Development of a cross-cultural instrument to assess the burden of treatment for patients with multiple chronic conditions allowing comparison between different languages and different countries (BOT)

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Table of contents

Summary

The burden of treatment represents the “work of being a patient”, coping with all prescriptions from his or her doctors. This work could affect adherence to care and outcomes, independently from illnesses. In a previous study, in France, we developed and validated a tool to assess burden of treatment among patients with multiple chronic conditions. However, in order to measure the burden of treatment in different settings, countries and languages, our instrument has to be adapted to reflect which aspects of healthcare present the greatest challenges to patients in different countries.

Classic approach involves multiple complex and time-consuming translations which have many pitfalls. To solve this problem, we will rethink how questionnaires are adapted in different languages, by directly generating cross-cultural items.

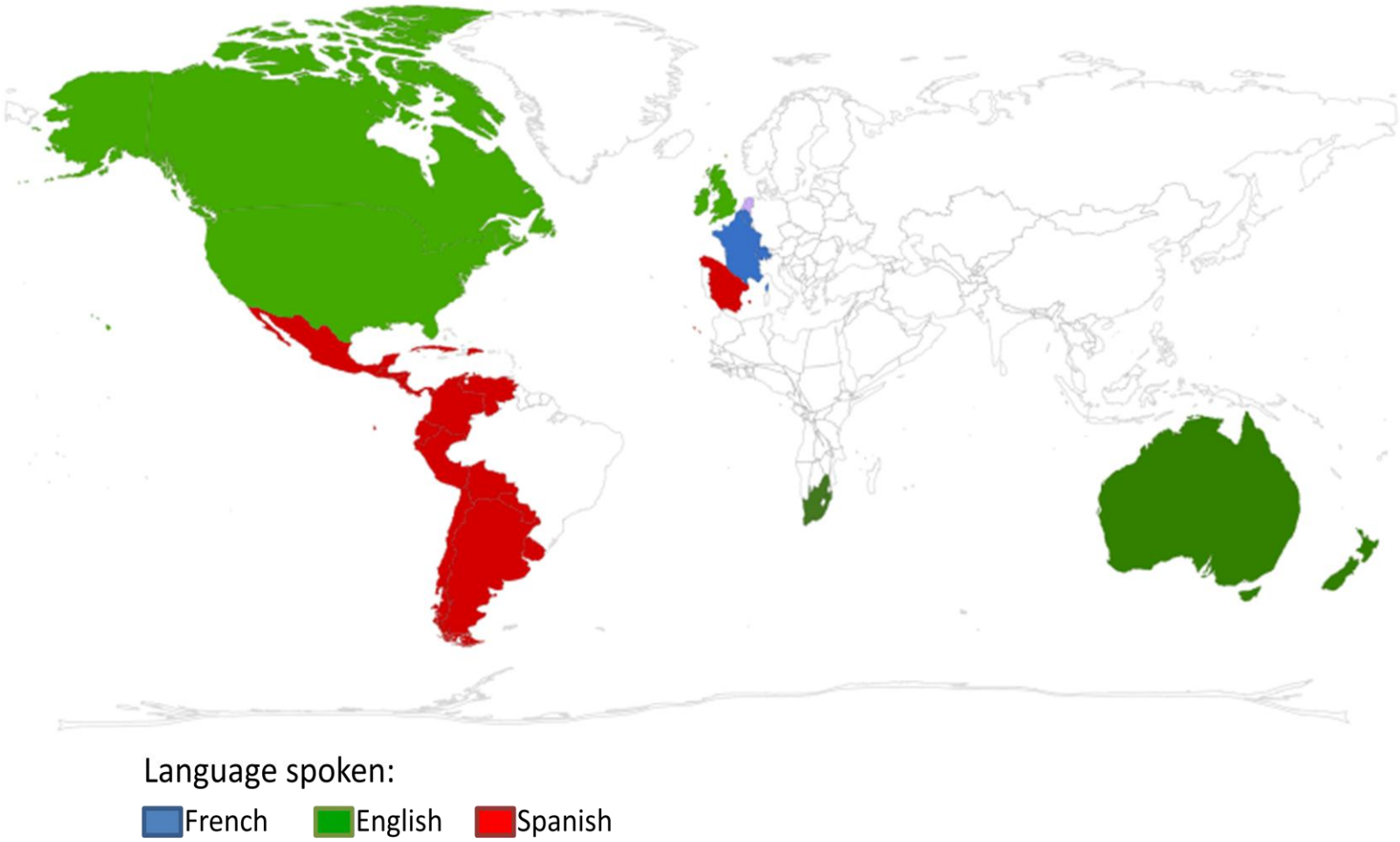
We will ask patients from different countries and languages about the burden of treatment during an international qualitative study using an internet tool. Their words and thoughts will be used to understand the determinants of the burden of treatment in each country. From these findings, we will design the first instrument to assess the burden of treatment allowing comparison between countries.

Participating countries (not definitive)

France
Belgium
Luxembourg
Switzerland
United States of America
Canada
United Kingdom
Australia and New Zealand
Spain
Argentina
Peru
Uruguay

Study languages

French
English
Spanish



Countries are colored according to spoken language and size of countries is proportional to internet penetration (as reported in Internet World Stats 2012).

1. Background

1.1. Burden of treatment

The burden of treatment can be defined as the impact of the "work of being a patient" on his functioning and well-being. It takes into account: taking medicines, drug management, self-monitoring, visits to the doctor, laboratory tests and lifestyle changes [1]. For example: patients with type 2 diabetes could spend 143 minutes per day taking care of themselves if they followed every doctors' orders. The burden of treatment is associated with adherence to therapeutic care independently of diseases [2].

This burden of treatment grows when patients have multiple conditions. Approximately 40% of patients have one or more chronic condition and, independently of age, most patients with any chronic condition have multiple conditions [3-5]. These patients must cope with increasingly complex treatment regimens [6]. For example, a physician following extant clinical practice guidelines could prescribe up to 12 medications for a patient with osteoporosis, osteoarthritis, type 2 diabetes mellitus, hypertension, and chronic obstructive pulmonary disease [7].

The burden of treatment is a relatively new concept to physicians [1] which is not often shared in depth during consultations [8]. Doctors are often not aware of the difficulties patients have taking care of themselves [9].

Therefore, they need reliable tools to identify overburdened patients in daily practice. These tools could serve to begin discussions with patients and encourage shared decision making. Moreover, these tools could be used to design therapeutic strategies and clinical guidelines that are both efficient and acceptable for patients.

According to a recent systematic review of patient reported measures of burden of treatment, many instruments assess burden of treatment for specific conditions or in specific treatment contexts, but none has been developed to assess this burden globally across multiple chronic diseases [10]. Because the burden of treatment increases from the combination of chronic diseases, an instrument that assesses it globally is more appropriate to help clinicians and researchers develop effective therapeutic programs that minimize the treatment workload patients face.

We have previously developed an instrument to measure the burden of treatment for patients with chronic conditions in France [9]. Items were derived from a literature review and qualitative semi-structured interviews with patients in France. The instrument was then validated in a sample of patients with chronic conditions recruited in hospitals and general practitioner clinics in France.

The burden of treatment does not only depend on patients' investment of time and effort in following their doctors' advice [11], but also on the care setting [1]. To measure and compare the burden of treatment in different countries, languages and settings, our instrument has to be adapted to take into account how similarities or differences between healthcare settings affect patients.

Research involving different populations from different cultural groups has specific methodological problems. It is not enough to translate a questionnaire literally; items must remain comprehensible without changing their original meaning, new items could arise in different contexts whereas some other might be irrelevant. Without such adaptation, validity of research could be challenged and comparison between countries and settings biased.

