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Persistent SOMAtic Symptoms ACROSS Diseases - From Risk Factors to Modification: Protocol of the Interdisciplinary SOMACROSS Research Unit (RU 5211)

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ABSTRACT:

Introduction: Persistent Somatic Symptoms (PSS) are highly prevalent in all areas of medicine; they are disabling for patients and costly for society. The subjective symptom burden often correlates poorly with the underlying disease severity, and patients' needs for effective treatment are far from being met. Initial evidence indicates that, in addition to disease-specific pathophysiological processes, psychological factors such as expectations, somatosensory amplification, and prior illness experiences contribute to symptom persistence in functional as well as in somatic diseases. However, prospective studies investigating the transition from acute to chronic somatic symptoms, integrating pathophysiological, psychological, and social factors, are scarce. A better understanding of the multifactorial mechanisms of symptom persistence is crucial to develop targeted mechanism-based interventions for effective prevention and treatment of PSS. Thus, the overall aim of the interdisciplinary SOMACROSS research unit is to identify generic and disease-specific risk factors and aetiological mechanisms of symptom persistence across a range of diseases.

Methods and analysis: Seven projects will investigate risk factors and mechanisms of symptom persistence in a total of 3,916 patients across ten medical conditions. All study designs are prospective and share common assessment points, core instruments, and outcome variables to allow comparison and validation of results across projects and conditions. Research will focus on the identification of generic and disease-specific mechanisms associated with unfavourable symptom course. The development of a multivariate prediction model will facilitate the understanding of the course of PSS across diseases.

Ethics and dissemination: All individual SOMACROSS studies were approved by the ethics committees of Hamburg and Münster, Germany. Findings will be disseminated through peer-reviewed publications, scientific conferences, and involvement of relevant stakeholders, patients and the lay public. This interdisciplinary research unit will fundamentally contribute to

earlier recognition of patients at risk, and to the development of prevention and tailored treatment concepts for PSS.

Key words

Persistent Somatic Symptoms; Mechanisms; Risk Factors; Expectations; Research Unit; Biopsychosocial Models; Prediction Models

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Although persistent somatic symptoms (PSS) are highly prevalent among various diseases, distressing and disabling for patients and costly for society, mechanisms of symptom persistence are rarely investigated and poorly understood.
- The SOMACROSS research unit goes beyond previous research by determining the complex and dynamic biopsychosocial interplay contributing to persistent symptom states in a number of different syndromes and diseases.
- In order to detect patterns of symptom persistence across diseases, the SOMACROSS research unit aims to identify potential risk factors and mechanisms of PSS across various somatic diseases, functional syndromes and somatoform disorders using a common working model, joint core measures, prospective designs and coordinated evaluation methods.
- The SOMACROSS research unit uses a multidisciplinary approach to overcome today's highly fragmented research on PSS and provide pathways to developing efficient disease-overarching intervention strategies.
- Despite investigating multiple potential risk factors and mechanisms of the persistence of somatic symptoms, other variables might be relevant; and conclusions can only be drawn for the conditions under investigation.

INTRODUCTION

State of the art

Definition: Persistent Somatic Symptoms (PSS)

The term 'Persistent Somatic Symptoms (PSS)' is used as an umbrella term to describe subjectively distressing somatic complaints, irrespective of their aetiology, that are present on most days for at least several months. PSS are operationalised by repeated measures of patients' subjective somatic symptom severity.

PSS across medical fields: PSS are highly prevalent in all fields of medicine, from primary to specialized care and mental health care,[1 2] yet remain greatly neglected in research.[3] Complaints may include pain, gastroenterological, cardiovascular, genito-urinary, neurological or other symptoms (**Figure 1**). Regardless of their aetiology, PSS cause substantial suffering, impaired quality of life and work participation.[4 5] Many somatic symptoms are neither exclusive correlates of somatic disease (e.g., vascular or inflammatory disease) nor exclusive symptoms of a mental disorder (e.g., depressive or anxiety disorders).[2 6 7] Thus, a dualistic view classifying symptoms as either somatic or psychological is neither evidence-based nor patient-centred.[8] With reference to the description of bodily distress disorder in the International Classification of Diseases, 11th edition (ICD-11), the term 'persistent' here defines somatic symptoms which are present on most days for at least several months.[9]

*Please insert **Figure 1** approximately here*

Impact on patients – challenges in health care: Eighty percent of the general population experience one or more symptoms within one month.[10-12] Somatic symptoms account for the majority of all primary and secondary care consultations.[13 14] Whereas in most cases, symptoms fluctuate naturally and eventually disappear, about one fourth of individuals with acute symptoms develop PSS and remain affected one year after their first consultation.[8]

Often, these symptoms are accompanied by comorbid depression and anxiety[2] and an increased risk for suicidal ideation and attempts.[15 16] PSS are costly for society,[17 18] and health care for PSS is challenging.[19] The clinical reality is characterized by fragmented treatment in specialized care (e.g., gastrointestinal symptoms in gastroenterology, chest pain in cardiology), even though patients often report multiple or overlapping symptoms.[20]

From ‘medically unexplained’ to a broader understanding of distressing persistent somatic symptoms: Most research on PSS has been conducted on so called ‘medically unexplained symptoms’, a term mainly used in primary care, while specialised medical fields more commonly employ the term 'functional syndromes'.[21] The 'medical inexplicability' of the symptoms was also the defining diagnostic criterion of the earlier diagnosis of somatoform and related disorders in the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV),[22] and the International Classification of Diseases, 10th edition (ICD-10).[23] The concept of medical inexplicability of somatic symptoms is considered problematic because (1) the label ‘medically unexplained’ for disabling symptoms creates distress in patients[24], (2) the reliability of assessing whether or not there is a pathophysiological explanation for a certain symptom is notoriously poor, (3) the concept reinforces a mind-body-dualism.[8], and (4) many patients disapproved of the term.[25] Therefore, a new conceptualization was introduced namely Somatic Symptom Disorder (SSD in DSM-5)[26] and Bodily Distress Disorder (BDD in ICD-10),[9] incorporating features of persistent and clinically significant somatic complaints which are accompanied by excessive and disproportionate health-related concerns, feelings, and behaviours. SSD and BDD may or may not be accompanied by a somatic disease.[27] Of note, patients with ‘medically explained’ and ‘unexplained’ symptoms are equally impaired.[4 5]

Transferability of psychosocial aetiological mechanisms from functional and somatoform disorders to somatic diseases: Most research on aetiological mechanisms of PSS has been conducted in somatoform and functional syndromes. The question arises whether these

findings can be transferred to SSD and BDS, and beyond that, to PSS in somatic diseases. There is initial evidence that – in addition to the underlying pathophysiology – psychosocial factors play a relevant role in the development and persistence of symptoms in somatic diseases. For example, previous studies by our group indicated that patients' beliefs about their disease strongly influence recovery after coronary artery bypass surgery,[28] that pre-treatment expectations significantly predict patient-reported long-term side-effects and quality of life in women receiving endocrine breast cancer treatment,[29] and that the extent of illness anxiety before gastrointestinal infection predicts the development of post-infectious irritable bowel syndrome after seven months.[30] The understanding of psychosocial factors, in turn, can help improve treatment for patients with PSS. First evidence in support of this is available from the PSY-HEART trial, a three-arm randomized clinical trial in which a preoperative optimisation of patient expectations prior to coronary artery bypass graft surgery led to a reduction of post-operative disability compared to usual surgery care alone.[31]

Even though it remains unclear how PSS evolve and are maintained over time, their presence in various somatic diseases is associated with a faster disease progression, more severe complications, and increased mortality.[32-34] Further evidence supporting the important role of psychosocial factors in the persistence of symptoms in somatic diseases is provided by the observation that symptom burden frequently persists although the underlying pathophysiology has been optimally treated.[5 35] In addition to disease-specific treatment, psychological treatment and centrally acting pharmacotherapy appear to be the most promising options, not only for functional and somatoform disorders but also for PSS in well-defined somatic diseases.[19] This suggests that generic, trans-diagnostic treatment principles[36] may be valuable in addition to the disease-specific treatment of the underlying pathophysiology. Across somatic diseases, a diverse array of psychological and social factors needs to be considered on equal footing with biological factors in their roles as potential risk factors, protective factors, and maintaining factors of PSS. Importantly, psychological and social factors are not solely secondary reactions to persistent symptoms; rather, they are deeply woven into the biopsychosocial processes that lead to PSS.

To conclude, sufficient evidence warrants the assumption that aetiological mechanisms derived from research on somatoform and functional disorders also contribute to the persistence of symptoms in somatic diseases. However, the applicability of generic and specific risk factors and mechanisms of PSS across medical diseases has yet to be investigated.

