Title: The Danish Fibromyalgia Registry (DANFIB)

Dansk titel: Det Danske Fibromyalgi register (DANFIB)

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Background

Fibromyalgia is a chronic pain condition with an estimated prevalence in the background population of 2% (1;2). The prevalence in rheumatic populations is reported to be 20% (3-5). Although common, management of fibromyalgia still represents a challenge to clinical practice. For a large part, these patients fall in between the medical specialities and interventions offered by the Danish healthcare system. The clinical picture and presented symptomatology are often complex, and several studies support a considerable heterogeneity in this patient population with regards to neurobiological, psychosocial and behavioural characteristics (6-8). The diversity of symptoms probably contributes to the lengthy and expensive processes patients undergo to get a diagnosis. This delay is unfortunate as studies have shown that a diagnostic label provides the patient with meaning and value for symptoms, which facilitate management and reduce health care utilization, with cost reduction further augmented by early diagnosis (9-11). Studies conducted at the department of rheumatology, Frederiksberg hospital confirm a considerable chronicity among patients referred for rehabilitation in specialized care, where the typical person averages over 10 years of pain duration, demonstrates extensive limitations in daily life activities and a potential need of support for community living. Only about 21% are part of the workforce at the time of referral, 82% report a change or permanent disability from usual working activity due to the pain condition, 25% are on long-term sick leave, and 34% are receiving some sort of social welfare payment (12;13).

Current evidence-based recommendations for the management of fibromyalgia are based on disease diagnosis and diagnosis-driven intervention (14;15). However, fibromyalgia is not a homogenous entity, and several interacting factors may add to this variability and influence patient prognosis and outcome of standardized intervention programs. Even though outcome studies indicate improvement in some key outcome domains, reported effects are on average limited, and a substantial proportion of patients do not demonstrate sustainable, clinically meaningful benefits. Several attempts have been made to define fibromyalgia subgroups primarily based on clinical characteristics. Although such studies substantiate the notion of a disease severity spectrum and considerable heterogeneity within fibromyalgia populations, longitudinal studies of patients with fibromyalgia using clinically relevant subgroups to direct interventions and predict outcome are still missing. Furthermore, available outcome studies are conducted on selected patient populations; mainly females between 30 and 60 years of age, excluding participants with pending social welfare litigation, and only few data are available on the socioeconomic outcomes, including changes in patients work status (16).

Also, studies analysing the patient perspective support that patients with fibromyalgia experience prolonged and incoherent pathways as well as uncertainty about their pain diagnosis as a legitimate disease state (17). Moreover, patients report that the support they get does not match the complex personal, social and work-related situation they find themselves in as a consequence of their pain condition (17). Thus, the patient perspective points toward the need for a more timely and targeted intervention (17). An early and tailored intervention would potentially assist patients to adjust to pain and adopt active self-management strategies before pain-related disability, and maladaptive pain behaviours create therapeutic inertia. Development of health care strategies aiming at early identification, diagnosis and provision of interventions matching individual patient needs should, therefore, be pursued to improve or maintain functional ability and social participation in this patient population.

Establishing a clinical register has the potential to improve patient care and outcomes and serve a number of evidence developments and decision-making purposes. For clinicians, registries can collect data about

disease presentation and outcomes on large numbers of patients, thereby producing a real-world picture of disease. Registries may be developed to serve one or more purposes:

1) To evaluate *the natural history of a disease*, meaning its characteristics, management, and outcomes with and/or without intervention. The natural history may be variable across different subgroups of patients, and it often changes over time. In many cases, the natural histories of diseases are not well described.

2) To determine the *clinical effectiveness or cost-effectiveness* in real-world clinical practice. Several studies have demonstrated disparities between the results of clinical trials and results in actual clinical practice. Thus, patient registries and randomized controlled trials (RCTs) have important and complementary roles in evaluating patient outcomes. Patient registries comprehensively collect data (with few excluded patients) and therefore produce outcome results that may be generalizable to a wider range of patients. They also evaluate care as it is actually provided. Registries may also be particularly useful for tracking effectiveness outcomes for a longer time period than is typically feasible with clinical trials.

3) To measure the *quality of care*. Quality-focused registries are being increasingly used to assess quality in care provision based on performance measures that take the patient perspective and preferences into consideration. Changes in clinical practice must be justified by better outcomes, as valued by patients, or more efficient delivery of health-care. Registry-based assessments may be used to demonstrate opportunities for improvement in care provision and development of interventions matching patients prioritised needs.

Objective

To establish a clinical research registry (DANFIB) that can collect uniform clinical and other data to be used in longitudinal monitoring and evaluation of specified health outcomes in patients with fibromyalgia.

