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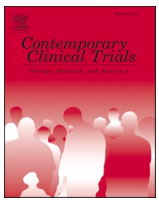

Early identification of functional somatic disorders in an internal medicine diagnostic clinic: The DISTRESS trial

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ABSTRACT

Background: Functional Somatic Disorders (FSDs) affect approximately 10 % of the general population (1) and often lead to reduced quality of life, extensive diagnostic evaluations and increased healthcare costs. The DISTRESS (Diagnostic Intervention in Secondary care Targeting patients Referred for Evaluation of bodily Stress Symptoms) trial protocol describes a randomised clinical trial evaluating a novel FSD Diagnostic Clinic, with the aim of providing early diagnosis and thereby helping patients and clinicians bring the diagnostic odyssey to a definitive and meaningful conclusion.

Methods/design: This pragmatic, randomised trial employs allocation concealment and blinded outcome assessment, although the randomisation allocation is unavoidably unmasked to patients and clinicians due to the nature of the intervention. Patients with suspected FSD are randomised 1:1 to either the FSD Diagnostic Clinic, where internal medicine specialists (internists) undertake the FSD diagnostic process, or to usual diagnostic assessment. The two co-primary outcomes evaluate (a) healthcare utilization and (b) costs-effectiveness, assessed alongside health-related quality of life measured by the SF-36 survey at 12 months post-intervention. Secondary outcomes include relevant clinical outcomes and overall public expenses.

Discussion: The DISTRESS trial addresses challenges in diagnosing FSDs by evaluating a novel Diagnostic Clinic model and its impact on patient outcomes, cost-effectiveness, and healthcare utilization. Insights from separately conducted qualitative studies will complement the trial by assessing the clinic's acceptability and integration within the healthcare system. By training internists to diagnose and manage FSDs using approaches typically employed by FSD specialists, the FSD Diagnostic Clinic expands access to timely care within a stepped care model.

Trial Registration: ClinicalTrials.gov Identifier: NCT06025617

1. Introduction

Functional Somatic Disorders (FSDs) are prevalent in all medical settings [1], and recent epidemiological studies find that FSDs affect approximately 10 % of the general population [2,3]. These disorders entail a range of symptoms that resemble other physical diseases, thus presenting complex diagnostic challenges. Furthermore, patients with FSD may also have physical comorbidities that increase the complexity of the diagnostic evaluation. Patients with undiagnosed FSD often endure a diagnostic odyssey, being referred to various specialists and

Abbreviations: BDS, Bodily Distress Syndrome; CGI, Clinical Global Improvement; DC, Diagnostic Center; DREAM, Danish Registry-based Evaluation of Marginalization; DRG, Diagnosis-Related Group; EQ-5D-5L, EuroQol 5-Dimensions 5-Levels; FP, Family Practitioner; FSD, Functional Somatic Disorder; IBS, Irritable Bowel Syndrome; ME/CFS, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; MCS, Multiple Chemical Sensitivity; RCT, Randomised Clinical Trial; REDCap, Research Electronic Data Capture; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SF-36, Short Form-36 Health Survey; SPIRIT, Standard Protocol Items Recommendations for Interventional Trials; TERM, The Extended Reattribution and Management Model; WHO, World Health Organization.

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undergoing numerous unnecessary procedures. This drives increased healthcare costs [4–6] and leads to increased risk of chronic disease progression, psychological distress, and iatrogenic harm [7].

Different terms are used to describe FSDs, including medically unexplained symptoms, somatoform disorders, Somatic Symptom Disorder (SSD) and Bodily Distress Disorder (BDD), as well as speciality-specific syndromes such as Fibromyalgia, Irritable Bowel Syndrome (IBS), Chronic Fatigue Syndrome (CFS)/Myalgic Encephalomyelitis (ME), and Multiple Chemical Sensitivity (MCS) [2,8,9]. FSDs are characterized by persistent, bothersome symptoms and can be categorized into single-organ or multi-organ involvement across four main symptom groups: cardiopulmonary, gastrointestinal, musculoskeletal, and general symptoms. An FSD phenotype has been identified based on empirical research, and equivalent to the Bodily Distress Syndrome (BDS) research diagnosis [8]. Diagnosis at specialised centres often includes structured assessments such as the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).

Family Practitioners (FPs), who serve as the primary point of care and gatekeepers to the secondary and tertiary services in the Danish healthcare system, play a crucial role in diagnosing FSDs. FPs report significant challenges in managing these patients [10–13], particularly in case of doubt about possible differential diagnoses, which may result in repeated and costly specialist referrals. This affects patients' health status and quality of life. It also places a potential strain on the healthcare system and society as a whole [4,14–16]. Recognizing this, the Danish National Health Authority (Sundhedsstyrelsen) recommends that only severe cases of FSD should be managed in one of five regional specialised clinics, while milder cases should be handled in primary care, supported by specialist advice [17].