Current aetiological knowledge on PSS: The aetiology of PSS across somatic diseases is not well understood. The unique way in which each individual perceives a somatic symptom and its severity, the expectation on how the symptom will evolve, and whether the treatment will be effective depends on the constellation of biological, psychological, and social factors. The comprehensive vulnerability-stress model by Henningsen et al.[19] defines predisposing, triggering, and maintaining/aggravating factors that determine the transition from short-term to persistent disabling symptoms. After extensively reviewing the literature for all targeted conditions included in the SOMACROSS research unit (RU), we developed a 'PSS working model' as a starting point for the investigation of disease-overarching generic and disease-specific risk factors and aetiological mechanisms (see **Figure 2**). The risk factors and aetiological mechanisms described below are considered most relevant to PSS:

Definitions: risk factors and aetiological mechanisms

'Risk factors' refer to variables associated with an increased risk of symptom persistence, although the relationship is not necessarily causal. 'Aetiological mechanisms' denote underlying mechanisms which are presumed to be causally involved in the persistence of symptoms.

a. Predisposing factors for PSS include sociodemographic risk factors such as female gender,[37] poor education and socioeconomic status,[3 38] sociocultural factors,[39] psychological aspects such as early adverse life experiences,[40-43] personality factors like

neuroticism and negative affectivity,[44] biomedical factors such as prior medical diseases,[44] certain (epi)genetic profiles,[45] and immunological correlates of these factors.[3 46 47]

b. Triggering factors for short-term somatic symptoms include acute infections, injuries, medical or surgical procedures, or current life stressors.[19 30]

c. Maintaining/aggravating factors: Most aetiological models on bodily complaints in somatoform and functional disorders[48-50] include the following core cognitive-perceptual and emotional mechanisms: selective attention towards interoceptive cues, amplified perception of bodily sensations, catastrophizing cognitive interpretations, somatosensory amplification,[51] and dysfunctional illness behaviours.[19 46 52] Affective factors such as alexithymia comprise deficits in the regulation of emotions.[53] On the level of dysfunctional behavioural processes, somatic symptoms are aggravated by learning processes, avoidance behaviour such as physical inactivity and subsequent deconditioning.[54-56] Further aggravating factors arise from unsatisfying encounters with the health care system, negative illness perceptions, and treatment experiences which result in the unnecessary and potentially harmful overuse of health care.[19] Social factors like work status, health literacy, access to medical care, stigmatisation, migration, and culture can be both predisposing and maintaining/aggravating factors of PSS.[57] Disease-specific biomedical factors (e.g., inflammation in inflammatory bowel disease) naturally influence the course of somatic symptom severity.[58] Additionally, disease-overarching psychobiological models postulate dysregulations of the endocrine, immune, and autonomic nervous systems as well as central sensitization to be potential links between psychosocial distress and PSS.[48 59] Other biopsychosocial interactions contributing to symptom persistence include treatment-related factors such as burdensome side effects of a treatment for an underlying disease. These side effects are difficult to disentangle from general bodily distress and likely to be influenced by nocebo effects through

patients' negative expectations and other psychological factors.[60] Central sensitization, defined as hyperexcitability of the central nervous system, has been suggested to contribute to the development and maintenance of chronic pain, while its role in other PSS is under debate.[61 62] Central sensitization is thought to be driven by neuroinflammation in the central and peripheral nervous system, as indicated by higher serum levels of interleukin 6 (IL-6) and tumour necrosis factor (TNF).[61] Recently, epigenetic modifications such as DNA methylation have been identified as potential contributors to altered resilience to environmental stress, pain, and somatic symptom burden.[38 63] Stool microbiota alterations are also hypothesized to be associated with the persistence of somatic symptoms. There is evidence of gut microbiota dysbiosis in patients with chronic fatigue and nonvisceral pain.[64 65]

d. Interactions of biopsychosocial factors: Recently, patients' expectations of symptoms have come into focus as having a central role in symptom processing and the relation between biological, psychosocial and treatment-related factors for persistent symptom development. Expectations are defined as future-directed cognitions regarding the anticipated course of symptoms.[66] As such, they constitute a common denominator of many psychological risk factors for PSS such as catastrophizing, illness perceptions and health anxiety. Thus, they can be regarded as a core feature of current aetiological models for PSS (e.g., somatosensory amplification).[46] Negative symptom expectations interact with actual somatic input and can fuel dysfunctional signal processing and the development of persistent symptoms. Relevantly, the power of expectations to predict symptom course, treatment benefit and negative treatment side effects has been demonstrated for a wide range of medical and psychological conditions, e.g., pain, rheumatoid arthritis, cancer, 'medically unexplained symptoms' and level of functioning after total hip and knee replacements.[29 67-71] Moreover, a growing body of research provides evidence that modifying expectations improves clinical outcomes.[31 72 73]

Expectations are also prominently conceptualized in emerging predictive processing models which suggest that symptom perception emerges through an integrative process of sensory input, prior experience (leading to implicit expectations, or "priors") and contextual cues (such as affective state).[74] These models show that the relationship between subjective symptoms and pathophysiological dysfunction is highly variable, both between and within individuals, and that pathophysiological dysfunction may even be completely absent in the presence of strong priors and ambiguous somatic input. Depending on relative strength and precision, the actual symptom experience may be more determined by somatic input or by priors.

Altogether, the above mentioned risk factors and mechanisms of somatic symptom persistence are less well studied in somatic diseases than in functional and somatoform disorders.[46] We assume that – in addition to disease-specific pathophysiological mechanisms – the processes underlying somatic symptom persistence in somatic diseases and in functional/somatoform disorders involve similar risk factors and mechanisms, opening new routes to modify symptom persistence in somatic diseases.

Novelty and innovation

SOMACROSS takes on a fundamentally new perspective, by including two new ways of thinking in medicine: First, the abandonment of the concept of medical inexplicability in the diagnostic concepts of functional and somatoform disorders; and second, the shift away from the idea that subjective suffering can essentially be explained by the extent of the underlying physiological pathology. Assuming that biological markers alone do not sufficiently explain aetiology and development of PSS, we will investigate the interaction of biological, psychological and social factors regarding their contribution to subjective symptom severity and symptom persistence n ten different medical conditions. In this way, SOMACROSS will critically challenge the still prevalent dualistic mind-body disease model in medicine. The use of a trans-symptomatic and trans-diagnostic approach will enable the identification of

patterns, risk factors and aetiological mechanisms of symptom persistence across diseases and syndromes.

Objectives of the overall project

The superordinate aim of this interdisciplinary RU is to identify risk factors and mechanisms for the persistence of somatic symptoms across diseases, and thereby create a basis for evidence-based interventions for patients suffering from PSS.

The research objectives of SOMACROSS are:

a. to identify generic (i.e., disease-overarching) biological, psychological, and social mechanisms contributing to the persistence of somatic symptoms across a range of medical diseases and syndromes;
b. to identify disease-specific mechanisms contributing to the persistence of somatic symptoms;
c. to formulate new, empirically testable hypotheses about the interaction of generic and disease-specific factors and to integrate the derived risk factors and mechanisms into comprehensive prediction models for PSS;
d. to derive generic and disease-specific clinically useful risk factors for symptom persistence;
e. to identify modifiable risk factors and mechanisms in the transition from acute to chronic symptoms; and,
f. to test whether the therapeutic optimisation of modifiable risk factors (e.g., dysfunctional symptom expectations) improves clinical outcomes.

The structural objectives of SOMACROSS are:

a. to raise awareness for a highly relevant research field across medical disciplines;
b. to disseminate knowledge regarding the development and treatment of PSS;
c. to build a strong interdisciplinary research structure focused on PSS; and,

d. to establish qualifications of the next generation of scientific experts in this field.

Working hypotheses of the overall project

Hypothesis 1: In all syndromes and diseases examined in SOMACROSS, biological, psychological and social factors contribute to the persistence of somatic symptoms individually or/and in interplay.

Hypothesis 2: Persistence of somatic symptoms is predicted by common risk factors across syndromes and diseases.

Hypothesis 3: Generic and syndrome- and/or disease-specific risk scores accurately predict the risk of persistence of somatic symptoms.

Hypothesis 4: Expectations play a relevant role in the development of persistent somatic symptoms. Thus, the modification of dysfunctional expectations constitutes a promising starting point for interventions to improve symptom severity in PSS.

METHODS AND ANALYSIS

Design

Investigated symptoms and composition of SOMACROSS: To ensure clinical relevance, symptoms with high prevalence in medical settings were chosen, i.e., fatigue, gastrointestinal symptoms, pruritus, and multiple co-existing symptoms.[75] To detect patterns, similarities, and discrepancies in symptom persistence across a range of medical conditions, syndromes typically classified as somatic (e.g., primary biliary cholangitis, ulcerative colitis) and syndromes considered as 'functional' or 'somatoform' (e.g., irritable bowel syndrome, somatic symptom disorder) were included. The seven projects of SOMACROSS including content and project leaders are listed in **Table 1**

*Please insert **Table 1** approximately here*

Each project will investigate specific predisposing, triggering, maintaining or aggravating factors for PSS based on the current state of knowledge in the respective disease or syndrome. Based on our extensive literature review, we compiled a 'PSS working model' (**Figure 2**), which serves as a starting point for rigorous testing of distinct factors with regard to their relevance for symptom persistence across all projects. These factors are assessed by the joint core set of measures (see below) that will be used across all projects. Other predictor variables, which are considered specific for defined diseases or syndromes only, will be tested in the respective individual projects. Of note, the classification of variables as predisposing, triggering, maintaining, and aggravating factors is preliminary and not always distinct.

*Please insert **Figure 2** approximately here*

Study designs and methodological approaches: The initial state of knowledge varies between the individual projects and health conditions. For some diseases, there is cross-sectional evidence on associations between symptom persistence and specific biopsychosocial variables. For others, longitudinal studies have identified relevant predictors for symptom maintenance. These different starting points in terms of current knowledge lead to different research aims (**Figure 3**). In an envisaged second funding phase, all projects will take a step towards modification of the relevant factors based on their individual project results.

*Please insert **Figure 3** approximately here*

Shared inclusion and exclusion criteria: All projects share common basic inclusion criteria, i.e.: age ≥18 years, sufficient oral and written German language proficiency, and written informed consent. Common exclusion criteria include: serious illness requiring immediate intervention; florid psychosis or substance abuse disorder, and acute suicidality. In addition

to these common criteria, the individual projects defined project-specific inclusion and exclusion criteria.

Shared assessment points: In order to compare results across projects, all projects (P) with prospective study designs (P1-5) will use identical assessment points, i.e., baseline, 6-, and 12-month follow-up. These enable the statistical evaluation of generic predictors across diseases and the pooling of data.

Patient and public involvement: Involvement of patients or members of the public varies among the projects of the research unit and is therefore described in detail in the study protocols of the individual projects.

Measures

Shared outcome measures: Severity of somatic symptoms is the primary outcome for all projects (**Table 2**). Given that a) somatic symptom severity must be specifically assessed for each symptom, and that b) generic instruments are needed to conduct comparisons and joint evaluations across projects, somatic symptoms are measured in two ways:

a. Symptom-specific assessment, using specific measures of somatic symptom severity,
b. Generic assessment of overall symptom severity, using the internationally well-established Patient Health Questionnaire-15 (PHQ-15)[76 77] and the Numeric Rating Scale for symptom intensity as recommended by the EURONET-SOMA group[78].

Additional shared secondary outcomes include symptom interference, disability, and quality of life.