1.2. "Classic" cross-cultural adaptation and its pitfalls

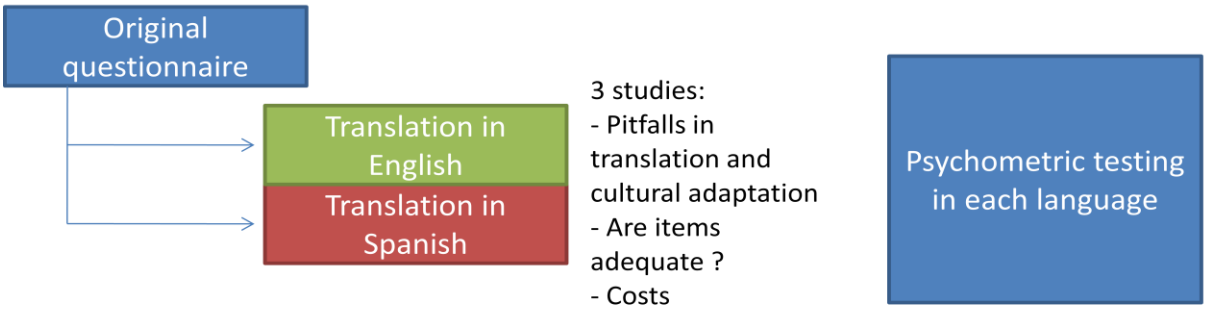
Translating and adapting a questionnaire for use in a different country than the one it was originally created is a long and complex process [12, 13]. A review of 12 sets of guidelines available for translation and cultural adaptation highlighted the traditional steps for cross cultural adaption of a questionnaire [14]: 1) Preparation, that is investigating the concepts of the instrument; 2) Forward translation, by at least two different qualified translators, some of them should be aware of the objectives and concepts underlying the original questionnaire while the others should not ; 3) Reconciliation, that is comparing and merging the forward translations; 4) Back translation and back translation review; 5) Harmonization, comparing the back translations to highlight discrepancies between the original and its derivative translations; 6) Cognitive debriefing, testing the instrument on a small group of relevant patients to test alternative wording and to check understanding, interpretation and cultural relevance of the translation and 7) Finalization, proofreading and final report.

Adaptation of a questionnaire using this method is arduous and requires a considerable time investment involving qualified professional translators working closely with medical specialists [15]. For example, translators have to be careful about terms which could be interpreted differently in different cultures or linguistically equivalent items which could be harder to understand after translation. In addition, it has been shown that authors use different methodologies to perform similar tasks or use different terminology to refer to the same aspects of the translation process [14].

Moreover, the objective of these translation studies is to verify "linguistic equivalence", meaning that original questionnaires and translations can be translated back and forth. Using this methodology to compare participants from different settings is therefore based on the assumption that there will be no difference in the concept across cultures and that rigorous translation will be sufficient to ensure cross culturally comparable questionnaires. This is often false as original items were determined in specific settings or populations. Other items and themes could arise in different settings [16, 17]: for example, if our questionnaire had been adapted using the classic approach with forward and backward translation, it would not have appraised the difference of burden of treatment that could arise in different settings. For example, in France, financial burden of treatment did not appear as a major problem for patients because our National Health Insurance program guarantees healthcare free of charge for patients with chronic conditions.

Besides methodological problems, adaptation of a questionnaire for multinational use is also costly, as researchers need to perform a separate study for each translation and setting. Because some populations might share the same language but could differ in cultural context, the work of adapting a specific questionnaire for use in different languages could result in a significant amount of research time and resource. To avoid a waste of time and ressources, we need to rethink the methodology of the development of cross cultural instruments.

Figure 1: Classic methods to obtain a questionnaire usable in different settings and languages and their limits. 3 studies are needed (one for developing the instrument (in French) and at least 2 to translate it in English and Spanish. Each version should then be psychometrically tested for validity (ie: "Does the instrument measures what it is intended to?") and reliability (ie: "How precise is the measure obtained?").

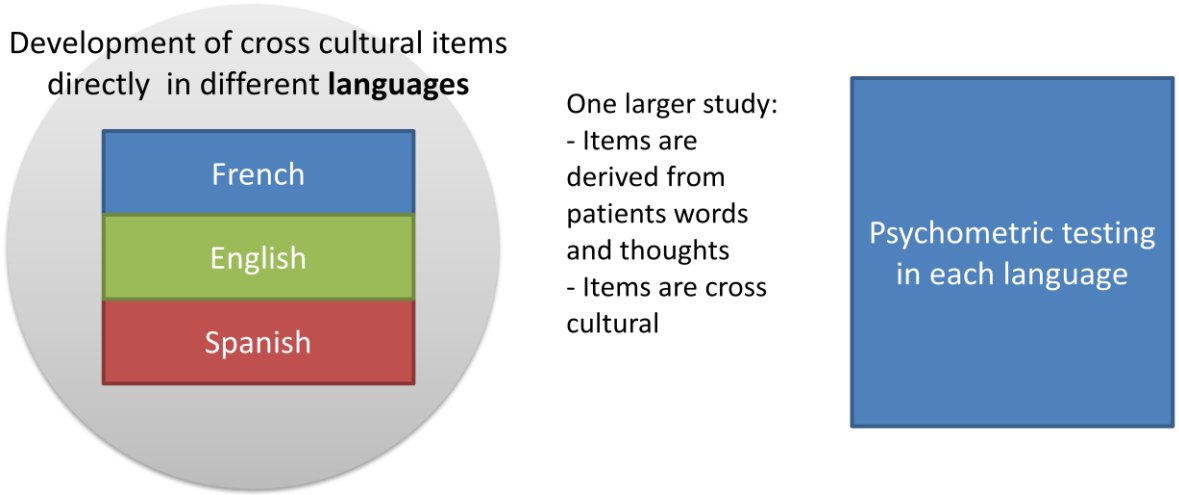


1.3. Changing the paradigm for the development of cross cultural tools

We believe that pitfalls occurring during translation and assessment of cultural equivalence in different countries and cultures could be avoided if the items of an instrument were developed simultaneously in different settings and countries, which would give equal weight to the norm and values of the different cultures involved [17].

To develop a cross-cultural instrument usable in different settings, countries and languages, we will collect patients' views about burden of treatment, in each setting. Patients' words will be used to directly generate the questionnaire items in multiple languages, instead of relying on translation of patients' words from another country. In addition, this method will help to ensure no missing items for a specific setting. The resulting instrument will be designed and assessed by the patients it is intended to help.

Figure 2: Cross cultural development of items in multiple languages.



Some studies have been conducted this way [18-21]. However, simultaneous generation of items in multiple countries was often very complex and expensive as it involved the participation of researchers in each country. As a matter of fact, until recently, it was impossible to recruit a large number of geographically distant patients without exorbitant study costs.

With increasing acceptability and ongoing technological advances, this can be done today using the internet [22]. About 74% of adults in the USA use the internet (and among these internet users, 80% have looked online for information about health topics) [23]. Participation in web surveys in very variable and dependent of the sampling and design [24], globally similar to participation in pen-and-paper. However literature on this topic is rather scarce. This combination of very low cost access to large number of patients and instantaneous responses gives us the opportunity to gain insight on the experiences of patients directly from them in order to develop cross-cultural and cross-linguistic questionnaires, rather than focusing on translations.

1.4. Choice of study languages

The burden of treatment depends on the context of health services provided at a structural/political level (lack of coverage in health, social policies, and health insurance, etc.) but also on the cultural context (representation of healthcare and illness, family structure,

etc.). Development of a cross-cultural instrument usable in different countries should take place in countries with similar level of healthcare services.

Therefore, we selected 3 languages (English, French and Spanish) because they were the official main languages for 50% of the 30 countries with the highest level of healthcare services (classification based on disability-adjusted life expectancy, speed of service, protection of privacy, quality of amenities and fair financial contribution [25]).

1.5. Conceptual framework and definitions

Burden of treatment is defined as 'the work of being a patient' dealing with increasingly complex treatment regimens. It is a subjective measure that relates to the impact on patients' functioning and well being of all the things they have to do to take care of their health: doctor visits, medical tests, treatment management, lifestyle changes, etc. [1].