Specified research objectives will be:

1) to describe the natural course and long-term prognosis across different subgroups of patients with fibromyalgia
2) to evaluate if early identification and diagnosis influence long-term health outcomes and the ability to cope with pain in patients with fibromyalgia
3) to identify patient characteristics that contribute to a poor prognosis (including loss of functional ability and ability to work) in patients with fibromyalgia that might guide future intervention matching and delivery of stratified interventions based on a prognostic classification
4) to evaluate the clinical effectiveness and long-term outcome of interventions targeted for patients with fibromyalgia when delivered in real-world clinical practice to a heterogeneous patient population
5) to identify opportunities for a value-based and patient-focused improvement in care provision achieved through assessment of patient identified goals and prioritised outcomes; which outcomes are wanted and needed for the patient with fibromyalgia

Method and materials

Registry design

The patient registry will be designed as an electronic registry where data are captured electronically directly from the source (respondents) based on a user-friendly, web-based IT solution (Cirkeline and REDCap).

Target population and clinical setting

The patient registry will be designed as a condition-specific registry including adult subjects (≥ 18 years of age) diagnosed with fibromyalgia at the department of rheumatology, Bispebjerg-Frederiksberg hospital.

Since 2007, a non-residential two-week rehabilitation program specifically tailored for patients with fibromyalgia has been part of the rheumatology service at Frederiksberg hospital. The rehabilitation program, which currently only is offered to patients with a confirmed diagnosis of fibromyalgia at referral, is group-based with eight patients participating in each group. The interventions in the rehabilitation program are delivered by a specialized interdisciplinary team; rheumatologist, psychologist, nurses, physiotherapists, and occupational therapists. The current capacity allows for the treatment of 21 groups of eight patients per year, in total 176 patients per year, enrolled from a waiting list.

Per 1. January 2018, this well-established clinical practice will be expanded to also include a diagnostic unit with an expected patient turn-over of 800 patients per year. Patients with chronic widespread pain (CWP), i.e. pain in all 4 body quadrants and axially, either as the primary pain problem or secondary to other established rheumatic disease will be accepted for screening. The diagnostic work-up will combine clinical examination, blood test screening, and a questionnaire- based multidimensional pain assessment, which also addresses patients prioritized needs and trainable skills that are consistent with the theme of self-management and may serve as a guide to therapeutic interventions. If diagnosed with fibromyalgia, patients will subsequently be offered a two-days, multidisciplinary group-based educational treatment course; education about the nature of persistent pain; information about physical exercise and recovery of valued activities, by gradual steps; information about cognitive therapeutic methods to address unhelpful beliefs and thinking processes around pain; encouraging changes in behaviour to maximise autonomy and confidence in managing the pain. Patients with a complex pain condition and need of further intervention will be offered additional referral to the two-week rehabilitation program at the end of the educational course.

Patients from this clinical setting will be invited to serve as the point of departure for the establishment of the fibromyalgia registry aiming at a longitudinal monitoring and evaluation of specified health outcomes in this specific patient population. Data will be collected on all patients at referral (baseline), 4 weeks after the two-day educational course, and after that on a yearly basis for a time period of 15 years. Also, data on patients referred for the two-week rehabilitation program will be collected before enrolment in the program (Fig. 1).