Joint psychosocial core instruments: The list of joint core instruments of SOMACROSS (**Table 2**) reflects the factors displayed in the PSS working model (**Figure 2**). All joint core instruments were chosen after considering construct relevance, reliability, validity, feasibility, acceptability, availability in German and statistical constraints. In order to assess the

comorbidity with DSM-5 somatic symptom disorder in all the diseases investigated, the relevant section of a German research version of the Structured Diagnostic Interview for Mental Disorders (SCID-5) will be conducted.[79 80]

*Please insert **Table 2** approximately here*

Joint biomedical factors: In addition to the joint core set of instruments, the various projects of SOMACROSS investigate further common variables with regard to their relevance for PSS. Disease overarching factors such as duration and subjective severity of disease, (prior) biomedical disease and comorbidities, and side effects and subjective treatment experiences will be assessed as potential generic predictors of symptom persistence across all projects. Serum levels of C-reactive protein (CRP), interleukin 6 (IL-6) and tumour necrosis factor (TNF) will be measured at baseline as systemic biomarkers of central sensitization[81] to shed light on the controversial role of central sensitization in the persistence of somatic symptoms both prospectively and in a cross-sectional view across P1 to P5. The contribution of epigenetic mechanisms (altered DNA methylation in an epigenome-wide association study) in the course from acute to persistent symptoms in kidney disease will be analysed in P3. Additionally, epigenetic mechanisms will be analysed and cross-validated in pilot samples across P1 to P5 (n=20 patients per diagnosis, n=10 with low vs. high baseline symptom burden according to the PHQ-15), led by P3. We will also investigate the role of microbiome alterations for fatigue persistence among patients with primary biliary cholangitis and patients with primary sclerosing cholangitis (P1). In P2 and P3 we will collect stool samples from participants at baseline (P2 also post-intervention). Depending on the results regarding the course of PSS (P2 and P3) and the response to the intervention (P2), we will then analyse the microbiome (metagenomic sequencing). We believe that the above-mentioned biomedical factors are potentially relevant across several symptoms and diseases. Further disease-specific biomedical predictors such as disease stage and disease-specific markers

of symptom persistence will be assessed within the individual projects, using appropriate methodology.

Statistical evaluation

Joint statistical evaluation strategy: The use of shared measures and assessment points across P1 to P6 enables collective statistical analyses (n=1,328 participants; *not* included are the n=2,432 participants from the cross-sectional analysis in P6 and the n=156 participants of the intervention groups in P2). The power calculations were performed individually for each project and are included in the projects´ study protocols. The joint cross-project evaluation will allow us to develop an overarching conceptual model for the persistence of somatic symptoms. We will test paths and associations between the key factors of the working model by using an exploratory approach and initial hypotheses testing. Given scarcity of data on PSS for most of our included diseases and syndromes, we included a large number of variables in the first funding phase. This will enable us to generate new hypotheses for rigorous testing in the second funding phase. P1 and P3 will use multi-method approaches by embedding qualitative and experimental studies. Both approaches represent a valuable possibility for an in-depth exploration of mechanisms of symptom perception, development and maintenance. The statistical evaluation across projects will be carried out by biostatistics experts using a structural equation model approach. The statistical analyses will also lead to a reduction in predictors of symptom persistence by removing irrelevant pathways, which will allow more distinct analyses in subsequent studies. Depending on the existing evidence for each condition, some of the projects follow a hypothesis-generating design while others perform confirmatory tests based on prior research (see also **Figure 3**). In exploratory analyses, we do not adjust for multiple testing in order to avoid the loss of power. However, we formulated testable, pre-specified initial hypotheses for each project as starting points, which contribute to the overarching hypotheses of the Z-Project. Statistical methods to adjust for multiple testing will be applied for the confirmatory analyses.

ETHICS AND DISSEMINATION

Ethical approval: All studies including patients (P1 to P6) were approved by the respective Ethics Committees of the Medical Associations Hamburg and Westphalia-Lippe / Westphalian Wilhelms University, Münster, Germany. The individual studies will be conducted in accordance with the WMA Declaration of Helsinki, guidelines for Good Clinical Practice, national and local laws. Eligible patients will be informed about the study verbally and in written form before providing written informed consent.

Data sharing: De-identified individual patient data will be made publicly available. The times and the conditions of the availability of data will be in accordance with the `Recommendations for Sharing Clinical Trial Data´ of the Institute of Medicine (IOM). Data sharing will follow the *FAIR* Data Principles (Findable, Accessible, Interoperable and Reusable) and international naming conventions (e.g., Systematized Nomenclature of Medicine) to maximize transparency and scientific reproducibility. The main findings of each project will be published in peer-reviewed journals and made publicly available. In addition, we will communicate scientific results in lay language via press releases, social media, and patient forums.

Impact and relevance: Regarding the impact on the research field of PSS, SOMACROSS will provide the urgently needed infrastructure to facilitate collaboration and knowledge exchange between medical disciplines. The research field of PSS will benefit from the measurement of larger sets of predisposing, triggering, and maintaining biopsychosocial variables, and from additional theoretical work on their interrelation. By providing information to the public, e.g., at a 'patient day' and the SOMACROSS webpage, we hope to improve the understanding of PSS, avoid unnecessary and potentially harming medical procedures and provide reliable information for patients' personalised decision-making. Greater awareness and

understanding of PSS in society might also lead to reduced stigma associated with PSS. SOMACROSS aims to open science to young researchers with innovative ideas, provide researchers with flexible career opportunities, and improve the way in which research is conducted. The most important measures of SOMACROSS are summarized in **Figure 4**.

*Please insert **Figure 4** approximately here*

Conclusion

Our patient-centred focus on subjectively distressing somatic symptoms has the potential to enable increased visibility of somatic symptom burden across different medical specialties. SOMACROSS will enhance the relevance of each individual project by integrating knowledge about individual risk factors and mechanisms of PSS into joint analyses and publications. While we also anticipate challenges regarding comparability, transferability, and complexity of such a translational approach, we expect to gain insights on PSS that could not be reached without this collaboration. Our results will inform the development of mechanism-based tailored interventions, and in the long term, SOMACROSS will enable the translation of cutting-edge scientific knowledge into clinical practice by providing clinicians with evidence-based prevention and treatment options.

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Author contributions

BL is the speaker of the SOMACROSS research unit. OvB is a Mercator Fellow of this research unit, all other authors lead the individual SOMACROSS projects. AZ and EV provide statistical expertise to all projects of the research unit. BL drafted the first version of the study protocol, MSM and AT contributed individual parts of the study protocol. All authors contributed to the refinement of the study protocol, read and approved the final version.

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Competing interests

None

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Table 1: Individual projects and project leaders of the SOMACROSS research unit

Project No.	Project title	Project content	Project leader(s)	Institution(s)
P1 	Fatigue in Primary Biliary Cholangitis: Factors Associated With Severity and Persistence as Future Therapeutic Targets	P1 examines the disease-specific biological and generic psychosocial factors which contribute to fatigue in patients with primary biliary cholangitis and primary sclerosing cholangitis and aims to determine its course over time.	Dr. Anne Toussaint, PhD	Department of Psychosomatic Medicine and Psychotherapy, UKE
			Prof. Dr. Christoph Schramm, MD	Martin Zeitz Centre for Rare Diseases and I. Department of Medicine, UKE
P2* 	Persistence of Gastrointestinal Symptoms in Irritable Bowel Syndrome and Ulcerative Colitis: From Risk Factors to Modification	P2 investigates whether somatic symptoms in patients with irritable bowel syndrome and ulcerative colitis are influenced by illness anxiety and symptom expectations and could therefore be improved by expectation management.	Prof. Dr. Bernd Löwe, MD	Department of Psychosomatic Medicine and Psychotherapy, UKE
			Prof. Dr. Ansgar W. Lohse, MD	I. Department of Medicine, UKE
P3 	Predictors of Somatic Symptom Persistence in Patients With Chronic Kidney Disease	P3 aims to identify multivariate predictors of PSS in patients with pre-dialysis chronic kidney disease (CKD) by testing biomedical, psychological, and treatment-related predictors using a mixed methods cohort study.	Prof. Dr. Meike Shedden Mora, PhD	Department of Psychosomatic Medicine and Psychotherapy, UKE, Department of Psychology, Medical School Hamburg
			Prof. Dr. Tobias B. Huber, MD	III. Department of Medicine, UKE
P4 	Biological and Psychosocial Factors Affecting the Persistence of Pruritus Symptoms	P4 examines the interplay of psychosocial and biological factors affecting the maintenance of pruritus in patients with atopic dermatitis, patients with pruritus on non-lesional skin, and healthy controls.	Prof. Dr. Stefan W. Schneider, MD	Department of Dermatology and Venerology, UKE
			Prof. Dr. Dr. Sonja Ständer. MD	Department of Dermatology, University of Münster
			Prof. Dr. Gudrun Schneider, ND	Department of Psychosomatic Medicine and Psychotherapy, University of Münster
P5* 	Modifiable Factors for Somatic Symptom Persistence in Patients With Somatic Symptom Disorder	P5 examines whether expectations about symptom severity and coping with symptoms determine symptom persistence in patients with somatic symptom disorder in interaction with somatic comorbidity and psychosocial factors.	Prof. Dr. Yvonne Nestoriuc, PhD	Department of Clinical Psychology, Helmut-Schmidt University, Hamburg
			Dr. Anne Toussaint, PhD	Department of Psychosomatic Medicine and Psychotherapy, UKE
P6 	Social Inequalities in Aggravating Factors of Persistent Somatic Symptoms	P6 examines whether socioeconomic and migration status are associated with risk factors for the persistence of irritable bowel syndrome and fatigue.	Prof. Dr. Olaf von dem Knesebeck, PhD	Institute of Medical Sociology, UKE
Z-Project* 	Generic and Disease-Specific Mechanisms of Somatic Symptom Persistence Across Diseases	The Z-Project will oversee the other projects with respect to adherence to the common methodology. The Z-Project will pool data from the individual projects to identify networks of interacting symptoms and mechanisms of symptom persistence across projects and diseases.	Prof. Dr. Antonia Zapf, PhD	Department of Medical Biometry and Epidemiology, UKE