Eton D. *et al.* identified 3 broad themes of burden of treatment: 1) work patients must do to take care of their health; 2) problem-focused strategies to facilitate self-care; and 3) factors that exacerbate perceived burden: challenges with taking medication, emotional problems with others, role and activity limitations, financial challenges, confusion about medical information, and systemic obstacles [26]. Gallacher K. *et al.* found similar themes with patients with chronic heart failure: 1) learning about treatments and their consequences; 2) engaging with others; 3) adhering to treatment and lifestyle changes and 4) monitoring their treatments [11]. Similar themes were found during a systematic review of qualitative studies about the burden of treatment in stroke patients [27].

In a review of existing questionnaires on quality of life, Sav A. *et al.* found 4 dimensions of burden of treatment: undesirable physical effects of treatment (side effects), the economic burden imposed by treatment (financial burden), time required to obtain, administer and manage treatment (time burden) and the psychosocial aspects of burden including the impact on family and lifestyle (personal burden) [28].

2. Objectives

2.1. Main objective

The main objective of the study is to develop an instrument to assess the burden of treatment usable across any disease or treatment context, allowing comparison between different countries (of similar economic levels) and languages (French, English and Spanish).

2.2. Secondary objectives

Secondary objectives are:

- Description of the determinants of the burden of treatment across different settings, countries, conditions and treatment types.
- Validation of a new method of cross cultural item development that relies on collecting patients' words in each different language and setting, using an internet tool instead of relying on complex translation methods. This method should strengthen the validity of comparison of questionnaire data between different countries and languages.

2.3. Originality and innovative aspects of the study

Innovative aspects of this study may include:

- Its objectives. It will be the first instrument to assess the burden of treatment in multiple countries and settings, allowing comparison between countries. This tool will be used in clinical research to design therapeutic strategies that take into account the burden of treatment, as well as in clinical practice to help physicians identify overburdened patients.

- Its design. We will directly collect patients' views on burden of treatment in different countries, and use their words to create the items of our instrument. This international

qualitative study will use an internet platform to assess the views of large number of geographically distant patients at a low cost. The resulting instrument will be designed and assessed by the patients it is intended to help.

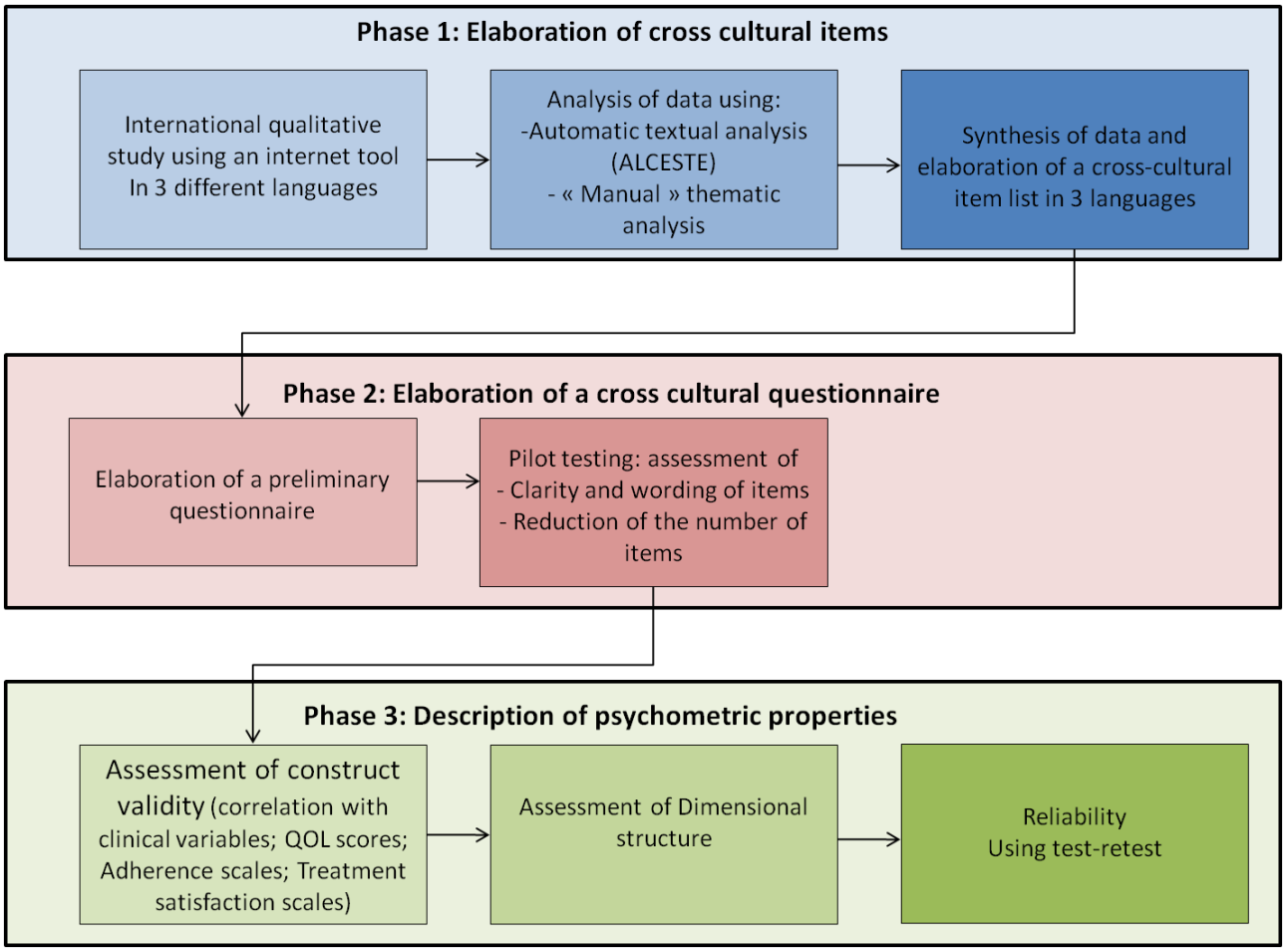
- Its impact. This will be the first study to explore the determinants of the burden of treatment across any disease or treatment context directly from patients' views. During the internet study, we will be able to identify which factors from patients, treatment, follow-up or care delivery system contribute the most to the burden of treatment in each country, disease or treatment context.

3. Methods

Development will consist of 3 phases:

- First, we will elaborate cross cultural items about the burden of treatment. In order to do so, we will create extensive list of burdens patients face when taking care of themselves during an international qualitative study using an internet tool. This list of burdens will serve to define the items of an instrument to measure the burden of treatment. They will therefore be derived directly from patients' experiences
- Second, we will create a cross cultural instrument from this list of items
- Finally, we will assess the measurement properties of obtained instrument

