select all recommendations from the "Choosing wisely" initiative [63] that apply to the patient according to his conditions or treatments. Choosing wisely recommendations have been developed by American Scientific Societies based on evidence published in the literature. Each scientific society published a list of exams or procedures that are commonly prescribed without benefits for patients. These lists will be adapted to the French context prior to the beginning of the study.

Preparation of written summaries for patients and physicians

Automatic analyses from the virtual case manager will be validated by a physician and a part-time pharmacist before they are summarized and sent to patients and physicians.

The physician's main role will be to assess: 1) conformity of patients' answers to follow-up questionnaires on burden of treatment and adherence to medication with the TBQ and SQ scores. He will use a the double interview technique (i.e. read patients answers to open ended questions and assess discrepancies between what is expressed by the patient and his answers to the questionnaire) to identify "false positive" answers [64]; and 2) to assess clarity and wording of the summaries sent to physicians and patients. If needed, he may add comments to the summaries sent. We estimate that the physician may review approximately 90 summaries during a 7-hour day.

A pharmacist (part-time) will ensure that potential pharmacy issues identified using PROMPT or START/STOPP are adequate. If needed, he may add comments to the summaries sent. We estimate that the pharmacist will be able to review about 100 prescriptions a day (about 14 prescriptions per hour). Thus, he will need approximately 20 days to review all prescriptions from patients. After the initial evaluation, the pharmacist will regularly check if patients had changes in their prescriptions using the COMPARE cohort tool.

Mode of delivery

Automatic assessments using the compare cohort will be summarized into concise documents. Document may be available online and will be sent to patients and physicians.

The objective of this pre-consultation summary is to provide the patient and his physician with a reliable and shared base for discussion during their consultations. Thus, the written summary will function like a decision aid. Final form of the written summary will be defined with the help of patients and physicians, using the user-centered approach used in the SHARE-IT project [32].

Document's attractiveness will be ensured by use of a professional designer. Tests with patients; communication specialists and physicians will ensure the document's clarity, wording and usefulness.