* Co-applicants: **P2:** PD Dr. Viola Andresen, MD; Prof Dr. Yvonne Nestoriuc, PhD; **P6** and **Z-Project:** Prof. Dr. Bernd Löwe, MD; UKE = Universitätsklinikum Hamburg-Eppendorf (University Medical Centre Hamburg-Eppendorf, Hamburg, Germany)

Table 2: Risk factors, mechanisms, and outcomes investigated by the SOMACROSS research unit

Predisposing, triggering and maintaining /aggravating factors	Single constructs	Instrument	Items	Months		
				0	6	12
Risk factors and mechanisms (assessed via self-report / laboratory test)						
Sociodemographic factors	Gender, age, nationality, heights, weights, marital status, migration status, current housing situation, insurance, education, occupational status, health care utilization	Single items	19	X	X	X
Psychosocial factors	Adverse childhood experiences	Adverse Childhood Experiences Questionnaire (ACE-D)	10	X		
	Personality: neuroticism	Big Five Inventory -10 (BFI-10)	10	X		
	Negative affectivity	Positive and Negative Affectivity Schedule (PANAS)	20	X		
	Life stressors	Perceived Stress Scale (PSS-10)	10	X		
	Perceived stigmatization	Single items	2	X		
Cognitive-perceptual and emotional mechanisms	Somatosensory amplification	Somatosensory Amplification Scale (SSAS)	10	X	X	X
	Catastrophizing	Coping Strategies Questionnaire - Catastrophizing Subscale (CSQ-CAT)	6	X	X	X
	Treatment expectations	Treatment Expectation Questionnaire (TEX-Q)	15	X	X	X
	Expectation of symptom severity	Numeric Rating Scale	1	X	X	X
	Expectation of symptom burden	Numeric Rating Scale	1	X	X	X
	Expectation of coping with symptoms	Numeric Rating Scale	1	X	X	X
	Psychological burden related to somatic symptoms or associated health concerns	Somatic Symptom Disorder – B Criteria Scale (SSD-12)	12	X	X	X
	Illness-related worries	Whiteley-Index Short Version (WI-7)	7	X	X	X
	Symptom perception	Illness perception questionnaire (B-IPQ)	8	X	X	X
	Anxiety	Generalized Anxiety Disorder-7 (GAD-7)	7	X	X	X
	Depression	Patient Health Questionnaire-9 (PHQ-9)	9	X	X	X
	Alexithymia	Toronto Alexithymia Scale (TAS-20)	20	X		
	Emotion regulation	Emotion Regulation Questionnaire (ERQ)	10	X		
Behavioral factors	Physical inactivity	International Physical Activity Questionnaire (IPAQ-SF)	7	X	X	X
Biomedical and treatment-related factors	(Prior) organic disease / comorbidity	Self-Administered Comorbidity Questionnaire (SCQ)	16	X		
	Medication adherence	Medication Adherence Report Scale (MARS-D)	5	X		
	Side effects	Numeric Rating Scale	1	X	X	X
	Treatment experiences	Numeric Rating Scale	2	X	X	X
	Systemic inflammation, markers of central sensitization (P1 to P5)	C-reactive protein (CRP)		X		
		Interleukin 6 (IL-6)		X		
		Tumor necrosis factor alpha (TNFα)		X		
	Duration of disease	Single interview questions	2	X		
	Medication	Single interview question	1	X	X	X
Outcome variables (assessed via self-report / diagnostic interview)						
Primary outcome: somatic symptoms	Somatic symptom burden	Patient Health Questionnaire-15 (PHQ-15)	15	X	X	X
	Symptom intensity	EURONET-SOMA Numeric Rating Scale	1	X	X	X
Secondary outcomes: functioning	Symptom interference	EURONET-SOMA Numeric Rating Scale	1	X	X	X
	Symptom related disability	Pain Disability Index – adapted (PDI)	7	X	X	X
	Health-related quality of life	Short Form Health Survey (SF-12)	12	X	X	X
Diagnosis of somatic symptom disorder (DSM-5)	Diagnostic classification	Structured Clinical Interview for the DSM-5 (SCID)	18	X		X
TOTAL (self-report items)			**266**			

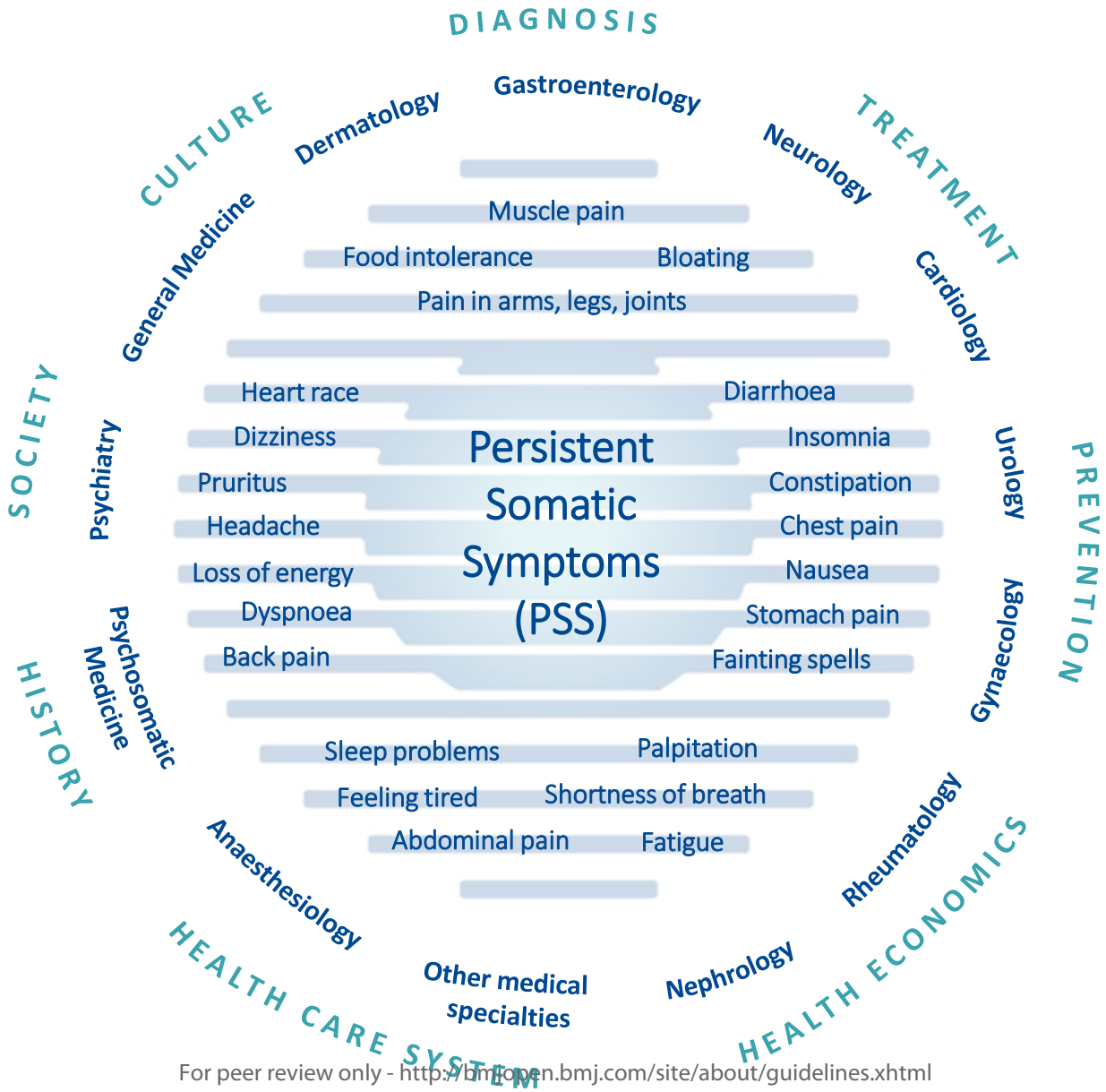
FIGURE LEGENDS

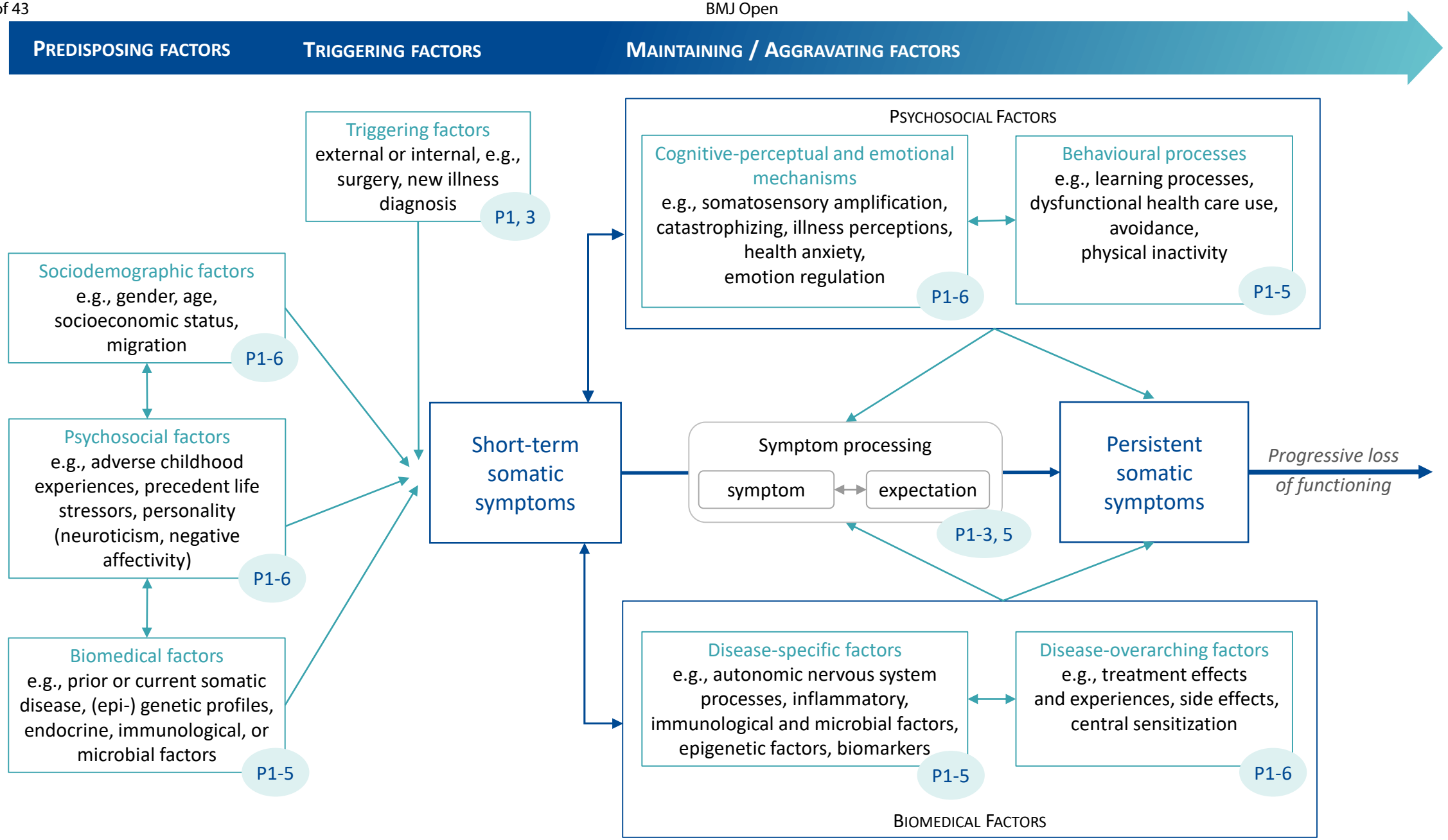
Figure 1. Relevance of Persistent Somatic Symptoms