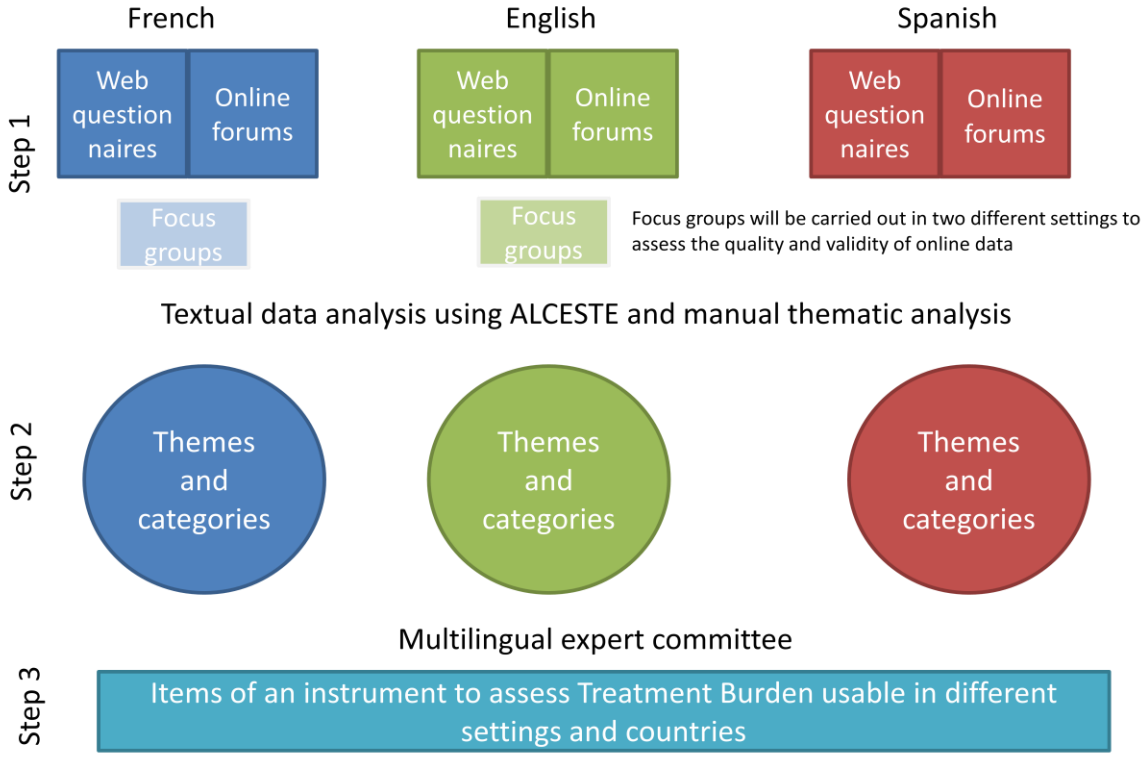
Figure 3: Outline of the research project phases.



Phase 1: Elaboration of a list of cross cultural items about the burden of treatment

Elaboration of an item list for an instrument to assess the burden of treatment usable across different settings, countries and languages will take 3 steps: 1) Creation of an extensive list of burdens patients face when taking care of themselves during a qualitative study involving different patient sources, countries and languages; 2) analysis of obtained data and definition of themes and categories which reflect what represents a burden to patients when they take care of their health, in each country and language and 3) synthesis of the data and elaboration of a list of potential cross cultural items.

Figure 4. Outline of phase 1



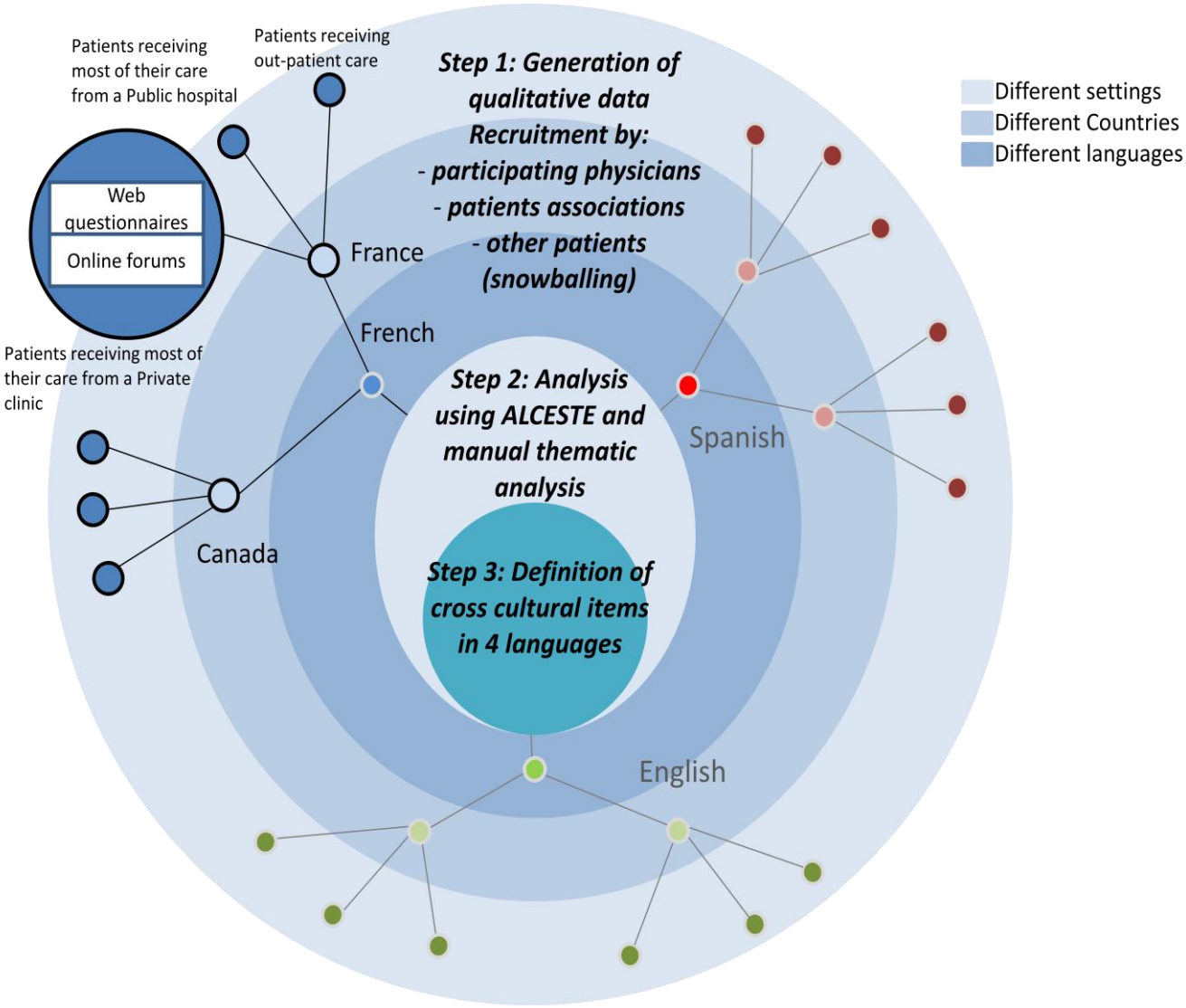


Figure 5. Outline of phase 1

3.1. Step 1: Qualitative study about the different burdens of treatment patients face in different settings, countries and languages

Qualitative data will be obtained using an internet tool, translated in 3 languages (French, English and Spanish).
To assess the quality of data obtained over the internet and complete it if necessary, we will also carry out "traditional" focus groups in predetermined settings.

3.1.1. Description of the internet tool

The internet tool is an open-access website. It will consist of: 1) an open access part describing the concept of burden of treatment, the objectives and requisite for our study; 2) a part dedicated to registered patients consisting of a standardized web questionnaire using open-ended questions and 3) an online discussion board used as an online focus group.

To participate in the study, patients will register on our website using their email and a password. This will ensure that they only answer the questionnaire once and that they can complete it over multiple points in time.

Benefits of using an internet tool include: 1) access to great number of patients and instantaneous responses 2) use of automatic checks and prompts to get more detailed answers and 3) lower costs [22]. Limits of such a tool are concerns about non response, reliability and validity of obtained data. Concerning non-response bias, it is considered similar as for paper questionnaires [24]. Lack of direct interaction with participants could hinder the quality of responses. However, we believe that this could be compensated by increasing the number of participants in our study. Finally, answering the questionnaire at home, without the presence of an investigator could reinforce honest responses and reduce social desirability bias.

3.1.2. Technical aspects and security

Our website will be developed using Hypertext Markup Language version 5 (html) and Hypertext Preprocessor (php) language. The number of pages, page layout, and navigation

will be assessed a convenient sample of selected physicians and patients and will respect HON code.

The internet website will be hosted by OVH (http://www.ovh.com/fr/index.xml). Communications will be secured with SSL encryption.