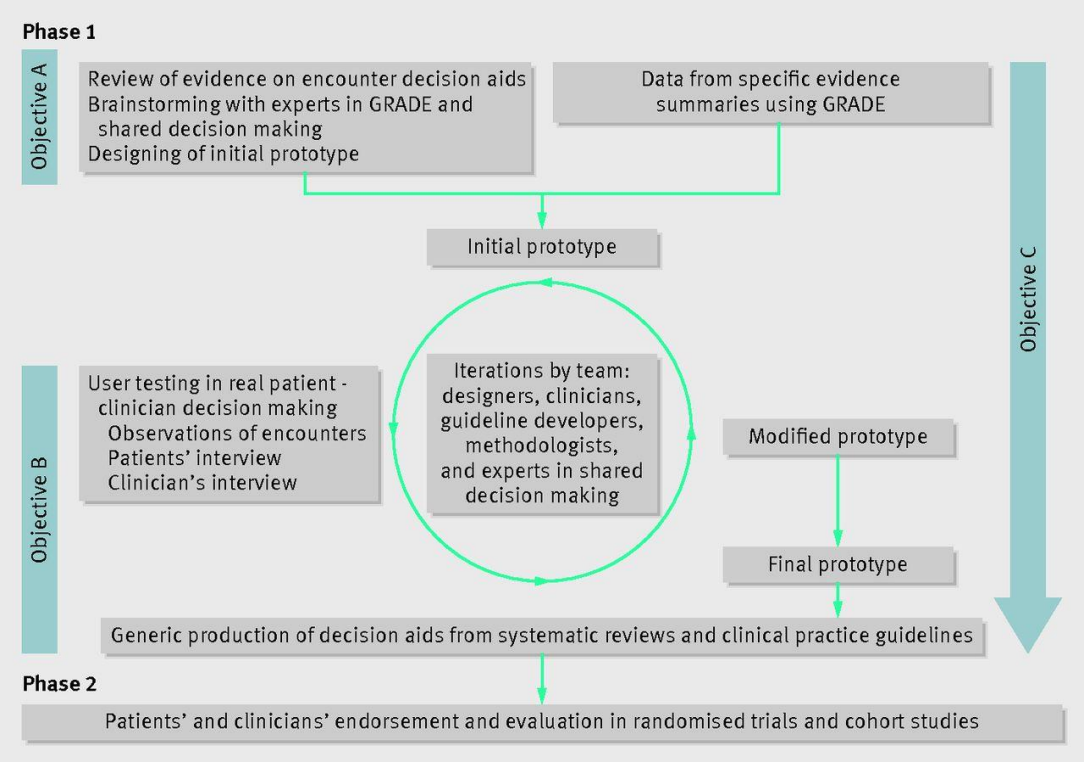


Figure 3 Conception of the written summary's form, adapted from [32]

We plan to have a document as concise as possible while retaining all relevant information. Information presented on the document could have a common base for shared discussion between patients and physicians and specific parts for each (e.g. patients could have specific tips or check lists of documents he should bring during consultations, while the physician could have summaries of recommendations applicable to the patient.)

We describe here an example of the information that could appear on the document:

- Patient's identity and his support system (informal and/or formal caregivers and the role they play)
- The patient's biggest concerns, adapted from the PROQOL questionnaire

- Results from the TBQ score and the summary of the potential subsequent(s) questionnaires(s). Similarly to the answers from the PROQOL, TBQ scores could be put into context by presenting the mean scores of patients in the population
- All medications taken by patients with information on:
    - Adherence: Results the SQ score and summary of the potential subsequent(s) questionnaires(s).
    - Potential inappropriateness according to the PROMPT or START/STOPP criteria
- Number of medical appointments the patient had during the last 4 months in the form of a time line.
- "Choosing Wisely" recommendations applicable to the patient because of his conditions or treatments.
- Physician and/or pharmacist's comment
- Tips to make the most of their doctor visits, adapted from the NHS document [65]

We present here a draft of what the written summary could look like. Both design and content will change according to meetings with patients, experts and designers.

Patient's biggest concerns

Patient X, 62 years old
Case manager's identity

Primary diagnosis
Rheumatoid arthritis

Support system
Wife
Daughter
Friend

Burden of treatment

32/150

Previous score (date): 47/150
Similar patients mean score: 25/150

Patient declares having problems to arrange transportations for medical visits.

Patient feels that he is a burden to his wife and daughter.

Medications

Name	Estimated Adherence	Potential inappropriate prescriptions*
Methotrexate	High	No
Folic acid	Moderate (1-2 omission of doses/month)	No
Fluindione	Good (Schedule errors)	No
Fluticasone + Salmeterol	Poor (Drug holidays >3 days/month + omission of at least 1 dose per week)	No
Salbutamol	NA	No
Aspirin	Good (Schedule errors)	Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation without a clear indication for aspirin (no added benefit from aspirin)

Infrastructure

The virtual case manager will use a software specifically developed for the study. This software functions as a module for the COMPARE project (i.e. it will add new functions to those existing on the platform). It is to be noted that this software may be adapted and serve future studies using the COMPARE project.

Final specifications of the software are not yet defined. We present here a list of potential features:

- Daily connect on the platform and list all patients in the study.
- Real time identification of patients with conditions, treatments or questionnaires updated.
- Automatic calculation of patients' scores from questionnaires.
- Automatic sending of follow-up questionnaires to patients with potential burden of treatment and/or adherence problems
- Automatic identification of potential inappropriate prescriptions using PROMPT and START/STOPP list.
- Automatic identification of Choosing Wisely recommendations applicable to the patient's conditions and treatments
- Automatic elaboration of written summaries to be validated by the physician.

Final specifications of the tool are not yet defined. It is to be noted that this tool will be developed as a module for the COMPARE project and may serve future studies.

Duration of intervention

Patients will be invited to answer the PROQOL, MYMOP, TBQ and SQ questionnaires as often as desired. Automatic assessments of questionnaire scores and written summaries will be sent to physicians every 4 months during a 2 year period.