The Extended Reattribution and Management (TERM) Model is an educational program designed to help non-psychiatric clinicians manage functional disorders by integrating patient-centred approaches and reattribution techniques. Despite having received training in diagnosing and managing FSDs using the TERM Model provided to the FPs in Western Denmark since 2008 [15,18,19], many FPs still feel unprepared to handle cases where patients either resist the diagnosis or especially where diagnostic uncertainty persists. When facing complex diagnostic cases, FPs in many locations have access to general (physical) medicine diagnostic centres that provide diagnostic services across various medical disciplines. These centres are typically equipped to offer a broad range of diagnostic tests, imaging, and specialist consultations aimed at evaluating patients in need of more comprehensive diagnostic assessment and ruling out physical diseases, thereby supporting FPs in timely management of patients with uncertain diagnoses. However, these diagnostic centres often lack the FSD-specific expertise necessary for effective diagnosis and management of FSDs, leaving a significant gap in the support provided to FPs in caring for patients with FSDs.

This protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [20].

1.1. Diagnostic clinic design and protocol

To bridge this gap, a Diagnostic Clinic for Functional Disorders (FSD Diagnostic Clinic) was established at the Silkeborg Regional Hospital's Diagnostic Center (DC), which includes all internal medicine subspecialties and radiology. The FSD Diagnostic Clinic represents a novel approach where internal medicine specialists (internists) undertake the FSD diagnostic process, using established tools such as a customised version of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) and The Extended Reattribution and Management Model (TERM). These tools have been developed and refined over more than a decade, supported by extensive observational and implementation studies, including a pilot confirming feasibility and diagnostic reliability in this setting [18,21–23]. What is new in this model is the delivery of these evidence-based methods by internists within an internal medicine diagnostic setting. For patients diagnosed with the most severe cases of multi-organ FSD, referrals are made directly to the Department for Functional Disorders at Aarhus University Hospital. This is a specialised department focusing on advanced diagnosis and management of severe functional disorders.

1.2. Training for internists

Prior to performing this work, the participating internists received training in a tailored FSD-focused protocol using the World Health Organization's Schedules for Clinical Assessment in Neuropsychiatry (WHO-SCAN) as well as The Extended Reattribution and Management (TERM) model [15,18]. This novel approach aims to increase the timeliness of FSD diagnosis and management, enhance patient acceptance of the diagnosis, and ultimately improve patient outcomes while reducing healthcare costs. The present protocol describes a randomised clinical trial designed to evaluate the clinical effectiveness and cost-effectiveness of this new diagnostic intervention compared to usual diagnostic assessment.

2. Aims and hypotheses

To the best of our knowledge, this trial represents the first large-scale effort worldwide to evaluate an internist-led approach to diagnosing FSDs in secondary care. The primary aim of the DISTRESS trial (Diagnostic Intervention in Secondary care Targeting patients Referred for Evaluation of bodily Stress Symptoms) is to evaluate the effectiveness and cost-effectiveness of the FSD Diagnostic Clinic as compared to usual diagnostic assessment. The DISTRESS trial will specifically assess to what extent the FSD Diagnostic Clinic can reduce healthcare utilization and costs while improving patient outcomes in the management of FSDs over a 12-month post-intervention period. Detailed trial registration can be found on clinicaltrials.gov under identifier NCT06025617 [24].

Alongside the DISTRESS trial's primary objectives, an implementation study will assess the clinic's integration within the healthcare system focusing on its reach and adoption by FPs. Subsequently, three qualitative sub-studies are planned to contextualize trial findings and explore broader system-level dynamics – the protocols for these studies are outlined elsewhere [25].

2.1. Hypotheses

Primary hypotheses:

1. Patients seen at the FSD Diagnostic Clinic will have lower overall healthcare utilization compared to those receiving usual diagnostic assessment as measured at the 12-month follow-up.
2. Compared to the control group, the intervention group will be significantly more cost-effective comparing incremental utility scores with incremental costs at the 12-month follow-up. Costs are evaluated from both a healthcare utilization (direct cost) as well as a societal (indirect cost) perspective.

Secondary hypotheses:

1. Public expenses associated with occupational status and social benefits will be lower for the intervention group compared to the control group as measured at 12 months after randomisation.
2. The intervention group will show significant improvements in health-related quality of life as quantified by the 36-item Short Form Survey (SF-36) compared to the control group at the 12-month follow-up.
3. Patients will have significantly better self-reported physical health as measured 12 months after randomisation by an aggregate score of "physical functioning", "bodily pain", and "vitality" subscales of the SF-36.

4. Patients in the intervention group will report a higher overall self-reported health improvement than those in the control group, measured at 12 months after randomisation.

3. Methods

3.1. Study design

The DISTRESS trial is a single-center, pragmatic randomised clinical trial designed to compare two approaches: A) the new diagnostic intervention, including diagnostic feedback and recommendations for ongoing patient management vs. B) the standard diagnostic processes (control). This pragmatic trial integrates direct diagnostic assessment with comprehensive data collection to assess both clinical and economic outcomes. For the trial profile, please see Fig. 1: Randomised clinical trial profile.

3.2. Setting

The new FSD Diagnostic Clinic has been set up at the Diagnostic Center at Silkeborg Regional Hospital. Silkeborg Regional Hospital is a small county hospital in the Central Denmark Region. The Diagnostic Center at Silkeborg Regional Hospital encompasses all internal medicine subspecialties as well as radiology.