Data will be stored on 3 separate databases: 1) identification of participants (that is: email and their password); 2) answers to the questionnaire and 3) forum content. Link between databases will use an internal identification number. Only the webmaster will be able to link identification (ie: email address) and questionnaire answers.

Critical data (for example participants' passwords) will be encrypted with HMAC protocol using a secret key.

Website will be developed for maximum performance using latest generation web browsers and will be tested using Microsoft IE7+, Mozilla Firefox and Google Chrome.

This study was approved by the CNIL (n° 1679914).

3.1.3. Participants recruitment

Patients will be included in the study by: 1) participating physicians; 2) patients associations (**appendix 1**) and 3) spontaneous participation from internet users who would come across the website. Patients who have already been invited will be able to invite their relatives and friends in the study, using a snowball sampling method [29]. Snowball sampling entails identifying an initial number of patients experiencing burden of treatment who will serve as 'seeds' to help identify other individuals experiencing the same problem. These individuals in turn are asked to provide information on other patients and the process continues.

The drawback of snowball sampling is the risk that the sample obtained is not representative of the larger population from which it was drawn from. In snowball sampling, sample composition is determined by the choice of initial 'seeds'. In practice, the method is biased towards favoring more cooperative individuals who are part of large networks as opposed to randomly chosen subjects [30]. To mitigate this risk, we will combine this method with other recruitment methods (directly by physicians, using patients associations, through advertising on specialized websites, etc.). In addition, as we will gather qualitative data, we are more interested by the diversity of patients and opinions than representativeness.

3.1.4. Number of participants

In qualitative studies, sample size is determined by saturation of data. In marketing research, it is admitted that 30 participants should ensure less than 5% chances of missing a particular perception [31]. We intend to recruit approximately 600 participants to be able to assess themes and aspects of burden of treatment in different subgroups of patients in each different study language.

Inclusion criteria are:

- Adults, above 18 years old
- Having at least one chronic condition (defined as a condition requiring healthcare for at least 6 months)

Informed consent will be obtained for all patients participating in the study. The study has been approved by the Institutional Review Board (IRB) of Hospital Cochin in France (N° 00001072) and examined by the IRB of Mayo Clinic (Rochester, MN, USA).

3.1.5. Web questionnaire

Web questionnaire (**appendix 2**) will consist of 5 parts:

1) Demographic data on respondents: sex, age, marital status, presence of an informal caregiver, level of education, country of residence and healthcare setting (defined as where the participant receives most of their healthcare).
2) Clinical data on their disease and treatment workload: main chronic conditions (as a list based on morbidities recommended as core for any multimorbidity measure [32]), drug intake (number of tablets, injections and intakes per day); medical follow-up (number of different physicians seen by a patient, medical appointments per month, care setting where they receive most of their healthcare (in-patient care or out-patient care); and daily time spent on self-care (time needed for organization or self monitoring).

   Besides gathering data, these questions are also used to familiarize the participant with the questionnaire's functioning before proceeding with more open-ended questions [33].

3) One first broad open-ended question, at the beginning of the questionnaire, to apprehend their views on burden of treatment.

> **The following question is crucial for our study. Take your time and feel free to write anything that crosses your mind. All comments will be taken into account.**
> Being a patient with chronic conditions can sometimes require a lot of time and effort, for example:
> - Visits to the doctor, arranging appointments...
> - Lab tests and other exams...
> - Taking medications everyday without forgetting them
> - Not being able to eat certain foods or drink alcohol, having to quit smoking...
>
> **All these things are very important but, sometimes, are also difficult to manage in everyday life.**
>
> **Think about what you do to take care of your health, and how this investment of time and effort can interfere with your everyday life.**

4) 16 open ended questions based on the 13 items composing the burden of treatment questionnaire (TBQ) [9]. TBQ items have been developed after a literature review and qualitative patient interviews in France. They assess burden of treatment associated with taking medicines, self-surveillance, laboratory tests, doctor visits, need for organization, administrative tasks, following advice on diet and physical exercise, and social impact of the treatment. To these 13 items, we added 2 items derived from findings of the literature about financial problems associated to the treatment and the burden related to transport [27, 34], and 1 item derived from expert opinions about the burden associated with their healthcare system (for example: health insurance coverage, access to care close to home, hospital organization, health policy ...).
5) Lastly, we will search for other aspects of burden of treatment that could have an impact on patients' quality of life but have been assessed in the previous questions.

To strengthen the quality of answers, prompts will encourage participants to answer all questions.

Items used to design the open-ended questions included in the web questionnaire
Taste, shape or size of tablets and/or the discomfort caused by injections (for example, pain, bleeding, scars)
The number medication intake per day
Remembering to take medication and/or managing treatment when away from home (for example: sorting out pillboxes)
Having to follow specific procedures when taking medications (for example, taking it at a specific time of the day or meal, not being able to do certain things after taking them like driving or lying down) or storing them (in their fridge…)
Having to visit doctors for medicine refills and having to go repeatedly to the pharmacy to pick up the refills
Frequency, time spent and/or inconvenience of lab tests and other exams (for example: scans, X-rays, blood tests…)
Frequency, time spent and/or inconvenience of self-monitoring (for example, measuring blood sugar levels or blood pressure)
Frequency, time spent and/or waiting time of doctor visits.
Fitting in appointments, doctor visits and lab tests and arranging transportation (for example: scheduling and waiting for public transportation or ambulances, having to ask someone for a ride, parking problems…).
Sorting out the paperwork from health insurance companies, welfare organizations, hospitals and/or social care (for example: complete forms or administrative tasks to schedule appointments or to get reimbursements)
The financial burden associated with your healthcare (for example: out of pocket expenses or expenses not covered by insurance)
Having to follow a specific diet, not being able to eat certain foods, to drink alcohol or having to quit smoking
Following doctors advice to regularly practice physical exercise?
How difficult it is to integrate healthcare needs in your family, social or professional life (for example: having to rely on others to do certain things, feeling uncomfortable taking medications in public, reconciling healthcare needs with culture and beliefs...)
"Looking after my health reminds me of my conditions"
We wish to understand the difficulties patients face so they can take care of themselves. Some of these difficulties may be related to the health system (health insurance coverage, access to care close to home, hospital organization, health policy ...)

Data entered by the participant will be checked for range and consistency [24]: for example, if a participant enters more daily medication inputs than the total number of pills/puffs/tablets and injections, the program will ask him to check for possible errors.

At the end of the questionnaire, participants will be invited to visit the online discussion board to discuss burden of treatment with other study participants and invite relatives or friends to participate in the study (snowball recruiting method).

The time required to complete the questionnaire is about 20 minutes.

Questionnaire wording, acceptability and richness of answers will be assessed during a pilot study. A convenient sample of 50 inpatients and outpatients in France, with different conditions and treatments will answer a pen and paper version of the questionnaire in French. Similarly, 5 to 10 patients abroad will assess the English and Spanish versions of the questionnaire.

3.1.6. Online forum

We will use an online discussion board as a focus group. Online forums represent a valid alternative to traditional face-to face focus groups [35, 36] by acting as asynchronous focus groups (participants do not need to be connected simultaneously to participate).

Advantages of online focus groups are: 1) new recruitment opportunities for those who would not have participated in traditional focus groups (for example: ill or disabled participants, housebound respondents, marginalized populations, geographically isolated people and busy participants); 2) better contributions from online participants: unconstrained by place and time, they contribute to the discussion at their leisure, choose their time and place to answer questions, allowing more time for reflection; 3) cost and time-savings for researchers due to the automatic and accurate capture of the discussion data.