5.7. Control

Control will receive usual care from their physicians.

5.8. Outcomes

Outcomes	Description	Time of assessment
Primary outcome		
Number of days hospitalized during the study period	Assessed using the SNIIR-AM data. Comparison between end values in the 2 groups	At 2 years
Secondary outcomes		
Number of hospital admissions	Includes all hospital admissions assessed using the SNIIR-AM data Comparison between end values in the 2 groups	At 2 years
Index of care fragmentation	Calculated as an Herfindahl-Hirschman concentration index of the cumulated numbers of visits and exams, using the SNIIR-AM data Comparison between end values in the 2 groups	At 2 years
Quality of life	Assessed using SF-36 Comparison between end values and changes from baseline in the 2 groups	Every 4 months
Symptoms and function	Assessed using the MYMOP Comparison between end values and changes from baseline in the 2 groups	Every 4 months
Burden of treatment	Assessed using the TBQ Comparison between end values and changes from baseline in the 2 groups	Every 4 months
Adherence to medication	Assessed using Sidorkiewicz questionnaire Comparison between end values in the 2 groups	Every 4 months
Patients' evaluation of their primary care physician's	Assessed using Safran's questions Comparison between end values in the 2 groups	At 2 years

5.8.1. Primary outcome

Primary outcome will be the total number of days hospitalized during the study period at 2 years. We chose this criterion because it provides information on both the number of hospitalization and the severity of the patients' status during those hospitalizations. There is evidence of an excess of hospital use that may be preventable by optimization of ambulatory care [3]. This is especially true for complex patients recently discharged from hospital which have often high preventable readmission rates [66].

- We consider that any hospital use (except outpatient consultation) lasts at least 1 day (for example, we consider that a patient entering the ER department in the morning and leaving in the afternoon has a total number of days hospitalized of 1). Hospital outpatient consultations do not count as hospital consultations.
- We consider that, for hospital stays lasting more than 1 day, the number of days hospitalized is the difference between the entry date and the discharge day (for example, entering the hospital in the evening and leaving the next morning represents a total number of days hospitalized of 2).

We will assess these numbers in, different ways.

- We will ask patients to report every 4 months whether they were hospitalized, for which reasons, and the number of days hospitalized. They will be invited to send the hospitalization reports.
- We will also use data from the SNIIR-AM databases which combine the information on all healthcare services uses by patients covered by the French universal health insurance system (National Health Insurance Fund for Salaried Workers (CNAMTS)) and the information from hospital databases (Program for the medical of information systems (PMSI)). It is planned as part of the COMPARE project to get an authorization to obtain these data.

We will compare the total number of days hospitalized between the two study arms at 2 years (24 months).

5.8.2. Secondary outcomes

Secondary outcomes will be:

1) The number of hospital admissions at 2 years. This will include both planned, unplanned hospitalizations and emergency department visits. Hospital outpatient consultations do not count as hospital admissions. Outcome data will be collected using data from the SNIIR-AM and by contacting patients (or other individuals designated as the contacts) by telephone or e-mail. We will compare the total number of admissions between the two study arms at 2 years (24 months).
2) Index of care fragmentation at 2 years. Index of care fragmentation will be calculated using a Herfindahl-Hirschman concentration index (HHI) [67] of the cumulated number of visits and exams, at 2 years. The HHI is commonly used in economic studies of industrial structure and is usually a measure of the degree to which a market is concentrated among a small number of companies. We will use the HHI to measure the degree to which a patient's care is concentrated among a set of providers. For that, we will construct an HHI for each patient by first calculating each provider's share of the total number of visits associated with that patient based on SNIIRAM data over the 2 year period. We will then sum the squares of the visits' shares across all providers that a patient sees. A patient's care would be considered to be the least fragmented when all care was from a single provider (HHI of 1). A patient's care would be considered maximally fragmented if their care was equally divided across a large number of providers (HHI approaching zero as the number of provider increases). We will compare the end value of the care fragmentation index between the 2 arms, at 2 years (24 months).
3) Quality of life. We will assess quality of life using the SF-36 scale [48]. It is a self administered questionnaire containing 36 items which takes about five minutes to complete. It measures health on eight multi-item dimensions, covering functional status, well being and overall evaluation of health. It is the most used questionnaire for

evaluation of quality of life in trials [50]. It has been validated in primary care settings [48]. We will compare the mean end value of quality of life between each group at 4, 8, 12, 16 and 24 months.