3.3. Recruitment and participants

Participants in the DISTRESS trial are recruited from the Central Denmark Region, comprising ~1.2 million people. To be included, patients must be referred by their FP for diagnostic evaluation due to symptoms giving rise to a diagnostic dilemma between FSD vs. non-FSD diseases. A range of educational and PR initiatives including lectures, information letters, and direct phone calls will be undertaken for the FPs to raise awareness of our project and encourage the FPs to refer their patients.

The inclusion and exclusion criteria are listed in Table 1: Trial inclusion and exclusion criteria. Participants are adults aged 18–60 years, experiencing symptoms consistent with FSD for at least six months but not more than three years, fluent in Danish, and of Western cultural upbringing. The requirement for Western cultural upbringing is due to the centrality of SF-36 as a key outcome instrument since the version used in this study has only been adequately validated in Western cultural contexts. The exclusion criteria include severe chronic physical diseases, previous evaluations at specialised FSD clinics, substance abuse,

Table 1
Trial inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Referred to the clinic by their FP for symptoms consistent with a possible diagnosis of moderate or severe FSD. • Symptoms present for at least 6 months and no more than 3 years. • Used the secondary healthcare sector (specialty clinics or hospitals) at least twice in the past year. • Age between 18 and 60 years. • Of Western cultural upbringing. • Fluent in Danish (written and spoken).	• Presence of another severe chronic disease, which explains the reduced level of functioning. • Previous referral to or evaluation for FSD at this or another clinic specializing in functional disorders. • Prior diagnosis of FSD. • Alcohol or other substance dependency or abuse. • Acute psychiatric illness or elevated risk of harm requiring acute psychiatric evaluation. • Current or prior diagnosis of psychosis, bipolar affective disorder, or depression with psychotic symptoms. • Currently pregnant.

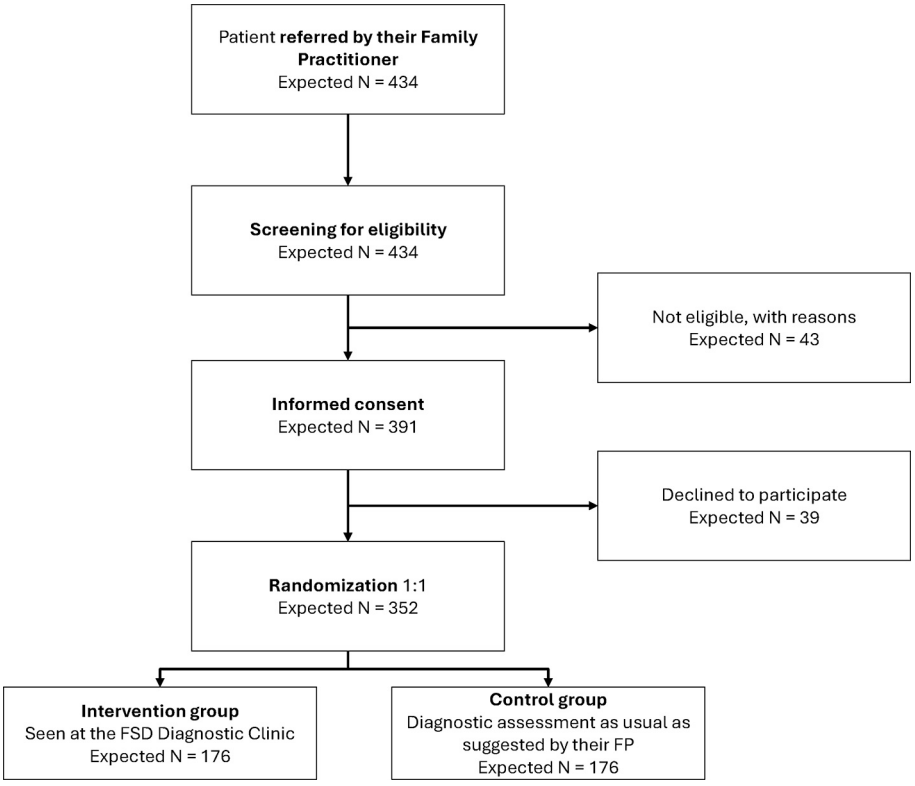

Fig. 1. Randomised clinical trial profile.
[Fig. 1 caption: Flowchart depicting the recruitment and randomisation process in the DISTRESS trial. Patients referred by Family Practitioners (FPs) to the diagnostic clinic are screened for eligibility, and those providing informed consent are randomised in a 1:1 ratio to either the intervention group (FSD diagnostic clinic) or the usual diagnostic assessment group. Expected participant numbers are provided at each stage.]

pregnancy, and severe psychiatric disorder, such as psychosis and bipolar affective disorder – but notably not personality disorders, anxiety, and depression.