Findings from traditional and online focus groups are comparable [37, 38]. In addition, online data collection offers better self-disclosure (i.e.: 'not revealing personal information to others') than traditional focus groups because of the anonymity. Perceived privacy reinforces honest and thoughtful responses and may reduce the social desirability bias (in traditional focus group discussions, participants may feel silenced or intimidated by more talkative people). Therefore, online focus groups could lead to greater equality in participation than traditional groups, providing a more balanced impression of all viewpoints expressed in the discussion.
Each participant will log onto the forums using a unique login name and password and will be able to view all posts. Investigators will be identified and will act as moderators establishing a creative, non-inhibiting environment for discussion by asking questions, encouraging discussions, and prompting participants to elaborate and clarify their thoughts.

3.1.7. Conduct of step 1

- *Development of open-ended questions for the Web questionnaire* (V-TT, BF and PR). Open-ended questions will be developed based on: 1) a literature review; 2) TBQ items and 3) physician opinions.
- *Feasibility study*. Questionnaire wording, acceptability and answers quality and completeness will be assessed using a convenient sample of 50 inpatients and outpatients. In addition, about 5 to 10 patients abroad will assess the English and Spanish versions of the questionnaire. (V-TT, BF and PR).
- *Development of the internet tool*. (V-TT).
- *Pretest of the internet tool with 10 patients and health professionals, in France* (V-TT, BF and PR).
- *Translation of the internet tool English and Spanish* (Investigators and translators fluent in the 3 languages).
- *Collection of online data:* - Participating physicians in selected countries and patient associations will invite patients in the study by simply providing them with the website address.
- The website will also be advertised on several specialized healthcare related websites and in social media (Facebook ®, Twitter ®).
- At the end of the online questionnaire, every participant will be prompted to invite relatives or friends with chronic conditions (snowballing recruitment).

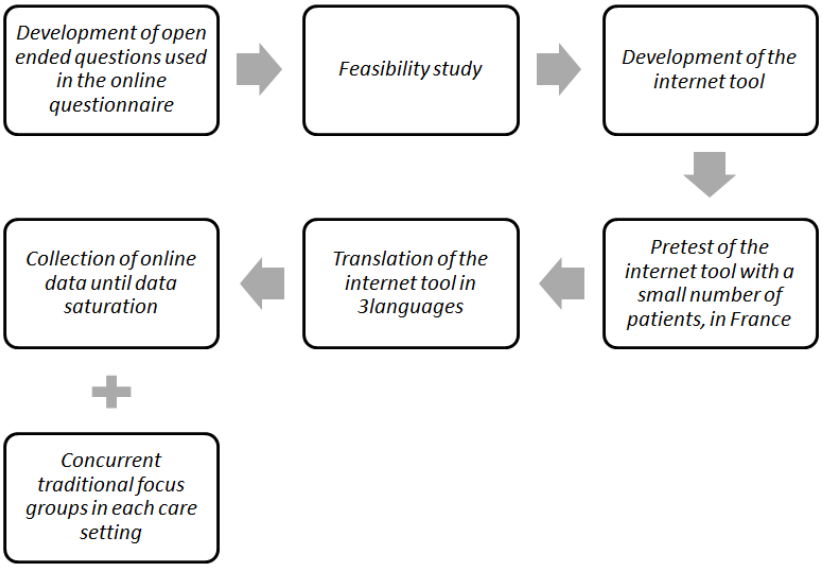


Figure 6: Conduct of step 1

3.1.8. Validation of quality of online data

To assess the quality of data gathered using our internet tool, we will carry out focus groups in two predetermined countries and settings. These focus groups will be led by a moderator who will direct the discussion and ensure that all of the important issues are discussed.

In each setting, 5 patients, recruited for their diversity will be invited in a focus group where they will talk about: 1) burden of treatment in general; 2) topics derived from the items of the TBQ; and 3) other aspects of healthcare which could impact patients' lives.

A standardized focus group guide will be developed following recommendations [39] and will describe the background, purpose, and expected outcomes of the study as well as information for carrying out the focus groups.

Focus groups will be audio-recorded and transcribed verbatim.

3.2. Step 2: Analysis of qualitative data and definition of themes and categories of burden of treatment in different countries and different languages.

For each language, qualitative data will be analyzed with: 1) textual data analysis using ALCESTE ® software; and 2) 'classic' thematic analysis.

3.2.1. Textual data analysis

Textual data analysis will be carried out using ALCESTE ® software available in English, French and Spanish [40, 41]. ALCESTE ® was developed by the Image society and the CNRS (French national council for scientific research). It incorporates statistical processing to help make sense of large amounts of text very quickly by identifying the word patterns most frequently used by participants. The ALCESTE method consists of 3 steps: 1) identification of meaningful words in the text; 2) fragmentation of the text into small parts called UCE (elementary contextual units) and; 3) Clustering of these UCE using hierarchical descending classification with chi-squared distance method according to their similarity regarding the meaningful words composing them.
Words are therefore grouped by their proximity in the text. Analysis of the obtained classes can reflect the main themes and ideas in large corpus of data [42, 43].

3.2.2. "Classic" thematic analysis

"Classic" thematic analysis will be used to extract meaningful statements from patients' comments and answers and summarize them into themes and categories. Thematic analysis seeks to describe, pinpoint and examine patterns within data [44] using a multistep approach:
1) Lecture of all comments by patients to be familiar with the different difficulties patients could have while taking care of them.
2) Extraction of significant statements that relate to burden of treatment in each questionnaire,
3) Formulation of initial codes (that is reducing statements to their main ideas)
4) Formulation of themes from these codes.
5) Reviewing and renaming of themes

6) Aggregation of similar themes and patterns from different questionnaires into larger categories.

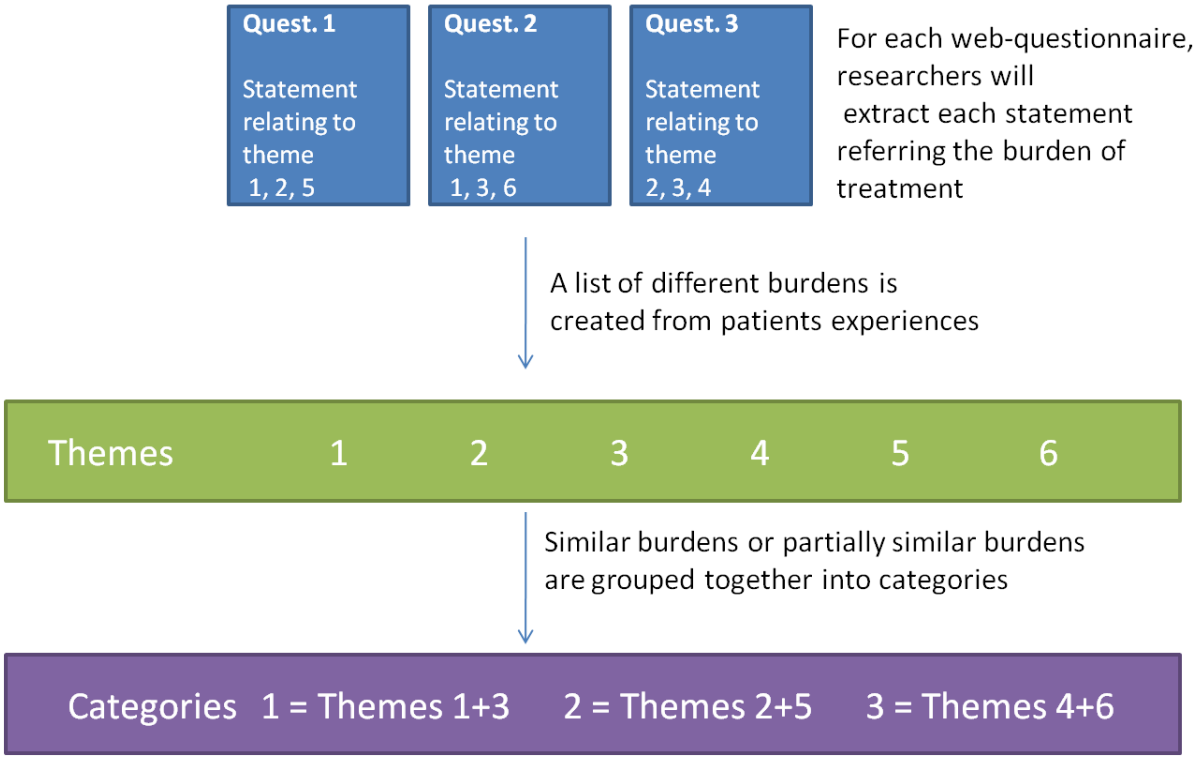


Figure 7: Thematic analysis and formation of themes and categories about the burden of treatment

3.2.3. Conduct of data analysis

For each language, two researchers fluent in the given language (with at least 1 researcher native in the language) will independently perform thematic analysis (coding and extracting themes). They will refine their findings using the classes obtained from automatic textual analysis.