4) Symptoms and function. We will assess symptoms and function using the MYMOP scale [51]. It is a self administered questionnaire which aims to measure the outcomes that the patient considers the most important which takes about five minutes to complete. The patient chooses one or two symptoms that they consider to be the most important. They also choose an activity of daily living that is limited. These choices are written down in the patient's own words and the patient scores them for severity over the past week on a seven-point scale. Lastly wellbeing is scored on a similar scale. On follow-up questionnaires the wording of the previously chosen items is unchanged. The MYMOP is practical, reliable and sensitive to change. It has been tested and validated in primary care settings [51]. We will compare both the mean end value and change from baseline of the MYMOP between each group at 4, 8, 12, 16 and 24 months.
5) Burden of treatment. We will assess the burden of treatment using the TBQ scale [14]. It is a self administered questionnaire containing 13 items which takes about ten minutes to complete. It evaluates the burden of treatment associated with. It has been developed and validated in primary care settings. We will compare both the mean end value and change from baseline of the TBQ between each group at 4, 8, 12, 16 and 24 months.
6) Adherence to medication. We will assess medication adherence using the Sidorkiewicz questionnaire for adherence. It is a self administered questionnaire asking for medication taking behaviors for each drug taken by a patient. It consists of 5 questions per drug. Responses are analyzed at either the drug level or the patient

level. We will compare the number of patients with poor adherence or lower according to the Sidorkiewicz questionnaire, between each group at 4, 8, 12, 16 and 24 months.

7) Patients' primary care experiences. We will assess patients' primary care experiences by using four questions used by Safran et al. [40], which assess patients' perceptions of their physicians' knowledge of: 1) their medical history; 2) their responsibilities at home or at work; 3) what worries them the most; and 4) them as a person. Participants answer these questions with 6 steps Likert scales ranging from Excellent to Very poor. We will compare the number of patients answering that their experience is fair or lower, between each group, at 24 months.

6. Data management

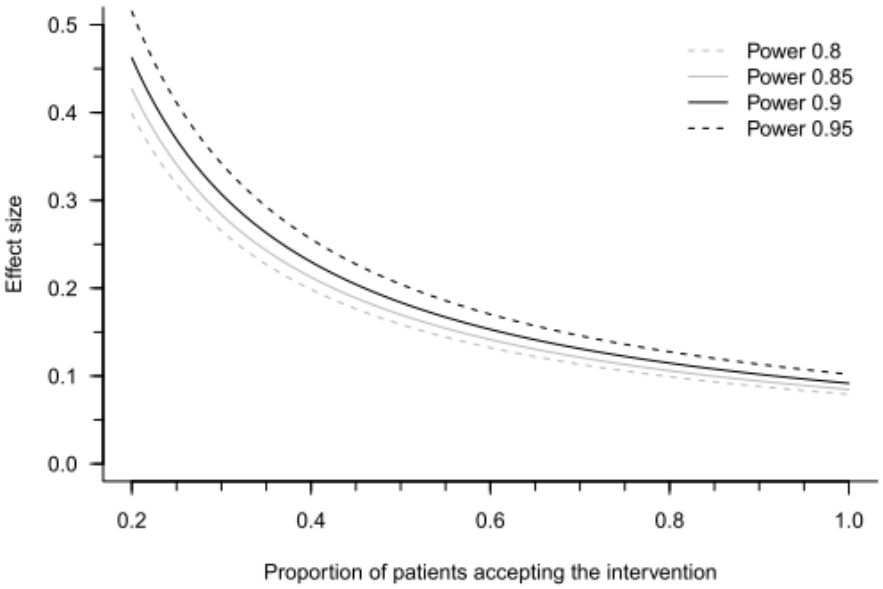
All data from the study will be directly collected using the COMPARE internet platform. By using an internet tool to collect data we will be able to use of automatic checks and prompts to get more detailed answers [68]. The e-cohort was designed in order to provide researchers structured data directly analyzable. Thus data management costs will be very low.