3.4. Randomisation

Upon referral, the FP shall also provide a referral for a diagnostic assessment, which is to be offered if the patient is randomised to "diagnostic assessment as usual". Subsequently, patients are randomised 1:1 to either the novel FSD Diagnostic Clinic or to usual diagnostic assessment, as indicated by their FP. Randomisation is done in the built-in randomisation module of our data management REDCap (Research Electronic Data Capture) system, overseen by a data manager completely separate from the clinical process. We have set random block sizes of 4–8 to ensure no one can predict the next patient randomisation outcome while ensuring balanced allocation of patients to the diagnostic arms. Due to the nature of the intervention, allocation unavoidably becomes unmasked to patients and clinicians, depending on where the patient is subsequently seen. However, outcome data are collected independently of the treating clinicians, and statistical analyses will be performed using masked group identifiers to ensure blinding of analysts until final interpretation.

4. Interventions

4.1. Intervention group

Participants in the intervention group will receive a comprehensive evaluation by internal medicine specialists using the new clinic's protocols that incorporate the SCAN [26] interviews and the Extended Reattribution and Management (TERM) Model [18]. The Clinic's objective is to support FPs by assessing whether a patient has FSD using the FSD diagnostic criteria, while also evaluating for other physical diseases. The process includes explanation of the diagnosis and symptom interpretation as part of the patient education and providing feedback on the diagnosis to the referring FP along with advice for further management of the patient.

SCAN is a comprehensive diagnostic framework that has been created for conducting structured psychiatric interviews based on the ICD-10 classification system, as recommended by the World Health Organization (WHO) [27]. SCAN has a semi-structured, phenomenological approach that provides a balance between flexibility and structure, allowing an explorative interaction that can capture a broad spectrum of psychiatric phenomena with consistency and reliability across different cultural and clinical contexts.

In our study, we use a tailored version of the Internet-based computer-assisted SCAN 3.0 that has been revised for use by internists at the FSD Diagnostic Clinic [22]. All internists received structured training in the use of SCAN and were supervised by experienced FSD specialists. To ensure diagnostic validity, a pilot study confirmed that internists could apply SCAN 3.0 reliably within the clinical context of this intervention [22]. SCAN 3.0 is an updated version of the widely used SCAN 2.1 with new sections on FSDs, physical diseases, health anxiety, and conversion and dissociative disorders. SCAN 3.0 is designed to cover the most relevant symptoms for the FSD Diagnostic Clinic's needs and includes screening questions for depression and anxiety, but not for psychotic disorders. After symptom rating, the SCAN 3.0 software uses an algorithm to determine if an FSD is present and whether it is a single-organ or multi-organ FSD. The algorithm also applies, e.g., the Rome, Fulda, and Oxford criteria to aid in diagnosing more specialty-specific conditions such as Fibromyalgia, Irritable Bowel Syndrome, and Chronic Fatigue Syndrome (CFS/ME).

Clinicians at the clinic, who are specialists in physical disorders, have received additional training in the diagnosis and communication of functional disorders from FSD specialists at the Department for Functional Disorders in Aarhus. The FSD specialists in Aarhus also have a consulting role, including supervision based on video-recorded patient consultations. In a separate pilot study of consecutive patients in the intervention arm, we explored the feasibility of trained internal medicine specialists in performing FSD diagnostic work employing the tailored SCAN 3.0 interview [22]. The pilot study's findings indicate that the internal medicine specialists can reliably apply the SCAN 3.0 interview to assess FSDs within a clinical setting.

When the diagnostic program has been completed, management advice for the patients and their FPs is provided. Afterwards, our trained specialists remain available to answer further questions from FPs on patient management by telephone. The specific intervention for each patient is thus to be assessed at the new FSD Diagnostic Clinic, where they may receive their FSD diagnosis along with the illness explanation and management guidance, as well as a letter to their FP detailing the recommended management and treatment options [28,29].

4.2. Control group

Participants in the control group will undergo usual diagnostic assessment in the Central Denmark Region without the specialised approach provided at the new clinic. The referring FP specifies the most relevant diagnostic evaluation for each patient, such as gastrointestinal or rheumatological diagnostic assessment. Like the intervention group, patients in the control group have been informed by their FPs about the suspicion of an FSD. To prevent contamination, we are careful to ensure that patients randomised to receive usual diagnostic assessment are not seen by clinicians who also work at the FSD Diagnostic Clinic.

5. Data sources and effect measures

In the DISTRESS trial, we evaluate the effectiveness and cost-effectiveness of the new diagnostic intervention compared to usual diagnostic assessment. Data collection is based on patient questionnaires at Inclusion, 3 months and 12 months after randomisation, supplemented by registry data from Danish registries. As in other Nordic countries, all Danish residents have a personal identification number (CPR number in Denmark), which enables high-fidelity linkage of individual-level data across registries. For pragmatic reasons, no additional clinical visits are planned beyond the initial visit (for the intervention group) or the usual diagnostic assessment (for the control group). For an overview of the data collection flow, please refer to Fig. 2: Data collection flow, and for an overview of data collection instruments, please see Table 2: Measures and data collection times.