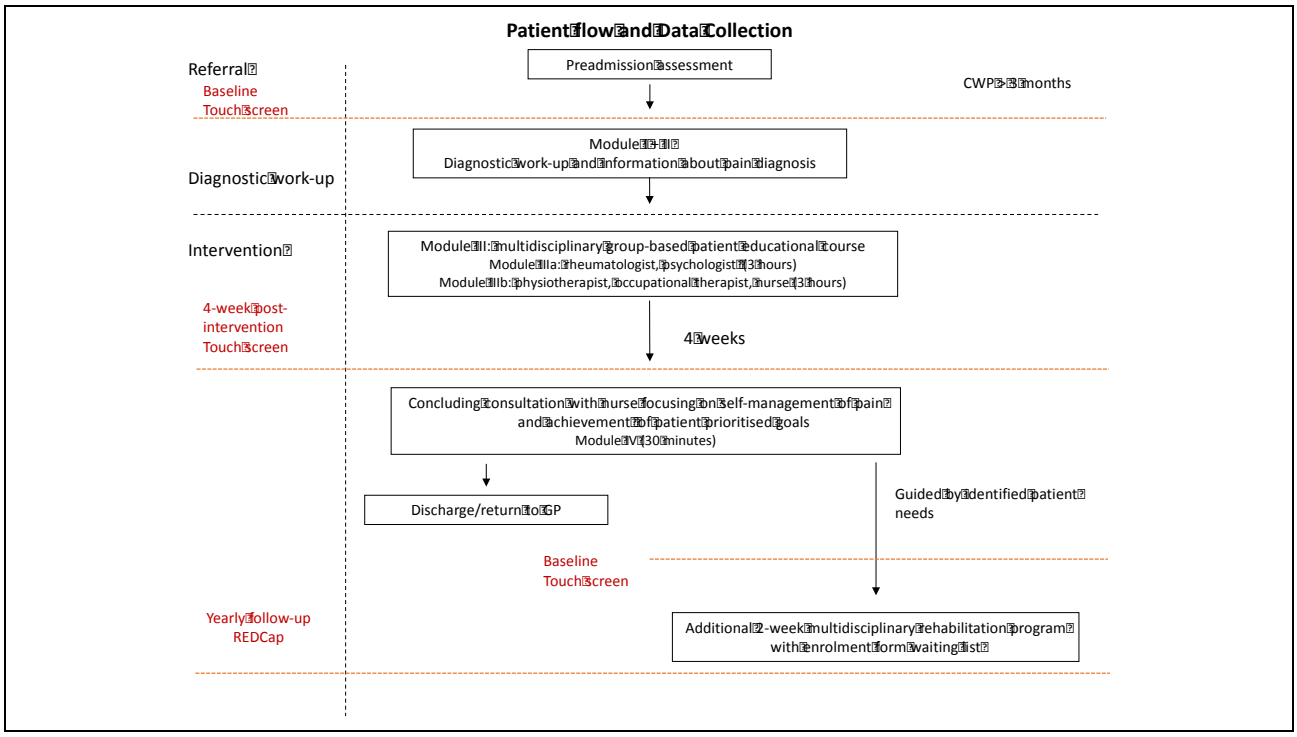

Figure 1. Patient flow and timing of questionnaire administration.

Data collection and data elements

Registry data will be obtained directly from patients and include personal, clinical and outcomes information. Data collection at baseline, 4-week post-intervention and before enrolment in the two-week rehabilitation program will be based on electronic questionnaires accessed via touchscreens placed in the clinic and data exported to a designated research database. Data collection at yearly follow-ups will be based on electronic questionnaires accessed via REDCap (Research Electronic Data Capture); a locked online it-platform hosted by the Capital Region. The use of computerised health status questionnaires in fibromyalgia populations has prior been validated by the Parker Institute (18). Questionnaires covering patient identified key evaluation and outcome domains will be implemented (19). The ICF will be applied as the theoretical measurement framework and data structured within the body domain (body structures and functions), activity domain (execution of tasks), domain of participation (involvement in life situations), and contextual factors (personal and environmental factors) (20).

Data extracted from electronic patient files, including findings at clinical examination and observation-based assessment of functional ability (AMPS test), which is routinely performed on all patients referred to the two-week rehabilitation program, will also be integrated into the research registry.

Sample characteristic data elements	
Enrollment data elements	• Patient identifiers • Permission/consent • Source of referral • Enrolment criteria
Medical history	• Family history of fibromyalgia and other rheumatic diseases • Pain onset/duration • Health care resource utilization due to pain • Outcome of examination (pain diagnosis) • Pain medications • Rheumatic comorbidities (RA, PsA, SpA, OA, CLP, other) • Treatment of comorbid rheumatic disease (medication, surgery) • Other comorbidities (somatic, mental health)
Patient demographics	• Health behaviours (alcohol, tobacco) • Marital status • Family history (number of children, etc.) • Education • Employment • Disability, work attendance, or absenteeism • Social welfare services
Diagnostic tests and results	• Manual tender point examination • Beighton score

Baseline data elements	Domain	Instrumentation
Body domain	Pain • Intensity • Quality • Distribution • Pain condition (pain diagnosis) Associated symptoms (sleep, fatigue, cognition, mood, organ systems) • Presence • Severity General health	Fibromyalgia questionnaire – diagnostic criteria 2016 Fibromyalgia Impact Questionnaire Revised (FIQ-R) PainDetect Questionnaire (PDQ) EuroQol 5D
Activity domain	Symptom interference with activities of daily living (ADL)	Questionnaire – patient prioritised problem identification FIQ-R
Participation domain	Symptom interference with social participation Symptom interference with working ability	Questionnaire – patient prioritised problem identification FIQ-R
Personal factors and pain coping	• Knowledge about cause of pain • In need of help to accept pain • In need of help to cope with pain	Questionnaire – patient prioritised problem identification

	• In need of help to manage ADL problems caused by pain • Pain self-efficacy	FIQ-R Pain Self-Efficacy Questionnaire (PSEQ)