7. Statistical Analyses

7.1. Sample size

For the present study, we have planned to recruit 5000 patients with >3 chronic conditions. It is difficult to justify the sample size calculated by simply applying usual formulas. Indeed, the sample size would depend on 1) the meaningful treatment effect that one wants to detect; 2) the variance of the outcome (number of days hospitalized); and 3) the fraction of patients accepting the intervention in the "offeree group". All these parameters are difficult to estimate a priori.

Instead of using an arbitrary effect size and proportion of patients who would accept the intervention, we preferred to determine a large but attainable sample size and to conduct a power analysis where effect size is estimated for various levels of power and fraction of patients accepting the intervention in the "offeree group".



The AP-HP network manages approximately 5 millions of outpatients. According to estimates from previous studies [2], approximately 42% of patients have at least one chronic condition

(2,100,000 patients) and 15% of patients (750,000) have > 3 chronic conditions. If one patient out of ten participates in the COMPARE project, that would result in approximately 200,000 patients with at least 1 chronic condition and 75000 patients with >3 chronic conditions.

The COMPARE project aims to recruit approximately 50 000 patients in 1 year, of whom approximately 19000 patients are expected to have >3 chronic conditions. As a comparison, another French e-cohort, the NUTRINET-Santé study enrolled 90 000 patients in 1 year. Therefore, we estimate a high feasibility for recruiting 5000 patients with > 3 chronic conditions.

7.2. Analyses

An expanded Statistical Analysis Plan (SAP) will be finalized before the first participant is enrolled. The following is a summary of the planned analyses. Any deviations to be made from this summary plan will be documented in the detailed SAP.

The analysis of the primary outcome will be performed using a Student's test. If the distribution of the data is skewed, a variance stabilizing transformation (e.g. log) will be used. Analyses of secondary outcomes using repeated measures during follow-up will be carried with the use of regression models to adjust for baseline measures, with generalized estimating equations to account for correlation over time.

A potential problem with the cmRCT approach is that significant numbers of patients may refuse to receive the intervention being trialed. An intention to treat analysis could therefore dilute any treatment effects. Relton et al. suggested to use a complier average causal effect (CACE) analysis [69], which provides unbiased estimates of the treatment effect for patients who comply with the protocol.

Thus, all primary analyses will be performed in both intention to treat (ITT) and Complier Average Causal Effect (CACE) basis. For this purpose, it will be assumed that patients decision not to accept the intervention will not affect the outcome [70].

For the ITT analysis, patients will be analyzed according to the treatment arm they were randomized to (i.e. offer or no offer group), even if the participant did not accept the intervention.

7.2.1. Subgroup analysis

We will analyze all outcomes in subgroups defined by:

1) Underprivileged patients. These patients will be identified as those receiving the "Couverture Médicale Universelle" (basic or complementary health insurances adapted for underprivileged French citizens) or the Aide Médicale d'Etat (health and medical emergency insurances adapted for underprivileged non French citizens living in France). Indeed, economic difficulties reduce patients' capacities to perform healthcare.
2) Main chronic conditions described by patients. We will assess intervention efficacy in groups of patients with at least one specific condition (e.g. diabetes, cardiac failure, etc.) or with given sets of conditions.

   Subgroup definitions will be determined by a group of expert (physicians, methodologists) before the enrollment of the first patient.