The primary outcomes will focus on utilization and cost-effectiveness analysis of healthcare services. We will compare the utilization of healthcare services in the secondary and the tertiary healthcare sectors between the intervention and the control groups in two periods: 12 months before and 12 months after randomisation. A cost-effectiveness analysis that incorporates both direct and indirect costs will also be carried out to evaluate the financial impact from a healthcare and a societal perspective, respectively. The aim of the cost-effectiveness analysis is to evaluate incremental costs and effects, adjusting for differences in mean utility scores and mean costs in the year before randomisation.

Secondary outcomes include an analysis of public expenses related to occupational status and social benefits, comparing these expenses between the two groups 12 months after randomisation. Health-related quality of life is assessed using the SF-36 health survey [30] at baseline and 3 and 12 months after randomisation. The SF-36 scores range from 0 (worst possible health status) to 100 (best possible health status). Perceived physical health is another secondary outcome, measured by an aggregate score of physical functioning, bodily pain, and vitality subscales of the SF-36, assessed at 3 and 12 months after randomisation.

Finally, we will measure Clinical Global Improvement (CGI) as a patient-reported outcome where patients compare their health status at 3 and 12 months after randomisation to their condition prior to

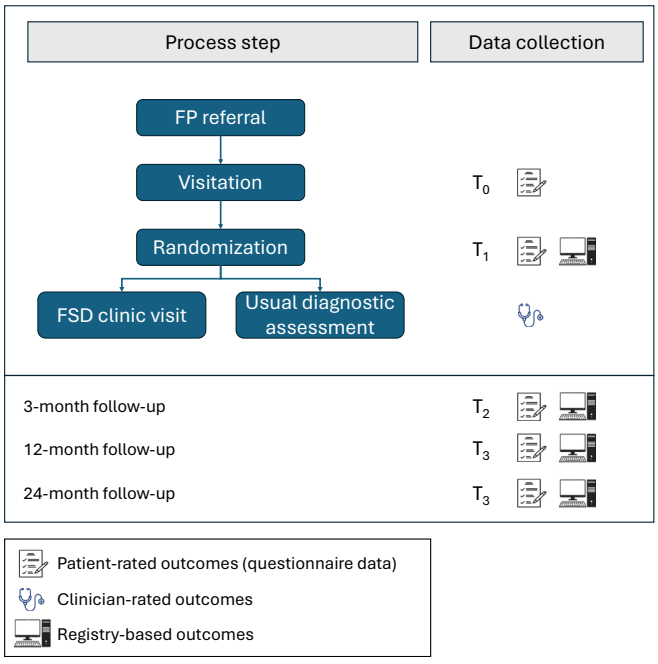

Fig. 2. Data collection flow.
[Fig. 2 caption: Overview of the DISTRESS trial process and data collection timeline. The process includes FP referral, visitation, randomisation, and subsequent allocation to either the FSD diagnostic clinic or another diagnostic pathway. Data collection at baseline, 3-month, and 12-month follow-up, encompassing both clinical and registry-based outcomes.]

randomisation, a format that has been used in functional neurological disorder and FSD studies [23,31]. The assessment categorizes their health on a Likert scale as "much worse", "somewhat worse", "about the same", "somewhat better", or "much better".

Other pre-specified outcomes (all evaluated at 3 and 12 months after randomisation) include a symptom level comparison using the Bodily Distress Syndrome 25 symptom checklist (BDS-25), which quantifies the number and severity of symptoms on a scale from 0 (not at all bothersome) to 4 (very bothersome). The sum score, which ranges from 0 to 100, is calculated by adding the scores of the 25 items. Health anxiety will also be evaluated using the Whiteley-6R index, a validated scale measuring health anxiety, in which a higher score (range 0 to 24) indicates increased health anxiety [32]. Psychological distress, anxiety, and depressive symptoms will be measured using abbreviated subscales of the Symptom Checklist (SCL-8, SCL-4anx, and SCL-6dep), respectively [33,34]. Illness perceptions are assessed using the Brief Illness Perception Questionnaire (B-IPQ) [35]. Finally, overall physical health is measured by a single item from the SF-36, estimating self-perceived health on a scale from "excellent"to "poor", where a higher score indicates poorer health [30].

5.1. Data sources and research infrastructure

Data are to be obtained from the high-fidelity, linkable and highly complete Danish health registries, clinical management systems, and patient questionnaires. Registry data shall be drawn from clinical management systems, the Danish National Patient Registry, the Danish Psychiatric Central Research Registry, the Danish National Prescription Reimbursement Database, and the Danish Registry-based Evaluation of Marginalization (DREAM). Healthcare utilization and costs will be drawn from Danish healthcare registries, whereas societal costs shall be obtained from the DREAM database. The DREAM database provides weekly information on social benefit payments for all citizens in Denmark, enabling detailed analysis of occupational status and public expenses. The cost data in the health service registries are based on Diagnosis-Related Group (DRG) codes for in- and out-patient treatment in Danish hospitals, on actual reimbursement for primary care and medical specialists, and on public expenses for prescription medication.

Questionnaire data are obtained from patients via electronic questionnaires using a REDCap database. This data collection is assisted by a dedicated study nurse, who is blinded to study group allocation in the process of reminding patients of filling in the questionnaire data. The study nurse is furthermore instructed to spend equal effort on reminders for all study participants. Baseline data is collected prior to randomisation. Follow-up questionnaires at 3 and 12 months after randomisation are sent to study participants electronically in a secure format.