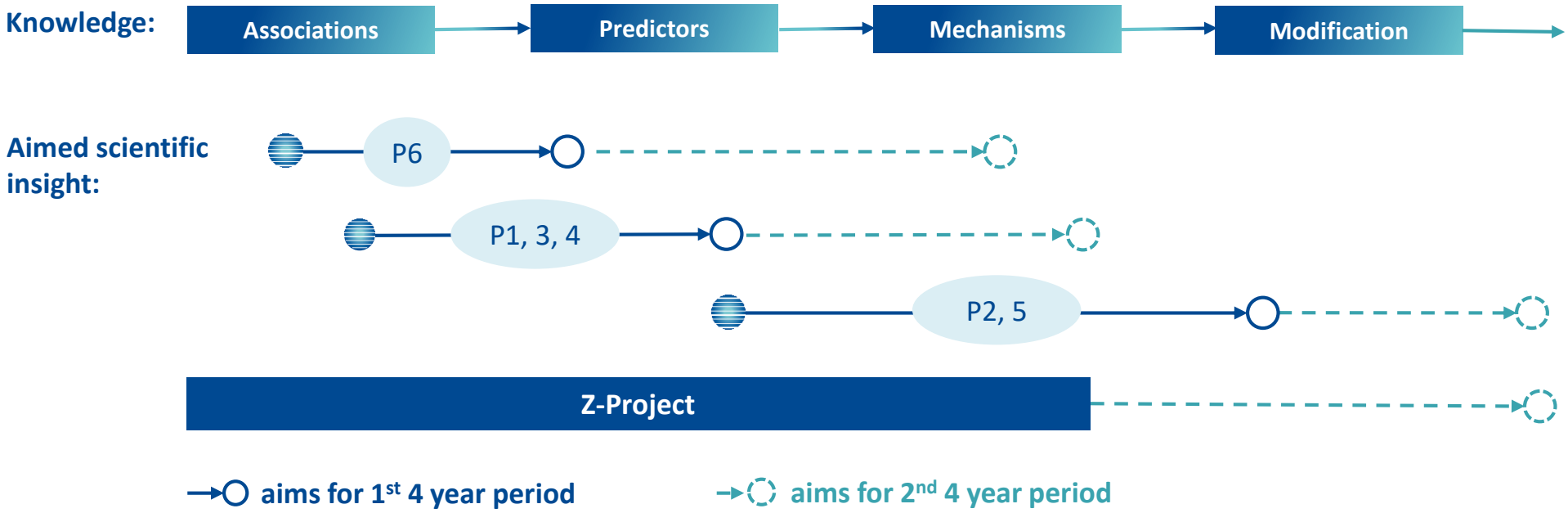
Figure 2. Working model of the SOMACROSS research unit: Risk factors and mechanisms for somatic symptom persistence as investigated by the individual projects (blue numbers indicate projects investigating the respective factors)

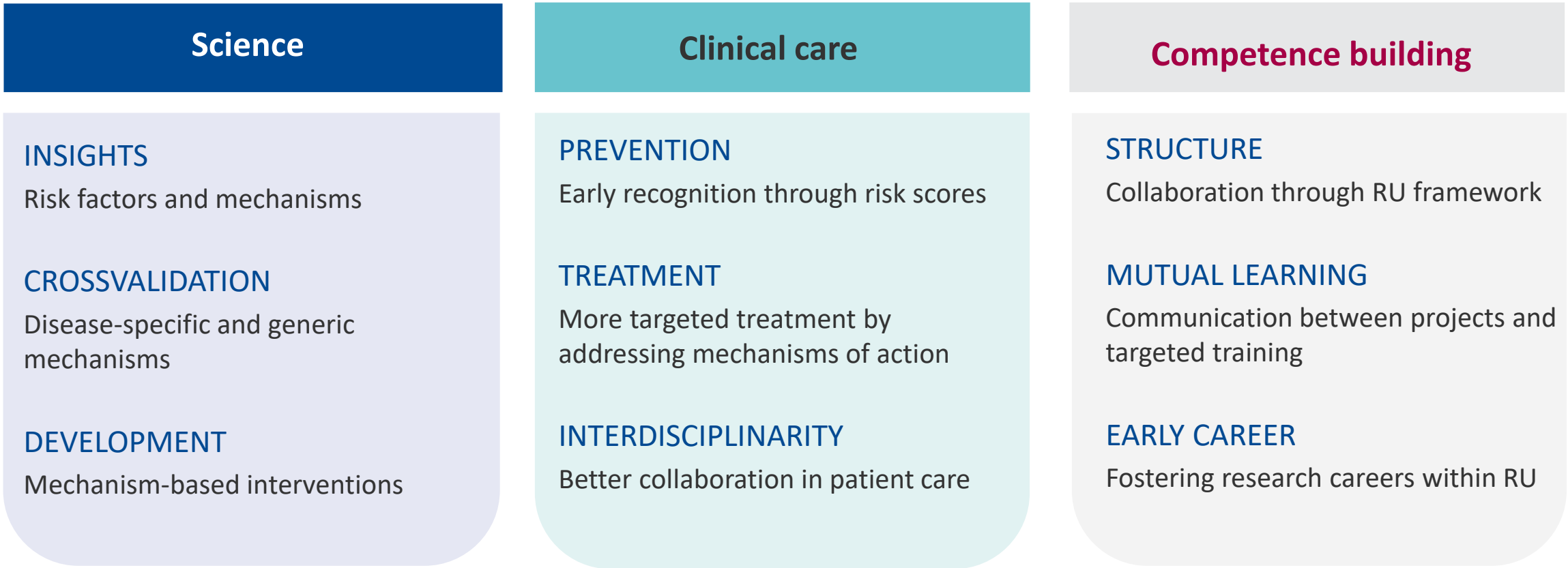
Figure 3. Projects 1-6 (P1-6): From current state of knowledge to aims of scientific insight

Figure 4. Steps forward through the SOMACROSS research unit






Knowledge:
Associations
Predictors
Mechanisms
Modification
Aimed scientific insight:
P6
P1, 3, 4
P2, 5
Z-Project
aims for 1st 4 year period
aims for 2nd 4 year period


Science
INSIGHTS
Risk factors and mechanisms
CROSSVALIDATION
Disease-specific and generic mechanisms
DEVELOPMENT
Mechanism-based interventions
Clinical care
PREVENTION
Early recognition through risk scores
TREATMENT
More targeted treatment by addressing mechanisms of action
INTERDISCIPLINARITY
Better collaboration in patient care
Competence building
STRUCTURE
Collaboration through RU framework
MUTUAL LEARNING
Communication between projects and targeted training
EARLY CAREER
Fostering research careers within RU

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	N/A – individual studies of research unit will be registered before start of recruitment (not this overall description of the research unit)
	2b	All items from the World Health Organization Trial Registration Data Set	N/A see above
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	21
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-13
	6b	Explanation for choice of comparators	9-13
Objectives	7	Specific objectives or hypotheses	13-14
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	14-18
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	14-15
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	15-16
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A – this is an overall study protocol for a research unit, not for an interventional study

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A – described in individual study protocols of SOMACROSS research unit
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A – see above
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A – see above
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	N/A – see above
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18 – described in individual study protocols of SOMACROSS research unit
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A – see above
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A – described in individual study protocols of SOMACROSS research unit

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A – see above
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A – see above
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A – see above
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A – see above
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-17, Table 2
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A – described in individual study protocols of SOMACROSS research unit
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18 – described in individual study protocols of SOMACROSS research unit
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A – see above
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A – see above
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A – see above
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A – see above
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A – see above
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18 – described in individual study protocols of SOMACROSS research unit

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	N/A – see above
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A – see above
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	N/A – see above
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18 – described in individual study protocols of SOMACROSS research unit
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A – proband insurance was concluded
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19-20
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19-20

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	15, 19 – described in detail in individual study protocols of SOMACROSS research unit
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	17– described in detail in individual study protocols of SOMACROSS research unit

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Persistent SOMAtic Symptoms ACROSS Diseases - From Risk Factors to Modification: Scientific Framework and Overarching Protocol of the Interdisciplinary SOMACROSS Research Unit (RU 5211)

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Persistent SOMAtic Symptoms ACROSS Diseases - From Risk Factors to Modification: Scientific Framework and Overarching Protocol of the Interdisciplinary SOMACROSS Research Unit (RU 5211)

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Project 4: 2020-676-f-S

ABSTRACT:

Introduction: Persistent Somatic Symptoms (PSS) are highly prevalent in all areas of medicine; they are disabling for patients and costly for society. The subjective symptom burden often correlates poorly with the underlying disease severity, and patients' needs for effective treatment are far from being met. Initial evidence indicates that, in addition to disease-specific pathophysiological processes, psychological factors such as expectations, somatosensory amplification, and prior illness experiences contribute to symptom persistence in functional as well as in somatic diseases. However, prospective studies investigating the transition from acute to chronic somatic symptoms, integrating pathophysiological, psychological, and social factors, are scarce. A better understanding of the multifactorial mechanisms of symptom persistence is crucial for developing targeted mechanism-based interventions for effective prevention and treatment of PSS. Thus, the overall aim of the interdisciplinary SOMACROSS research unit is to identify generic and disease-specific risk factors and aetiological mechanisms of symptom persistence across a range of diseases.