8. Feasibility of the project

8.1. Feasibility of recruitment

Recruitment will use the COMPARE project. It is a large e-cohort sponsored and funded by the APHP, a network of 39 university hospitals in and around Paris managing yearly 5 million of outpatients and more than one million inpatients. We estimate that there are 2 millions of outpatients consulting for a chronic condition yearly. As part of the COMPARE project, it is planned to recruit 10% of these patients (200 000 patients). For comparison, the NUTRINET study has enrolled nearly 200 000 participants. Given the success of online communities of patients such as PatientsLikeMe in the USA, it is very likely that patients suffering from chronic conditions will be more motivated to enter the cohort to help advance research on their diseases.

8.2. Expertise of the team

Feasibility of this project is also ensured by the high expertise of our working group is composed of:

- Clinicians with experience in the care of chronic conditions, including specialists of management of multimorbidity. Dr Tran and Pr Ravaud are leaders in the development and research on the burden of treatment [6, 14, 36].
- Methodologists with experience in both conduct of trials and management of large cohorts. Pr Ravaud is internationally renowned for his work in the methodology of clinical trials. He was the principal investigator of the ARTIST trial, a pragmatic trial with a highly standardized intervention [71]. He has experience in large cohorts in

rheumatology (e.g. ESPOIR, etc) [72] and is also the principal investigator for the COMPARE project, used for the present study.

- Our team includes researchers with renowned experience in the methodology and design of clinical trials with non pharmacological interventions [73].

8.3. Involvement of primary care researchers

It is to be noted that, among the potential reasons, the "Virtual Ward" did not reduce readmissions in previous studies, was the difficulty for virtual ward team members to communicate with the patients' primary care physicians and/or personal support workers providing care to a patient. To avoid this problem, our study will be backed up by the Department of General Medicine (DMG) of Paris Diderot University, which is one of the biggest departments of general medicine in France. Researchers from our group have experience in large RCTs in primary care [74].

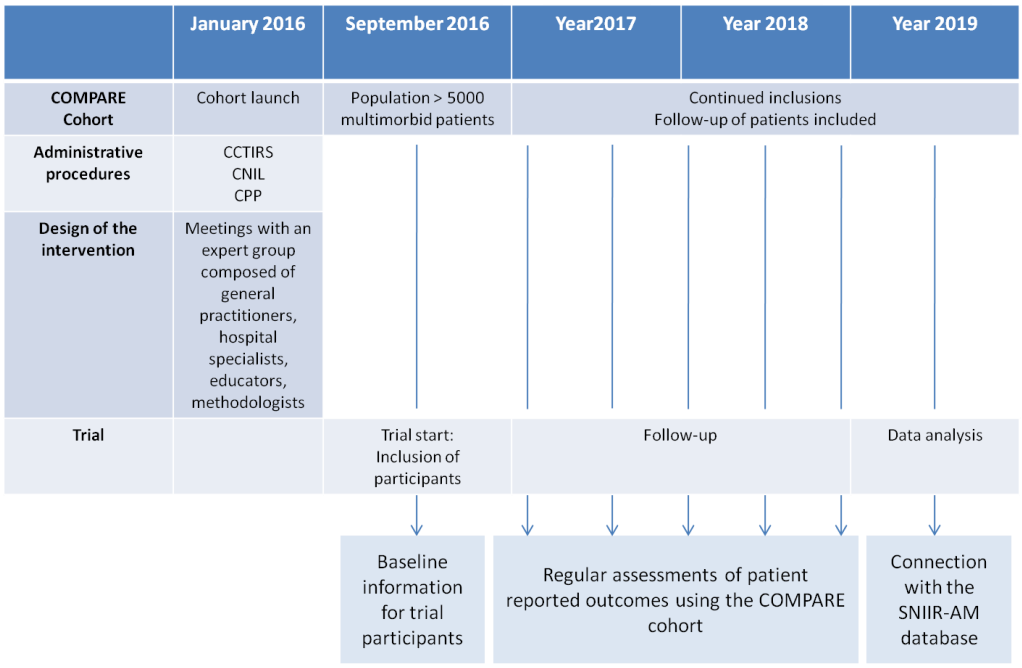
8.4. Use of new technologies

In this study, we will use the COMPARE cohort and develop an intervention using an internet platform to help patients and physicians in the management of multimorbidity. It improves the study feasibility for 2 reasons: 1) it allows recruitment of geographically distant patients easily by enabling patients (especially those with chronic illnesses to answer from their homes); and 2) it fastens data collection and management.