All collected data is stored in a secure REDCap database, created and managed by a data manager with experience in REDCap management of research questionnaires.

6. Power calculation

The power calculation is based on the first primary outcome (i.e., the difference in healthcare utilization between the two groups). A difference of 0.3 standard deviations (SD) has been established as a meaningful effect size in health economics for powering cost-effectiveness studies [36]. We therefore powered the study to detect a 0.3-SD difference in healthcare utilization. To obtain a realistic estimate of the outcome's variability, we used variance parameters from a previous study of healthcare utilization in the same source population [3]. We prespecified two co-primary outcomes - an accepted approach in randomised trials - and acknowledge that testing four secondary outcomes carries a multiplicity risk, so those findings will be interpreted with

Table 2
Measures and data collection times.

Measures	Assessment Tool	Key	Baseline	3 Months	12 Months
Patient-rated outcomes					
Health-related quality of life	SF-36	Health survey assessing quality of life	✓	✓	✓
Life quality	EQ-5D-5L	Health-related quality of life	✓	✓	✓
Overall health improvement	CGI	Clinical global improvement (CGI) – patient reported	✓	✓	✓
Symptoms of FSD	BDS Checklist	Bodily Distress Syndrome (BDS) symptoms	✓	✓	✓
Illness worry	Whiteley-6R	Health anxiety	✓	✓	✓
Psychological distress	SCL-8	Symptom Checklist 8-items for psychological distress	✓	✓	✓
Symptoms of anxiety	SCL-4anx	Symptom Checklist 4-items focused on anxiety	✓	✓	✓
Symptoms of depression	SCL-6dep	Symptom Checklist 6-items focused on depression	✓	✓	✓
Illness perception	B-IPQ	Illness perceptions	✓	✓	✓
Registry data					
Health-economic data		Danish National Registries (healthcare services, prescriptions, sickness absence, and social benefits)	✓	✓	✓

appropriate caution. While we did not assume a specific distribution of the outcome, we used a two-sample *t*-test to estimate required sample size, as this is a standard and robust approximation in health services research [37]. Final analyses will apply appropriate methods for skewed data. We performed our calculation with a two-sample t-test with a significance level (alpha) of 0.05 and a power (beta) level of 0.80. This yielded a sample size of 352, with 176 participants 1:1 randomised to each group. We used Stata version 15 by StataCorp. LLC for the power calculation.

7. Ethical considerations

The DISTRESS trial is registered at clinicaltrials.gov under the study ID number 147304 [24] and in the internal list of research projects at the Central Denmark Region (case number 1–16–02-160-19). The Ethical Committee for Health Science Research in the Central Denmark region has reviewed our protocol and decided that, based on the nature of the interventions involved, this project does not require ethical approval according to §2, section 1, and §14, section 1 of the Committee law. Written informed consent was obtained for each participant prior to inclusion in the trial and stored in the REDCap database.

8. Discussion

This study protocol describes the DISTRESS trial, a randomised clinical trial aiming to evaluate the effectiveness and cost-effectiveness of a novel FSD Diagnostic Clinic compared to usual diagnostic assessment. The DISTRESS trial represents a significant effort to address the clinical and economic challenges posed by FSDs. The potential is to increase the healthcare service offered and address the knowledge gap between primary care and highly specialised FSD clinics.

A key strength of our study is the availability of comprehensive, linkable national registries in Denmark, which facilitates detailed and reliable analyses of healthcare utilization and economic outcomes. The Danish CPR (civil registration number) system enables precise linkage of data across registries, enhancing the accuracy and reliability of cost and utilization evaluations. Additionally, Denmark's primary care model, where patients have free access to a specific FP who serves as a gatekeeper to secondary care, provides a well-structured framework for tracking patient pathways and healthcare interventions. The pragmatic design of the trial, conducted within the secondary hospital sector, further supports the applicability of findings to real-world settings, potentially increasing their generalizability.

Our trial also has several limitations. As a single-centre trial, the findings may not be readily generalizable to other healthcare settings with different organizational structures. Although the study population of the DISTRESS trial is representative of the vast majority of FSD patients, some restrictions to the inclusion and exclusion criteria are relevant. Firstly, we include only those of western cultural upbringing because the Danish SF-36 instrument has only been validated in this population. Secondly, we have also restricted the upper age range to 60 years to reduce risk of exclusions due to comorbidities. Finally, patients suffering from severe or emergent mental illness are excluded since that is not within the purview of our physical diagnostic centre setting. Additionally, the unavoidable unmasking of study group allocation for patients and clinicians in this study must be carefully considered when interpreting the results. While patients and clinicians necessarily become aware of the randomisation outcome depending on which clinic they are subsequently seen at, all outcome data are collected independently of the treating clinicians, and statistical analyses will be conducted using masked group identifiers to ensure analyst blinding until final interpretation.