Methods and analysis: Seven projects will investigate risk factors and mechanisms of symptom persistence in a total of 3,916 patients across ten medical conditions. All study designs are prospective and share common assessment points, core instruments, and outcome variables to allow comparison and validation of results across projects and conditions. Research will focus on the identification of generic and disease-specific mechanisms associated with unfavourable symptom course. The development of a multivariate prediction model will facilitate the understanding of the course of PSS across diseases.

Ethics and dissemination: All individual SOMACROSS studies were approved by the ethics committees of Hamburg and Münster, Germany. Findings will be disseminated through peer-reviewed publications, scientific conferences, and the involvement of relevant stakeholders, patients and the lay public. This interdisciplinary research unit will fundamentally contribute to

earlier recognition of patients at risk, and to the development of prevention and tailored treatment concepts for PSS.

Key words

Persistent Somatic Symptoms; Mechanisms; Risk Factors; Expectations; Research Unit; Biopsychosocial Models; Prediction Models

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Although persistent somatic symptoms (PSS) are highly prevalent among various diseases, distressing and disabling for patients and costly for society, mechanisms of symptom persistence are rarely investigated and poorly understood.
- The SOMACROSS research unit goes beyond previous research by determining the complex and dynamic biopsychosocial interplay contributing to persistent symptom states in a number of different syndromes and diseases.
- In order to detect patterns of symptom persistence across diseases, the SOMACROSS research unit aims to identify potential risk factors and mechanisms of PSS across various somatic diseases, functional syndromes and somatoform disorders using a common working model, joint core measures, prospective designs and coordinated evaluation methods.
- The SOMACROSS research unit uses a multidisciplinary approach to overcome today's highly fragmented research on PSS and provide pathways to developing efficient disease-overarching intervention strategies.
- Despite investigating multiple potential risk factors and mechanisms of the persistence of somatic symptoms, other variables might be relevant; and conclusions can only be drawn for the conditions under investigation.

INTRODUCTION

State of the art

Definition: Persistent Somatic Symptoms (PSS)

The term 'Persistent Somatic Symptoms (PSS)' is used as an umbrella term to describe subjectively distressing somatic complaints, irrespective of their aetiology, that are present on most days for at least several months. PSS are operationalised by repeated measures of patients' subjective somatic symptom severity.

PSS across medical fields: PSS are highly prevalent in all fields of medicine, from primary to specialized care and mental health care,[1 2] yet remain greatly neglected in research.[3] Complaints may include pain, gastroenterological, cardiovascular, genito-urinary, neurological or other symptoms (**Figure 1**). Regardless of their aetiology, PSS cause substantial suffering, impaired quality of life and work participation.[4 5] Many somatic symptoms are neither exclusive correlates of somatic disease (e.g., vascular or inflammatory disease) nor exclusive symptoms of a mental disorder (e.g., depressive or anxiety disorders).[2 6 7] Thus, a dualistic view classifying symptoms as either somatic or psychological is neither evidence-based nor patient-centred.[8] With reference to the description of bodily distress disorder in the International Classification of Diseases, 11th edition (ICD-11), the term 'persistent' here defines somatic symptoms which are present on most days for at least several months.[9]

*Please insert **Figure 1** approximately here*

Impact on patients – challenges in health care: Eighty percent of the general population experience one or more symptoms within one month.[10-12] Somatic symptoms account for the majority of all primary and secondary care consultations.[13 14] Whereas in most cases, symptoms fluctuate naturally and eventually disappear, about one fourth of individuals with acute symptoms develop PSS and remain affected one year after their first consultation.[8]

Often, these symptoms are accompanied by comorbid depression and anxiety[2] and an increased risk for suicidal ideation and attempts.[15 16] PSS are costly for society,[17 18] and health care for PSS is challenging.[19] The clinical reality is characterized by fragmented treatment in specialized care (e.g., gastrointestinal symptoms in gastroenterology, chest pain in cardiology), even though patients often report multiple or overlapping symptoms.[20]

From ‘medically unexplained’ to a broader understanding of distressing persistent somatic symptoms: Most research on PSS has been conducted on so called ‘medically unexplained symptoms’, a term mainly used in primary care, while specialised medical fields more commonly employ the term 'functional syndromes'.[21] The 'medical inexplicability' of the symptoms was also the defining diagnostic criterion of the earlier diagnosis of somatoform and related disorders in the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV),[22] and the International Classification of Diseases, 10th edition (ICD-10).[23] The concept of medical inexplicability of somatic symptoms is considered problematic because (1) the label ‘medically unexplained’ for disabling symptoms creates distress in patients[24], (2) the reliability of assessing whether or not there is a pathophysiological explanation for a certain symptom is notoriously poor, (3) the concept reinforces a mind-body-dualism.[8], and (4) many patients disapproved of the term.[25] Therefore, a new conceptualization was introduced namely Somatic Symptom Disorder (SSD in DSM-5)[26] and Bodily Distress Disorder (BDD in ICD-10),[9] incorporating features of persistent and clinically significant somatic complaints which are accompanied by excessive and disproportionate health-related concerns, feelings, and behaviours. SSD and BDD may or may not be accompanied by a somatic disease.[27] Of note, patients with ‘medically explained’ and ‘unexplained’ symptoms are equally impaired.[4 5]

Transferability of psychosocial aetiological mechanisms from functional and somatoform disorders to somatic diseases: Most research on aetiological mechanisms of PSS has been conducted in somatoform and functional syndromes. The question arises whether these

findings can be transferred to SSD and BDS, and beyond that, to PSS in somatic diseases. There is initial evidence that – in addition to the underlying pathophysiology – psychosocial factors play a relevant role in the development and persistence of symptoms in somatic diseases. For example, previous studies by our group indicated that patients' beliefs about their disease strongly influence recovery after coronary artery bypass surgery,[28] that pre-treatment expectations significantly predict patient-reported long-term side-effects and quality of life in women receiving endocrine breast cancer treatment,[29] and that the extent of illness anxiety before gastrointestinal infection predicts the development of post-infectious irritable bowel syndrome after seven months.[30] The understanding of psychosocial factors, in turn, can help improve treatment for patients with PSS. First evidence in support of this is available from the PSY-HEART trial, a three-arm randomized clinical trial in which a preoperative optimisation of patient expectations prior to coronary artery bypass graft surgery led to a reduction of post-operative disability compared to usual surgery care alone.[31]

Even though it remains unclear how PSS evolve and are maintained over time, their presence in various somatic diseases is associated with a faster disease progression, more severe complications, and increased mortality.[32-34] Further evidence supporting the important role of psychosocial factors in the persistence of symptoms in somatic diseases is provided by the observation that symptom burden frequently persists although the underlying pathophysiology has been optimally treated.[5 35] In addition to disease-specific treatment, psychological treatment and centrally acting pharmacotherapy appear to be the most promising options, not only for functional and somatoform disorders but also for PSS in well-defined somatic diseases.[19] This suggests that generic, trans-diagnostic treatment principles[36] may be valuable in addition to the disease-specific treatment of the underlying pathophysiology. Across somatic diseases, a diverse array of psychological and social factors needs to be considered on equal footing with biological factors in their roles as potential risk factors, protective factors, and maintaining factors of PSS. Importantly, psychological and social factors are not solely secondary reactions to persistent symptoms; rather, they are deeply woven into the biopsychosocial processes that lead to PSS.

To conclude, sufficient evidence warrants the assumption that aetiological mechanisms derived from research on somatoform and functional disorders also contribute to the persistence of symptoms in somatic diseases. However, the applicability of generic and specific risk factors and mechanisms of PSS across medical diseases has yet to be investigated.

Current aetiological knowledge on PSS: The aetiology of PSS across somatic diseases is not well understood. The unique way in which each individual perceives a somatic symptom and its severity, the expectation on how the symptom will evolve, and whether the treatment will be effective depends on the constellation of biological, psychological, and social factors. The comprehensive vulnerability-stress model by Henningsen et al.[19] defines predisposing, triggering, and maintaining/aggravating factors that determine the transition from short-term to persistent disabling symptoms. After extensively reviewing the literature for all targeted conditions included in the SOMACROSS research unit (RU), we developed a 'PSS working model' as a starting point for the investigation of disease-overarching generic and disease-specific risk factors and aetiological mechanisms (see **Figure 2**). The risk factors and aetiological mechanisms described below are considered most relevant to PSS:

Definitions: risk factors and aetiological mechanisms

'Risk factors' refer to variables associated with an increased risk of symptom persistence, although the relationship is not necessarily causal. 'Aetiological mechanisms' denote underlying mechanisms which are presumed to be causally involved in the persistence of symptoms.