Today, it is estimated that 80% of patients go on the internet for health information [75]. In a near future, almost all people in developed countries will have an access to computers and Internet. A recent paper published in the JAMA estimated that there would be approximately 50 billion mobile devices connected via the Internet in 2020 [76]. We acknowledge that our study population may be biased in favor of patients who are more computer literate. However,

as tomorrow's population is likely to have basic computer literacy, we can hypothesize that an internet based intervention will be relevant to all future patients with chronic conditions.

9. Trial agenda



10. Perspectives

The intervention aims at evaluating a new organization of care for patients with chronic conditions to assess and reduce patients' burden of treatment.

Our project took into account previous trials on management of multimorbidity and is one of the few to focus on: 1) patients with multimorbidity without focusing on particular sets of conditions; 2) patient important outcomes (i.e. hospital use, hospital admission rates, etc.) and 3) an intervention that will easily generalizable, as it does not require extensive changes in current management of patients. Indeed, our intervention focuses on use of new technologies with use of an intelligent internet platform where patients may prepare their consultations

with their physicians by completing validated questionnaires about problems not usually discussed in depth during consultation [37].

This project may have important consequences on patients' quality of life and adherence to treatments. This may reduce acute complications and lead to improved outcomes, including decreased mortality and morbidity. It may also help physicians to better organize health care management for these patients that are particularly difficult to manage and decrease their workload.

From a public health perspective, there is an urgent need to improve the organization of health care system to face the challenge of multimorbidity. Our current system is still relying on multiple consultations with different physicians, each focusing on a given problem. Thus, management of interactions between conditions and treatments are rarely considered in medical decision making [42]. In this trial, we want to assess the efficacy of an intervention where the patient and a case manager team will collect data on topics not usually covered by physicians on overall management of patients' care. We have hypothesized that, this intervention may help reduce unnecessary care and reduce drug-disease or drug-drug interactions.

On a methodological level, this study will be of the first cmRCT to use an e-cohort. The combination of an e-cohort and the cmRCT design offer a way to optimize the way clinical research is performed: patients are recruited only once in the cohort, outcomes are collected over time and can be adapted to incorporate questionnaires adapted to new research questions and the only costs left are those of the interventions in cmRCT.

11. Ethical and legal considerations

11.1. Information and consent

Consent at enrolment in the cohort

All patients in the COMPARE cohort will:

- Have to consult the explicative note concerning the frame and objectives of the study before participating in the cohort.
- Be informed concerning the process of the project and the confidentiality of the data. The data collected will be secured and encrypted. The access to personal data will only be granted to administrator and researchers allowed to access those data during their study. IT specialists will be in charge of the management and the securitisation of data. All the laws concerning the protection of data will of course be respected.
- Provide electronic consent for general participation to the cohort: the inclusion questionnaires will have to be filled and the participant will be regularly contacted for the updated of his/her record and new questionnaires concerning their disease.
- Provide consent for access of medico-administrative data. This consent allows researchers to access health-related data of the patients taken from the medico-administrative databases. Patients will therefore be explained why they need to securely provide their social security number.
- Provide consent for contact by the research of the e-cohort team for trials inside or outside the e-cohort. This consent is for accepting to be contacted. Providing consent does not imply accepting to participate in any trial. Participation in a trial requires specific consent.

Consent at enrollment in the trial

In accordance with Article L1122-1-1 of the French Public Health Code, no biomedical research can be carried out on a person without free and informed consent, after the person has been given the information specified in the aforementioned article.

In this study, following the cmRCT design, information will be given to patients in a similar manner to routine healthcare (i.e. non disclosure to non offerees policy).