9. Perspectives

The DISTRESS trial explores an intermediate step in a stepped-care approach, potentially expanding access to FSD diagnostic assessment beyond the capacity of highly specialised FSD clinics. By training internists in a highly specialised FSD-focused approach, this model may enable FPs to arrive at earlier diagnoses and more effective management strategies, potentially halting the odyssey and thus preventing symptoms from worsening, as well as improving the quality of life for patients and reducing healthcare costs. By addressing gaps in FSD diagnostic availability and improving patient pathways within the healthcare system, this approach can provide a building block in a stepped care model that offers better and more accessible service for patients who can benefit from less specialised care, aligning healthcare services with the needs of both FPs and patients.

CRediT authorship contribution statement

Michael M. Madsen: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Christian Trolle:** Writing – review & editing, Supervision, Project administration, Investigation. **Lotte V. Fynne:** Writing – review & editing, Project administration, Investigation. **Michele Colombo:** Writing – review & editing, Project administration, Investigation. **Rasmus L. Pedersen:** Writing – review & editing, Investigation. **Vibeke N. Sørensen:** Investigation, Writing – review & editing. **Susan R. Christensen:** Writing – review & editing, Investigation. **Per Fink:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Lise K. Gormsen:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis.

Declaration of competing interest

None of the authors have any financial or personal relationships that could have influenced the work presented in this paper.

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Data availability

Data will be made available on request.

References

[1] P. Fink, C. Burton, J. De Bie, W. Söllner, K. Fritzsche, Current State of Management and Organisation of Care. Medically Unexplained Symptoms, Somatisation and Bodily Distress: Developing better Clinical Services, Cambridge University Press, Cambridge, 2011, p. 97.

[2] M.W. Petersen, A. Schröder, T. Jørgensen, E. Ørnbøl, T. Meinertz Dantoft, M. Eliasen, et al., Irritable bowel, chronic widespread pain, chronic fatigue and related syndromes are prevalent and highly overlapping in the general population: DanFunD, Sci. Rep. 10 (1) (2020) 3273.

[3] A. Budtz-Lilly, M. Vestergaard, P. Fink, A.H. Carlsen, M. Rosendal, Patient characteristics and frequency of bodily distress syndrome in primary care: a cross-sectional study, Br. J. Gen. Pract. 65 (638) (2015) e617–e623.

[4] A.J. Barsky, E.J. Orav, D.W. Bates, Somatization increases medical utilization and costs independent of psychiatric and medical comorbidity, Arch. Gen. Psychiatry 62 (8) (2005) 903–910.

[5] A. Budtz-Lilly, A. Schröder, M.T. Rask, P. Fink, M. Vestergaard, M. Rosendal, Bodily distress syndrome: a new diagnosis for functional disorders in primary care? BMC Fam. Pract. 16 (1) (2015) 180.