Therefore, they will create for each language an extensive list of themes related to the burdens experienced by patients. This list of themes will be illustrated by meaningful quotes from patients in the 3 different languages.

The investigators will share their findings regularly. Disagreement and inconsistencies arising during the process will be resolved through discussion.

3.3. Step 3: Synthesis of data obtained in different languages

3.3.1. Synthesis using a method derived from meta synthesis of qualitative studies

To synthesize obtained data in different languages, an expert committee representing each study language (including patients, physicians, translators and methodologists), we will use a method derived from those used in synthesis of qualitative data [45].

1) All themes and categories identified will be translated in English.

2) The expert committee will compare themes and categories identified in French and English together. The synthesis of this analysis will then be compared with the Spanish themes.
   They will identify:
   1) Similar themes, which are themes similar in at least two settings.
   2) Partially similar themes, which is a group of themes, which could be related to a common factor without being substitutable.
   3) Themes present in some languages and absent in others.

   Then, they will work together to define broad underlying themes by merging and collapsing categories.

3) The expert committee will back translate the list of broad underlying themes in French and Spanish. When possible, they will use words and expressions extracted during step 2. They will consolidate the themes common to all languages and reflect on themes unique to one or two study languages using patients' words. All findings will be described using quotes from patients.

4) To ensure that findings from this step remain close to patients experiences, we will send this consolidated list of cross cultural themes to all patients who participated in the internet study for feedback. Participants will be encouraged to comment and reformulate the material presented to them.

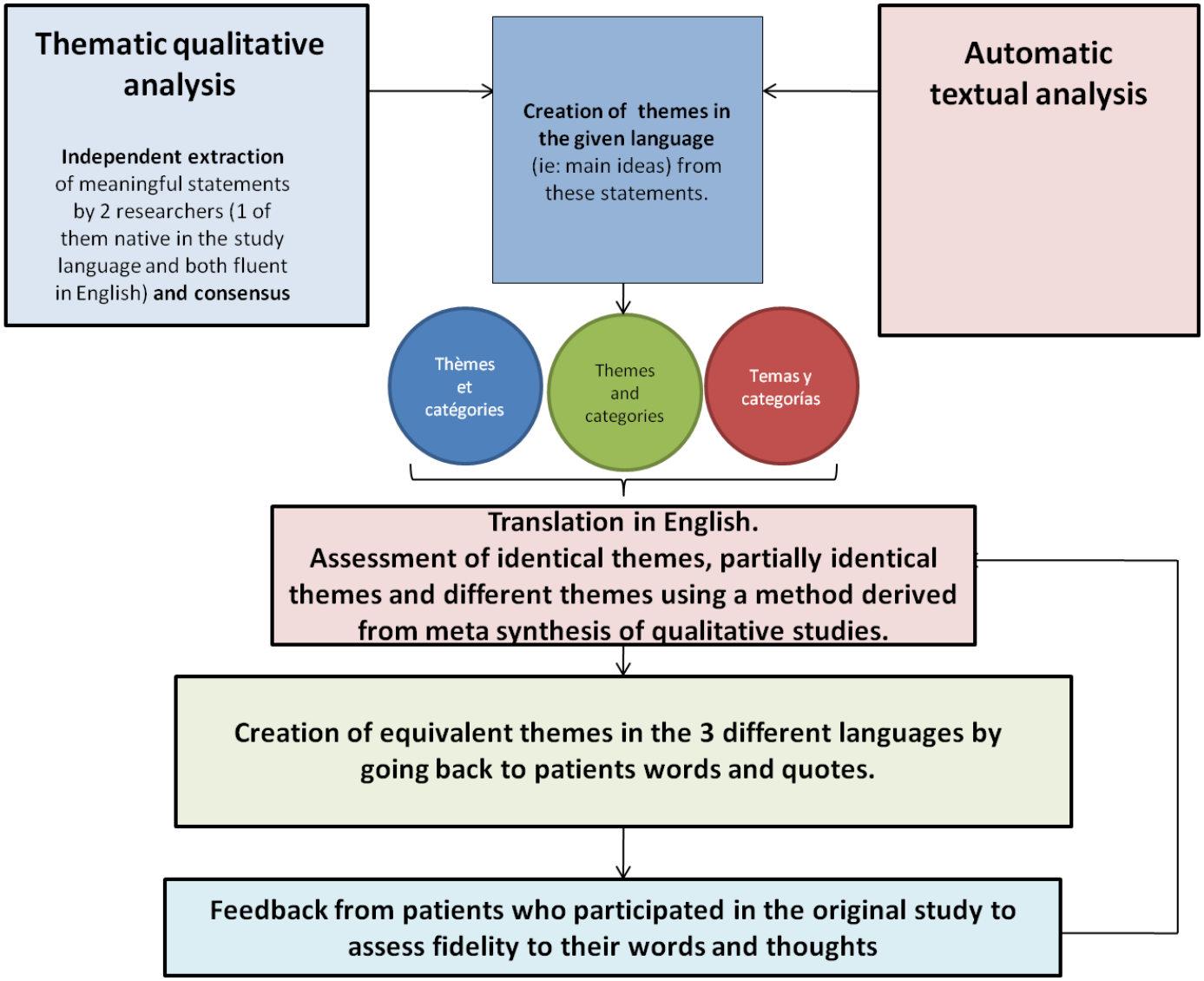


Figure 8: Synthesis and creation of cross cultural themes, equivalent in the 3 different languages

3.3.2. Elaboration of a theoretical model of the burden of treatment

The researchers will create a theoretical model from the burden of treatment. The model will describe the "sources" of the burden of treatment (for example: the burden related to pharmacological treatment or the burden related to visits to the doctors) and the impact of the burden of treatment on patients' lives (for example: impact on professional, family or social life) and how these concepts interact with each other.

For each theme, we will also consider how frequently it was mentioned among patients globally and in the first open-ended question.

3.3.3. Subgroup analysis

We will assess what bother patients the most in different subgroups defined by clinical and demographic data obtained from patients (conditions, settings, type of treatment…) by considering how frequently each theme will be mentioned by patients in each subgroup and if the theme was mentioned in the first open ended question.

Phase 2: Elaboration of a preliminary questionnaire

We will construct a questionnaire adapted for quantitative assessment of the burden of treatment following the multi-step method described by Guyatt G. *et al* [46]. First, we will use the themes obtained from direct patients' inputs during phase 1 to create the items of the questionnaire and then we will pretest the instrument to assess clarity, wording and reduce the number of items.

3.4.From themes to items

We will create a list of items from the previous list of themes for each study language.
Each item will consist of a statement (for example: "How would you rate the burden associated with dietary restrictions?") and relevant examples (for example: "not being able to eat certain foods or drink alcohol…") and a 7-step Likert scale with end-anchors. The statement and the examples will be derived directly from patients' words.

3.5.Pilot study

To ensure that the preliminary questionnaire obtained is comprehensible and relevant to patients, we will test it during a pilot study.
Preliminary questionnaires will be tested on a convenient sample of approximately 50 participants in each language (total of 150 patients, as recommended by Guyatt *et al.* [46]) to: 1) assess clarity and wording and 2) reduce the number of items.
Patients will be conveniently recruited in different cohorts of patients (for example, INVEST cohort [47] and DESIR cohort [48]) with different conditions and different types of treatment. To participate, they must have at least 1 chronic condition (defined as a condition requiring healthcare for at least 6 months).