- Eligible patients will not be told about treatments they would not be offered. They will not be given information that their treatment is decided by chance before randomization [43, 44].
- Post randomization, patients offered to participate in the intervention will be told that they were randomly selected to the "offer group". They will provide free and informed consent, electronically before the inclusion of the subject in the research. The information sheet and a copy of the consent form, dated using the COMPARE platform, will be printable and sent electronically to patients prior to his or her participation in the research.
- The subject will be granted a reflection period (of 1 month) between the time when the subject receives the information and the time when he or she signs the consent form.

We will obtain approval from an Institutional Review Board before the beginning of the study.

Subject prohibited from participating in another research

There is no exclusion period for this study. Thus, the subject may participate in any other biomedical research protocols during his or her participation of this study.

Compensation for subjects

No compensation will be provided for the patients for the inconveniences relating to the research.

11.2. Scientific committee

The scientific committee is composed of:

Pr Philippe Ravaud, Dr Viet-Thi Tran, Dr Agnes Dechartres, Pr. Hercberg Serge, Pr. Boitard Christian, Pr. Aubert Jean-Pierre, Pr. Cohen Ariel, Pr. Legrain Sylvie and one patient

The scientific committee will oversee all scientific aspects of the study from conception of the scientific project to publication of results. It will be in charge of analysing and validating the demands to access data from the study.

11.3. Security of data

Confidentiality

The positive endorsements of the following committees will be obtained:

- Qualification Committee (IRB)
- Consultative Committee on the processing of the information concerning research in the field of health (CCTIRS in French)
- French Data Protection Authority (CNIL in French)

Data entries

Patients will directly enter their questionnaires on the COMPARE platform using a secured account protected by an ID user and a password. The COMPARE platform will be hosted on an IT server secured by a certificate and a firewall.

Access to data

All information concerning participants will be confidential and the anonymity of the participant will be ensured. The access of data concerning the participants and researchers and the internet website will be crypted by SSL (https) and only available with a user name and a password.

A limited number of people will be allowed to have access to nominative data for a logistics and scientific purpose only.

Publication of data

Data published will be anonymous.

Destruction of data

Data of participants will be stored for 15 years and then destroyed.

11.4. Legal obligations

The positive endorsements of the following committees will be obtained:

- Qualification Committee (IRB)
- Consultative Committee on the processing of the information concerning research in the field of health (CCTIRS in French)
- French Data Protection Authority (CNIL in French)

Opinion from the Comité de Protection des Personnes (CPP)

We will obtain for this biomedical research, prior to starting the research, the favourable opinion of the appropriate CPP, within the scope of its authority and in accordance with the legislative and regulatory provisions in force.

Modifications to the research

Any substantial modification to the protocol will be sent to the sponsors for approval. After approval is given, the sponsor will obtain, prior to starting the research, a favorable opinion from the CPP.

The information sheet and the consent form can be revised if necessary; in particular if there is a substantial modification to the research or if adverse reactions occur.

Final research report

The final biomedical research report referred to in Article R1123-60 of the French Public Health Code is drawn up and signed by the sponsor and the investigator. A summary of the report written according to the competent authority's reference plan will need to be sent to the competent authority and ethical review board within one year after the end of the research, meaning the end of the participation of the last research subject.

Data sharing

We plan to share data from this project to academic research teams. Whatever the demand, a protocol justifying the objectives of the research, the scientific interest of the demand, the targeted population, the criteria, the nature of the data needed and funding will have to be given.

Any demand will be studied on this very basis by the scientific committee.

11.5. Funding

Besides the actual grant proposal (PHRC 2015), this study is not expected to receive any additional funding.

11.6. Insurance

For the duration of the research, the Sponsor will take out an insurance policy covering the sponsor's own civil liability as well as the civil liability of all the doctors involved in carrying out the research. The sponsor will also provide full compensation for all harmful consequences of the research for the research subjects and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any agent. The act of a third party or the voluntary withdrawal of the person who initially consented to participate in the research cannot be invoked against the aforementioned compensation.

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