a. Predisposing factors for PSS include sociodemographic risk factors such as female gender,[37] poor education and socioeconomic status,[3 38] sociocultural factors,[39] psychological aspects such as early adverse life experiences,[40-43] personality factors like

neuroticism and negative affectivity,[44] biomedical factors such as prior medical diseases,[44] certain (epi)genetic profiles,[45] and immunological correlates of these factors.[3 46 47]

b. Triggering factors for short-term somatic symptoms include acute infections, injuries, medical or surgical procedures, or current life stressors.[19 30]

c. Maintaining/aggravating factors: Most aetiological models on bodily complaints in somatoform and functional disorders[48-50] include the following core cognitive-perceptual and emotional mechanisms: selective attention towards interoceptive cues, amplified perception of bodily sensations, catastrophizing cognitive interpretations, somatosensory amplification,[51] and dysfunctional illness behaviours.[19 46 52] Affective factors such as alexithymia comprise deficits in the regulation of emotions.[53] On the level of dysfunctional behavioural processes, somatic symptoms are aggravated by learning processes, avoidance behaviour such as physical inactivity and subsequent deconditioning.[54-56] Further aggravating factors arise from unsatisfying encounters with the health care system, negative illness perceptions, and treatment experiences which result in the unnecessary and potentially harmful overuse of health care.[19] Social factors like work status, health literacy, access to medical care, stigmatisation, migration, and culture can be both predisposing and maintaining/aggravating factors of PSS.[57] Disease-specific biomedical factors (e.g., inflammation in inflammatory bowel disease) naturally influence the course of somatic symptom severity.[58] Additionally, disease-overarching psychobiological models postulate dysregulations of the endocrine, immune, and autonomic nervous systems as well as central sensitization to be potential links between psychosocial distress and PSS.[48 59] Other biopsychosocial interactions contributing to symptom persistence include treatment-related factors such as burdensome side effects of a treatment for an underlying disease. These side effects are difficult to disentangle from general bodily distress and likely to be influenced by nocebo effects through

patients' negative expectations and other psychological factors.[60] Central sensitization, defined as hyperexcitability of the central nervous system, has been suggested to contribute to the development and maintenance of chronic pain, while its role in other PSS is under debate.[61 62] Central sensitization is thought to be driven by neuroinflammation in the central and peripheral nervous system, as indicated by higher serum levels of interleukin 6 (IL-6) and tumour necrosis factor (TNF).[61] Recently, epigenetic modifications such as DNA methylation have been identified as potential contributors to altered resilience to environmental stress, pain, and somatic symptom burden.[38 63] Stool microbiota alterations are also hypothesized to be associated with the persistence of somatic symptoms. There is evidence of gut microbiota dysbiosis in patients with chronic fatigue and nonvisceral pain.[64 65]

d. Interactions of biopsychosocial factors: Recently, patients' expectations of symptoms have come into focus as having a central role in symptom processing and the relation between biological, psychosocial and treatment-related factors for persistent symptom development. Expectations are defined as future-directed cognitions regarding the anticipated course of symptoms.[66] As such, they constitute a common denominator of many psychological risk factors for PSS such as catastrophizing, illness perceptions and health anxiety. Thus, they can be regarded as a core feature of current aetiological models for PSS (e.g., somatosensory amplification).[46] Negative symptom expectations interact with actual somatic input and can fuel dysfunctional signal processing and the development of persistent symptoms. Relevantly, the power of expectations to predict symptom course, treatment benefit and negative treatment side effects has been demonstrated for a wide range of medical and psychological conditions, e.g., pain, rheumatoid arthritis, cancer, 'medically unexplained symptoms' and level of functioning after total hip and knee replacements.[29 67-71] Moreover, a growing body of research provides evidence that modifying expectations improves clinical outcomes.[31 72 73]

Expectations are also prominently conceptualized in emerging predictive processing models which suggest that symptom perception emerges through an integrative process of sensory input, prior experience (leading to implicit expectations, or "priors") and contextual cues (such as affective state).[74] These models show that the relationship between subjective symptoms and pathophysiological dysfunction is highly variable, both between and within individuals, and that pathophysiological dysfunction may even be completely absent in the presence of strong priors and ambiguous somatic input. Depending on relative strength and precision, the actual symptom experience may be more determined by somatic input or by priors.

Altogether, the above mentioned risk factors and mechanisms of somatic symptom persistence are less well studied in somatic diseases than in functional and somatoform disorders.[46] We assume that – in addition to disease-specific pathophysiological mechanisms – the processes underlying somatic symptom persistence in somatic diseases and in functional/somatoform disorders involve similar risk factors and mechanisms, opening new routes to modify symptom persistence in somatic diseases.

Novelty and innovation

SOMACROSS takes on a fundamentally new perspective, by including two new ways of thinking in medicine: First, the abandonment of the concept of medical inexplicability in the diagnostic concepts of functional and somatoform disorders; and second, the shift away from the idea that subjective suffering can essentially be explained by the extent of the underlying physiological pathology. Assuming that biological markers alone do not sufficiently explain aetiology and development of PSS, we will investigate the interaction of biological, psychological and social factors regarding their contribution to subjective symptom severity and symptom persistence in ten different medical conditions. In this way, SOMACROSS will critically challenge the still prevalent dualistic mind-body disease model in medicine. The use of a trans-symptomatic and trans-diagnostic approach will enable the identification of

patterns, risk factors and aetiological mechanisms of symptom persistence across diseases and syndromes.

Objectives of the overall project

The superordinate aim of this interdisciplinary RU is to identify risk factors and mechanisms for the persistence of somatic symptoms across diseases, and thereby create a basis for evidence-based interventions for patients suffering from PSS.

The research objectives of SOMACROSS are:

a. to identify generic (i.e., disease-overarching) biological, psychological, and social mechanisms contributing to the persistence of somatic symptoms across a range of medical diseases and syndromes;
b. to identify disease-specific mechanisms contributing to the persistence of somatic symptoms;
c. to formulate new, empirically testable hypotheses about the interaction of generic and disease-specific factors and to integrate the derived risk factors and mechanisms into comprehensive prediction models for PSS;
d. to derive generic and disease-specific clinically useful risk factors for symptom persistence;
e. to identify modifiable risk factors and mechanisms in the transition from acute to chronic symptoms; and,
f. to test whether the therapeutic optimisation of modifiable risk factors (e.g., dysfunctional symptom expectations) improves clinical outcomes.

The structural objectives of SOMACROSS are:

a. to raise awareness for a highly relevant research field across medical disciplines;
b. to disseminate knowledge regarding the development and treatment of PSS;
c. to build a strong interdisciplinary research structure focused on PSS; and,

d. to establish qualifications of the next generation of scientific experts in this field.

Working hypotheses of the overall project

Hypothesis 1: In all syndromes and diseases examined in SOMACROSS, biological, psychological and social factors contribute to the persistence of somatic symptoms individually or/and in interplay.

Hypothesis 2: Persistence of somatic symptoms is predicted by common risk factors across syndromes and diseases.

Hypothesis 3: Generic and syndrome- and/or disease-specific risk scores accurately predict the risk of persistence of somatic symptoms.

Hypothesis 4: Expectations play a relevant role in the development of persistent somatic symptoms. Thus, the modification of dysfunctional expectations constitutes a promising starting point for interventions to improve symptom severity in PSS.

METHODS AND ANALYSIS

Design

Investigated symptoms and composition of SOMACROSS: To ensure clinical relevance, symptoms with high prevalence in medical settings were chosen, i.e., fatigue, gastrointestinal symptoms, pruritus, and multiple co-existing symptoms.[75] To detect patterns, similarities, and discrepancies in symptom persistence across a range of medical conditions, syndromes typically classified as somatic (e.g., primary biliary cholangitis, ulcerative colitis) and syndromes considered as 'functional' or 'somatoform' (e.g., irritable bowel syndrome, somatic symptom disorder) were included. The seven projects of SOMACROSS including content and project leaders are listed in **Table 1**.

*Please insert **Table 1** approximately here*

Each project will investigate specific predisposing, triggering, maintaining or aggravating factors for PSS based on the current state of knowledge in the respective disease or syndrome. Based on our extensive literature review, we compiled a 'PSS working model' (**Figure 2**), which serves as a starting point for rigorous testing of distinct factors with regard to their relevance for symptom persistence across all projects. These factors are assessed by the joint core set of measures (see below) that will be used across all projects. Other predictor variables, which are considered specific for defined diseases or syndromes only, will be tested in the respective individual projects. Of note, the classification of variables as predisposing, triggering, maintaining, and aggravating factors is preliminary and not always distinct.

*Please insert **Figure 2** approximately here*

Study designs and methodological approaches: The initial state of knowledge varies between the individual projects and health conditions. For some diseases, there is cross-sectional evidence on associations between symptom persistence and specific biopsychosocial variables. For others, longitudinal studies have identified relevant predictors for symptom maintenance. These different starting points in terms of current knowledge lead to different research aims (**Figure 3**). In an envisaged second phase, all projects will take a step towards modification of the relevant factors based on their individual project results.

*Please insert **Figure 3** approximately here*

Shared inclusion and exclusion criteria: All projects share common basic inclusion criteria, i.e.: age ≥18 years, sufficient oral and written German language proficiency, and written informed consent. Common exclusion criteria include: serious illness requiring immediate intervention; florid psychosis or substance abuse disorder, and acute suicidality. In addition

to these common criteria, the individual projects defined project-specific inclusion and exclusion criteria.

Shared assessment points: In order to compare results across projects, all projects (P) with prospective study designs (P1-5) will use identical assessment points, i.e., baseline, 6-, and 12-month follow-up. These enable the statistical evaluation of generic predictors across diseases and the pooling of data.

Patient and public involvement: Involvement of patients or members of the public varies among the projects of the research unit and is therefore described in detail in the study protocols of the individual projects.

Measures

Shared outcome measures: Severity of somatic symptoms is the primary outcome for all projects (**Table 2**). Given that a) somatic symptom severity must be specifically assessed for each symptom, and that b) generic instruments are needed to conduct comparisons and joint evaluations across projects, somatic symptoms are measured in two ways:

a. Symptom-specific assessment, using specific measures of somatic symptom severity,
b. Generic assessment of overall symptom severity, using the internationally well-established Patient Health Questionnaire-15 (PHQ-15)[76 77] and the Numeric Rating Scale for symptom intensity as recommended by the EURONET-SOMA group[78].

Additional shared secondary outcomes include symptom interference, disability, and quality of life.