Follow-up data elements	Domain	Instrumentation
Body domain	Pain • Intensity • Quality • Distribution • Pain condition (pain diagnosis) Associated symptoms (sleep, fatigue, cognition, mood, organ systems) • Presence • Severity General health	Fibromyalgia questionnaire – diagnostic criteria 2016 Fibromyalgia Impact Questionnaire Revised (FIQ-R) PainDetect Questionnaire (PDQ) EuroQol 5D 7-point transition scale (pain, associated symptoms)
Activity domain	Symptom interference with activities of daily living (ADL)	Questionnaire – patient prioritised problem identification FIQ-R 7-point transition scale
Participation domain	Symptom interference with social participation Symptom interference with working ability	Questionnaire – patient prioritised problem identification FIQ-R Follow-up questionnaire
Personal factors and pain coping	• Knowledge about cause of pain • In need of help to accept pain • In need of help to cope with pain • In need of help to manage ADL problems caused by pain • Pain self-efficacy	Questionnaire – patient prioritised problem identification FIQ-R Pain Self-Efficacy Questionnaire (PSEQ) 7-point transition scale (pain accept, pain coping)
Medical history	• Health care resource utilization due to pain within the last year • Pain medications within the last year • Current pain medication • Comorbidities (somatic, mental health) diagnosed within the last year	Follow-up questionnaire
Patient demographics	• Changes in marital status within the last year	Follow-up questionnaire

	• Change in employment status, work attendance, or absenteeism within the last year • Social welfare services within the last year	

Registry team and governance

Kirstine Amris is the project coordinator and manager of the research database. Christian Cato Holm and Peter Krusager, both database specialists, employed at the Parker Institute, and psychometrician Eva Ejlersen Wæhrens will be responsible for the development of the it-platform and implementation of the computerised questionnaires. Further, it will be possible to involve other relevant expertise from the Parker Institute if needed, to ensure high-quality data, data availability and usability.

Data collection will take place in close collaboration with the department of rheumatology, Bispebjerg-Frederiksberg hospital, where Kirstine Amris is employed as a consultant and responsible for the clinical management of fibromyalgia patients. Filled in questionnaires from the baseline assessment and assessment 4-weeks post-intervention will be applied in the clinical work and contribute to the clinical decision-making. The close collaboration with clinical practice will ensure data completeness at these specific assessments points.

Ethics, data ownership and data security

The project has been notified to the Danish Data Protection Agency and granted authorisation for the period January 2018 to January 2033 (j.nr.: 2012-58-0004). Sensitive personal data will be anonymised according to regulations stipulated by the Danish Data Protection Agency, and informed consent will be obtained from all patients before enrolment in the registry. The project does not require notification to the regional scientific ethical committee.

The research database will be established at the Parker Institute, who are data responsible. A steering committee will be formed with representatives from the Parker Institute and Videnscenter for Reumatologi og Rygsygdomme (VRR), Rigshospitalet-Glostrup. The chair of the steering committee is the project coordinator and manager of the research database. The steering committee sets the parameters for data handling to ensure that data governance processes are followed and defines how the data is to be used by authorised research personnel.

The following members have been a pointed to form the steering committee:
Chair: Kirstine Amris, Project Coordinator
From the Parker Institute: Lars Erik Kristensen, Head of Research
From VRR, Rigshospitalet-Glostrup: Henrik Røgind, Head of Clinic

Clinical implications

The considerable heterogeneity that characterises fibromyalgia populations may explain why randomised controlled trials investigating the efficacy of interventions often report generally modest treatment outcomes

and poor responder rates. Thus, the current literature points toward the need for differential intervention models adjusted to patients' characteristics and prioritised needs, and outcome evaluation based on subgrouping of patients. Identification of clinical characteristics shared by patients that respond positively to a given intervention, and those that do not, is necessary to develop differential intervention models, and outcome measures that are relevant for the patient-experienced complex situation.

The Danish fibromyalgia registry is foreseen to collect data about disease presentation and long-term outcomes on a large number of patients based on performance measures that take the patient perspective and preferences into consideration. Thus, the collected data and subsequent data analyses are anticipated to contribute with relevant knowledge that may be used to demonstrate opportunities for improvement in care provision and development of interventions matching patients prioritised needs in this specific patient population. The established intervention model at Frederiksberg Hospital will be adjusted according to findings, including intervention variables, such as program content and weighting of treatment modalities, the timing of care delivery and duration of intervention programs.

Publication

An ongoing publication of papers in international peer-reviewed journals based on the collected data is foreseen. The papers will be authored by the involved researchers from the Parker Institute and future scientific partners. Thus, it will be possible for researchers to use data for publications based on individually defined researcher-initiated projects if in agreement with the frames of data handling set by the steering committee

Funding

Public and private funding will be applied for to cover expenses related to the establishment and running costs for the research database. Additionally, there will be applied for the financing of individually defined researcher-initiated projects that are based on data collection in the research database.

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