3.6.Clarity and wording

Clarity and wording will be tested during interviews. These interviews will fall into 2 parts:

1) Each participant will be asked to answer the preliminary questionnaire "by himself", without the help of the investigators.

2) After the participant has completed the questionnaire, an investigator will read each answer and ask the participant how he came with this answer [49]. Discrepancies between what was expected and what the patient understood will be investigated. In the same fashion, the investigator will assess any problem that could have occurred during completion of the questionnaire (clarity, wording, ambiguities…)

We will obtain face validity (ie: empirical evidence that the questionnaire measures the concept it purports to measure) by successive revisions to the text.

3.7.Reducing of number of items

From the answers to the pilot testing, we will reduce the number of items according to criteria proposed in the literature [46, 50] on: 1) the relevance of the items, assessed by the number of answers for which patients checked "Does not apply"; 2) item redundancy, suspected when inter-item correlations by Spearman's correlation coefficient will be > 0.80 [51] and 3) floor effect or ceiling effect (considered present if >15% of participants answer the lowest or highest answer on the likert type scale. A large floor effect would mean that the burden represented by the item is infrequent and may not fit a generic measure of the burden of treatment).

Phase 3: Description of the psychometric properties of the instrument

We will assess the psychometric properties of the questionnaire obtained during phase 2 assessed using a multistep approach [50, 52]: 1) testing of dimensionality, 2) assessment of construct validity and 3) assessment of reliability.
Finally, we will compare results from different countries, settings, conditions and treatment types.

3.8.Participants

A sample of patients, in different countries and settings, who did not participate in the first study, will be invited to participate in the validation study.
To participate patients must:

- Be over 18 years old
- Have at least one chronic condition and receive treatment for at least 6 months
- Have no cognitive impairment that would interfere with the questionnaire comprehension

Patients will be recruited:

- 1) On the internet, using the ORE platform (http://www.openresearchexchange.com) developed by PatientsLikeMe. PatientsLikeMe is a patient network that serves as a real-time research platform: people connect with others who have the same disease or condition and track and share their own experiences. This platform has successfully been used for questionnaire development previously [53, 54]
- 2) In existing cohorts of patients with multiple chronic conditions (for example, the INVEST cohort [47] and DESIR cohort [48]).

Recruitment through ORE and existing cohorts will allow us to recruit regular internet users (ORE) as well as potentially infrequent users (existing cohorts) in different settings, and from different origins.

Sample size will be determined to achieve a consistent factor analysis. A sample size of 300 patients is optimal for assessing validity of scales with low number of items in psychiatry

[55]. To be able to conduct factor analysis in subgroups by study language, we will need approximately 900 patients.

3.9.Dimensional structure

Dimensional structure of a scale tells us how its items relate to underlying factors and can be grouped together into subscales. It will be assessed using factor analysis. Scree plots will help visualize a break between factors with large and small Eigenvalues. Internal consistency will be assessed by Cronbach's alpha [56] and considered acceptable between 0.70 and 0.95 [57].

3.10. Construct validity

Construct validity will be determined by confirming constructs theorized on the burden of treatment.

1) We will assess the correlation between the score of burden of treatment and different variables on 1) drug intake (number of tablets, injections and intakes per day); 2) medical follow-up (number of different physicians, medical appointments per month and hospitalizations per year); 3) lifestyle modifications (dietary restrictions); and 4) daily time spent on self-care (time needed to organize the treatment and time needed for self-monitoring). These correlations will be assessed by Spearman correlation coefficient (r_s) and considered high with $r_s > 0.50$ and moderate with r_s 0.35–0.50 [58].

2) We will then study the correlation between the score of Burden of treatment with:
    - SF-36 (Short Form Health Survey questionnaire). This 36-item questionnaire assesses quality of life on 8 aspects (physical activity, physical ability to accomplish everyday tasks, physical pain, general health, vitality, social functioning, emotional state, perceived general mental health status).
    - Morisky Medication adherence scale (MMAS-8) [59, 60] assessing Treatment Adherence. MMAS-8 assesses adherence to treatment using 8 items. This tool has a high sensitivity and moderate specificity to detect those with low adherence to treatment. It has been used in numerous studies concerning treatment adherence.

- Treatment Satisfaction questionnaire for medication (TSQM) [61]. The TSQM is an 11-item questionnaire validated in a population with diverse chronic conditions, measuring patient satisfaction with various medications designed to treat, control or prevent a wide variety of medical conditions. TSQM scores range from 0 to 100 and measure patient satisfaction with the treatment's effectiveness, side effects, convenience and globally.

3.11. Reliability

Reliability of the instrument will be determined using a test–retest method. Patients will complete the new instrument twice: at baseline and after a 2 week interval. According to guidelines, this interval must be short enough to ensure no change in the burden of treatment of participants and long enough to avoid recall bias [50]. Reliability will be assessed by the intra-class correlation coefficient (ICC) for agreement [62].

3.12. Assessment of differences between the 3 languages

To assess the difference between the 3 linguistic versions, analysis will be carried globally and in each language (French, English, Spanish) for item selection and factor analysis.
Mean scores of burden of treatment will be compared between countries and languages.

3.13. Comparison of burden of treatment measures between countries, settings, conditions and treatment types.

Scores of burden of treatment (global score and item scores) will be analyzed in different subgroups defined by countries, conditions (for example: diabetes, stroke patients…) and treatment types (for example: patients with physical therapy, diet restrictions, etc.)

4. Feasibility of the project

This work is conducted by a team experienced with large scale projects. Pr Ravaud, Pr Montori and Pr Falissard are internationally renowned for their work in the field of epidemiology and patient reported outcomes. In addition, Pr Montori is one of the founders of the concept of Minimally Disruptive Medicine and Burden of treatment and has already published numerous works on this new subject [1, 9-11, 63, 64]. Dr Tran has previously worked on the subject of Burden of treatment and in the development of the first instrument to assess it in France [9].

Moreover, the investigators work in a department including biostatisticians, bioinformatic specialists and multilingual healthcare professionals, experienced in large scale internet studies, who will participate in the development of the internet platform and analysis of data.

5. Perspectives

The burden of treatment is a new concept [1] which is not yet fully understood. Most studies designed to explore the determinants of treatment burden have focused on specific conditions (for example: chronic heart failure [11] or stroke [27]) or groups of conditions [10], or specific countries [9]. Our large international qualitative study will help us get a better picture of how the burden of treatment affects patients in different settings and countries.

This knowledge will lead to the development of the first valid and reliable instrument to assess Burden of treatment allowing comparison between different countries and languages.

Our instrument, created from patients' words and evaluated by patients, will be used in clinical research, to help design therapeutic strategies and clinical guidelines that are both efficient and acceptable for patients and in daily practice by physicians, as a framework to begin a conversation with patients on burden of treatment and encourage shared-decision making. Therefore, this instrument will contribute to the development of a Minimally Disruptive Medicine[1], a medicine adapted to the realities of a patient's life and destined to patients' outcomes.

We will use and assess a new method to generate cross cultural items, directly from patients in different countries with an internet tool. This new method should strengthen the validity of comparison of questionnaire results between countries and languages. This study, including hundreds of patients from different contexts in multiple countries, will help researchers understand how patients live with their disease and healthcare and what they find limiting in their care.

Finally, we will explore the determinants of burden of treatment from the patient's perspective qualitatively (during phase 1) as well as quantitatively (phase 3). This may help researchers, physicians and policy-makers determine the sources of burdens with the greatest impact and which factors contribute to improve or decrease them in each setting. This may, in turn, lead to the development of adapted solutions to reduce burden of treatment.

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