[6] P. Fink, Surgery and medical treatment in persistent somatizing patients, J. Psychosom. Res. 36 (5) (1992) 439–447.
[7] A. Schröder, J. Dimsdale, Management of Somatic Symptoms, Scientific American Medicine, 2014.
[8] P. Fink, T. Toft, M.S. Hansen, E. Ørnbøl, F. Olesen, Symptoms and syndromes of bodily distress: an exploratory study of 978 internal medical, neurological, and primary care patients, Psychosom. Med. 69 (1) (2007) 30–39.
[9] W. Rief, C. Burton, L. Frostholm, P. Henningsen, M. Kleinstäuber, W.J. Kop, et al., Core outcome domains for clinical trials on somatic symptom disorder, bodily distress disorder, and functional somatic syndromes: European network on somatic symptom disorders recommendations, Psychosom. Med. 79 (9) (2017) 1008–1015.
[10] K. Yon, S. Nettleton, K. Walters, K. Lamahewa, M. Buszewicz, Junior doctors' experiences of managing patients with medically unexplained symptoms: a qualitative study, BMJ Open 5 (12) (2015) e009593.
[11] S.R. Hahn, K.S. Thompson, T.A. Wills, V. Stern, N.S. Budner, The difficult doctor-patient relationship: somatization, personality and psychopathology, J. Clin. Epidemiol. 47 (6) (1994) 647–657.
[12] J.L. Jackson, K. Kroenke, Difficult patient encounters in the ambulatory clinic: clinical predictors and outcomes, Arch. Intern. Med. 159 (10) (1999) 1069–1075.
[13] E.H. Lin, W. Katon, M. Von Korff, T. Bush, P. Lipscomb, J. Russo, et al., Frustrating patients, J. Gen. Intern. Med. 6 (3) (1991) 241–246.
[14] M.T. Rask, E. Ørnbøl, M. Rosendal, P. Fink, Long-term outcome of bodily distress syndrome in primary care: a follow-up study on health care costs, work disability, and self-rated health, Psychosom. Med. 79 (3) (2017) 345.
[15] M. Rosendal, F. Bro, P. Fink, K.S. Christensen, F. Olesen, Diagnosis of somatisation: effect of an educational intervention in a cluster randomised controlled trial, Br. J. Gen. Pract. 53 (497) (2003) 917–922.
[16] H. Grupp, C. Kaufmann, H.H. König, F. Bleibler, B. Wild, J. Szecsenyi, et al., Excess costs from functional somatic syndromes in Germany - an analysis using entropy balancing, J. Psychosom. Res. 97 (2017) 52–57.
[17] Funktionelle lidelser - anbefalinger til udredning, behandling, rehabilitering og afstigmatisering, Sundhedsstyrelsen, 2018.
[18] P. Fink, M. Rosendal, T. Toft, Assessment and treatment of functional disorders in general practice: the extended reattribution and management model–an advanced educational program for nonpsychiatric doctors, Psychosomatics 43 (2) (2002) 93–131.
[19] P. Fink, M. Rosendal, A. Schröder, C.U. Rask, A. Ostenfeld-Rosenthal, L. Sanchez Toscano, et al., Functional Disorders and Medically Unexplained Symptoms, Assessment and treatment: Aarhus Universitetsforlag, 2015.
[20] A.-W. Chan, J.M. Tetzlaff, D.G. Altman, A. Laupacis, P.C. Gøtzsche, K. Krleža-Jerić, et al., SPIRIT 2013 statement: defining standard protocol items for clinical trials, Ann. Intern. Med. 158 (3) (2013) 200–207.
[21] P. Fink, A. Schröder, One single diagnosis, bodily distress syndrome, succeeded to capture 10 diagnostic categories of functional somatic syndromes and somatoform disorders, J. Psychosom. Res. 68 (5) (2010) 415–426.
[22] M.M. Madsen, C. Trolle, L. Fynne, E. Ørnbøl, P. Fink, L.K. Gormsen, Can internal medicine specialists diagnose functional somatic disorders (FSDs)? Training and comparison with FSD specialists, PLoS One 19 (7) (2024) e0307057.
[23] J.L. Agger, A. Schröder, L.K. Gormsen, J.S. Jensen, T.S. Jensen, P.K. Fink, Imipramine versus placebo for multiple functional somatic syndromes (STreSS-3): a double-blind, randomised study, Lancet Psychiatry 4 (5) (2017) 378–388.
[24] M.M. Madsen, L.K. Gormsen, C. Trolle, P. Fink, DISTRESS Trial Functional Disorders - the DISTRESS Trial (DISTRESS): clinicaltrials.gov, 2024 [NCT06025617:[Comprehensive Evaluation of a New Diagnostic Clinic for Functional Disorders - the DISTRESS Trial]. Available from: ClinicalTrials.gov.
[25] E.D.S. Connelly, P. Vedsted, M.T. Høybye, S. Madden, L.K. Gormsen, User Perspectives of a Complex Healthcare Intervention for Functional Somatic Disorders: A Qualitative Process Evaluation, Aarhus University, 2023, 2023/11/01.
[26] J.K. Wing, N. Sartorius, T.B. Üstün, Diagnosis and Clinical Measurement in Psychiatry: A Reference Manual for SCAN, Cambridge University Press, 1998.
[27] A. Bertelsen, A life in psychiatry—as I remember it, Acta Psychiatr. Scand. 136 (3) (2017) 333–338.
[28] G.R. Smith Jr., R.A. Monson, D.C. Ray, Psychiatric consultation in somatization disorder, N. Engl. J. Med. 314 (22) (1986) 1407–1413.
[29] T.M. Kashner, K. Rost, G.R. Smith, S. Lewis, An analysis of panel data: the impact of a psychiatric consultation letter on the expenditures and outcomes of care for patients with somatization disorder, Med. Care 811-21 (1992).
[30] J.E. Ware Jr., C.D. Sherbourne, The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection, Med. Care (1992) 473–483.
[31] S. Pick, D.G. Anderson, A.A. Asadi-Pooya, S. Aybek, G. Baslet, B.R. Bloem, et al., Outcome measurement in functional neurological disorder: a systematic review and recommendations, J. Neurol. Neurosurg. Psychiatry 91 (6) (2020) 638–649.
[32] P. Fink, E. Ørnbøl, K.S. Christensen, The outcome of health anxiety in primary care. A two-year follow-up study on health care costs and self-rated health, PLoS One 5 (3) (2010) e9873.
[33] P. Fink, E. Ørnbøl, M.S. Hansen, L. Søndergaard, P. De Jonge, Detecting mental disorders in general hospitals by the SCL-8 scale, J. Psychosom. Res. 56 (3) (2004) 371–375.
[34] K.S. Christensen, P. Fink, T. Toft, L. Frostholm, E. Ørnbøl, F. Olesen, A brief case-finding questionnaire for common mental disorders: the CMDQ, Fam. Pract. 22 (4) (2005) 448–457.
[35] E. Broadbent, K.J. Petrie, J. Main, J. Weinman, The brief illness perception questionnaire, J. Psychosom. Res. 60 (6) (2006) 631–637.
[36] M.F. Drummond, M.J. Sculpher, K. Claxton, G.L. Stoddart, G.W. Torrance, Methods for the Economic Evaluation of Health Care Programmes, Oxford university press, 2015.
[37] T. Lumley, P. Diehr, S. Emerson, L. Chen, The importance of the normality assumption in large public health data sets, Annu. Rev. Public Health 23 (1) (2002) 151–169.