Joint psychosocial core instruments: The list of joint core instruments of SOMACROSS (**Table 2**) reflects the factors displayed in the PSS working model (**Figure 2**). All joint core instruments were chosen after considering construct relevance, reliability, validity, feasibility, acceptability, availability in German and statistical constraints. In order to assess the

comorbidity with DSM-5 somatic symptom disorder in all the diseases investigated, the relevant section of a German research version of the Structured Diagnostic Interview for Mental Disorders (SCID-5) will be conducted.[79 80]

*Please insert **Table 2** approximately here*

Joint biomedical factors: In addition to the joint core set of instruments, the various projects of SOMACROSS investigate further common variables with regard to their relevance for PSS. Disease overarching factors such as duration and subjective severity of disease, (prior) biomedical disease and comorbidities, and side effects and subjective treatment experiences will be assessed as potential generic predictors of symptom persistence across all projects. Serum levels of C-reactive protein (CRP), interleukin 6 (IL-6) and tumour necrosis factor (TNF) will be measured at baseline as systemic biomarkers of central sensitization[81] to shed light on the controversial role of central sensitization in the persistence of somatic symptoms both prospectively and in a cross-sectional view across P1 to P5. The contribution of epigenetic mechanisms (altered DNA methylation in an epigenome-wide association study) in the course from acute to persistent symptoms in kidney disease will be analysed in P3. Additionally, epigenetic mechanisms will be analysed and cross-validated in pilot samples across P1 to P5 (n=20 patients per diagnosis, n=10 with low vs. high baseline symptom burden according to the PHQ-15), led by P3. We will also investigate the role of microbiome alterations for fatigue persistence among patients with primary biliary cholangitis and patients with primary sclerosing cholangitis (P1). In P2 and P3 we will collect stool samples from participants at baseline (P2 also post-intervention). Depending on the results regarding the course of PSS (P2 and P3) and the response to the intervention (P2), we will then analyse the microbiome (metagenomic sequencing). We believe that the above-mentioned biomedical factors are potentially relevant across several symptoms and diseases. Further disease-specific biomedical predictors such as disease stage and disease-specific markers

of symptom persistence will be assessed within the individual projects, using appropriate methodology.

Statistical evaluation

Joint statistical evaluation strategy: The use of shared measures and assessment points across P1 to P6 enables collective statistical analyses (n=1,328 participants; *not* included are the n=2,432 participants from the cross-sectional analysis in P6 and the n=156 participants of the intervention groups in P2). The power calculations were performed individually for each project and are included in the projects´ study protocols. The joint cross-project evaluation will allow us to develop an overarching conceptual model for the persistence of somatic symptoms. We will test paths and associations between the key factors of the working model by using an exploratory approach and initial hypotheses testing. Given scarcity of data on PSS for most of our included diseases and syndromes, we included a large number of variables in the first funding phase. This will enable us to generate new hypotheses for rigorous testing in the second funding phase. P1 and P3 will use multi-method approaches by embedding qualitative and experimental studies. Both approaches represent a valuable possibility for an in-depth exploration of mechanisms of symptom perception, development and maintenance. The statistical evaluation across projects will be carried out by biostatistics experts using a structural equation model approach. The statistical analyses will also lead to a reduction in predictors of symptom persistence by removing irrelevant pathways, which will allow more distinct analyses in subsequent studies. Depending on the existing evidence for each condition, some of the projects follow a hypothesis-generating design while others perform confirmatory tests based on prior research (see also **Figure 3**). In exploratory analyses, we do not adjust for multiple testing in order to avoid the loss of power. However, we formulated testable, pre-specified initial hypotheses for each project as starting points, which contribute to the overarching hypotheses of the Z-Project. Statistical methods to adjust for multiple testing will be applied for the confirmatory analyses.

ETHICS AND DISSEMINATION

Ethical approval: All studies including patients (P1 to P6) were approved by the respective Ethics Committees of the Medical Associations Hamburg and Westphalia-Lippe / Westphalian Wilhelms University, Münster, Germany. The individual studies will be conducted in accordance with the WMA Declaration of Helsinki, guidelines for Good Clinical Practice, national and local laws. Eligible patients will be informed about the study verbally and in written form before providing written informed consent.

Data sharing: De-identified individual patient data will be made publicly available. The times and the conditions of the availability of data will be in accordance with the `Recommendations for Sharing Clinical Trial Data´ of the Institute of Medicine (IOM). Data sharing will follow the *FAIR* Data Principles (Findable, Accessible, Interoperable and Reusable) and international naming conventions (e.g., Systematized Nomenclature of Medicine) to maximize transparency and scientific reproducibility. The main findings of each project will be published in peer-reviewed journals and made publicly available. In addition, we will communicate scientific results in lay language via press releases, social media, and patient forums.

Impact and relevance: Regarding the impact on the research field of PSS, SOMACROSS will provide the urgently needed infrastructure to facilitate collaboration and knowledge exchange between medical disciplines. The research field of PSS will benefit from the measurement of larger sets of predisposing, triggering, and maintaining biopsychosocial variables, and from additional theoretical work on their interrelation. By providing information to the public, e.g., at a 'patient day' and the SOMACROSS webpage, we hope to improve the understanding of PSS, avoid unnecessary and potentially harming medical procedures and provide reliable information for patients' personalised decision-making. Greater awareness and

understanding of PSS in society might also lead to reduced stigma associated with PSS. SOMACROSS aims to open science to young researchers with innovative ideas, provide researchers with flexible career opportunities, and improve the way in which research is conducted. The most important measures of SOMACROSS are summarized in **Figure 4**.

*Please insert **Figure 4** approximately here*

Conclusion

Our patient-centred focus on subjectively distressing somatic symptoms has the potential to enable increased visibility of somatic symptom burden across different medical specialties. SOMACROSS will enhance the relevance of each individual project by integrating knowledge about individual risk factors and mechanisms of PSS into joint analyses and publications. While we also anticipate challenges regarding comparability, transferability, and complexity of such a translational approach, we expect to gain insights on PSS that could not be reached without this collaboration. Our results will inform the development of mechanism-based tailored interventions, and in the long term, SOMACROSS will enable the translation of cutting-edge scientific knowledge into clinical practice by providing clinicians with evidence-based prevention and treatment options.

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Author contributions

Bernd Löwe is the speaker of the SOMACROSS research unit. Omer Van den Bergh is a Mercator Fellow of this research unit. Viola Andresen, Tobias B. Huber, Olaf von dem Knesebeck, Bernd Löwe, Ansgar W. Lohse, Yvonne Nestoriuc, Gudrun Schneider, Stefan W. Schneider, Christoph Schramm, Meike Shedden-Mora, Sonja Ständer, Anne Toussaint, and Antonia Zapf lead the individual SOMACROSS projects. Antonia Zapf and Eik Vettorazzi provide statistical expertise to all projects of the research unit. Bernd Löwe drafted the first version of the protocol, Meike Shedden Mora and Anne Toussaint contributed individual parts of the protocol. All authors, i.e., Viola Andresen, Omer Van den Bergh, Tobias B. Huber, Olaf von dem Knesebeck, Bernd Löwe, Ansgar W. Lohse, Yvonne Nestoriuc, Gudrun Schneider, Stefan W. Schneider, Christoph Schramm, Meike Shedden-Mora, Sonja Ständer, Anne Toussaint, Eik Vettorazzi, and Antonia Zapf, contributed to the refinement of the study protocol, read and approved the final version.

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Competing interests

None

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Table 1: Individual projects and project leaders of the SOMACROSS research unit

Project No.	Project title	Project content	Project leader(s)	Institution(s)
P1 	Fatigue in Primary Biliary Cholangitis: Factors Associated With Severity and Persistence as Future Therapeutic Targets	P1 examines the disease-specific biological and generic psychosocial factors which contribute to fatigue in patients with primary biliary cholangitis and primary sclerosing cholangitis and aims to determine its course over time.	Dr. Anne Toussaint, PhD	Department of Psychosomatic Medicine and Psychotherapy, UKE
			Prof. Dr. Christoph Schramm, MD	Martin Zeitz Centre for Rare Diseases and I. Department of Medicine, UKE
P2* 	Persistence of Gastrointestinal Symptoms in Irritable Bowel Syndrome and Ulcerative Colitis: From Risk Factors to Modification	P2 investigates whether somatic symptoms in patients with irritable bowel syndrome and ulcerative colitis are influenced by illness anxiety and symptom expectations and could therefore be improved by expectation management.	Prof. Dr. Bernd Löwe, MD	Department of Psychosomatic Medicine and Psychotherapy, UKE
			Prof. Dr. Ansgar W. Lohse, MD	I. Department of Medicine, UKE
P3 	Predictors of Somatic Symptom Persistence in Patients With Chronic Kidney Disease	P3 aims to identify multivariate predictors of PSS in patients with pre-dialysis chronic kidney disease (CKD) by testing biomedical, psychological, and treatment-related predictors using a mixed methods cohort study.	Prof. Dr. Meike Shedden Mora, PhD	Department of Psychosomatic Medicine and Psychotherapy, UKE, Department of Psychology, Medical School Hamburg
			Prof. Dr. Tobias B. Huber, MD	III. Department of Medicine, UKE
P4 	Biological and Psychosocial Factors Affecting the Persistence of Pruritus Symptoms	P4 examines the interplay of psychosocial and biological factors affecting the maintenance of pruritus in patients with atopic dermatitis, patients with pruritus on non-lesional skin, and healthy controls.	Prof. Dr. Stefan W. Schneider, MD	Department of Dermatology and Venerology, UKE
			Prof. Dr. Dr. Sonja Ständer. MD	Department of Dermatology, University of Münster
			Prof. Dr. Gudrun Schneider, ND	Department of Psychosomatic Medicine and Psychotherapy, University of Münster
P5* 	Modifiable Factors for Somatic Symptom Persistence in Patients With Somatic Symptom Disorder	P5 examines whether expectations about symptom severity and coping with symptoms determine symptom persistence in patients with somatic symptom disorder in interaction with somatic comorbidity and psychosocial factors.	Prof. Dr. Yvonne Nestoriuc, PhD	Department of Clinical Psychology, Helmut-Schmidt University, Hamburg
			Dr. Anne Toussaint, PhD	Department of Psychosomatic Medicine and Psychotherapy, UKE
P6 	Social Inequalities in Aggravating Factors of Persistent Somatic Symptoms	P6 examines whether socioeconomic and migration status are associated with risk factors for the persistence of irritable bowel syndrome and fatigue.	Prof. Dr. Olaf von dem Knesebeck, PhD	Institute of Medical Sociology, UKE
Z-Project* 	Generic and Disease-Specific Mechanisms of Somatic Symptom Persistence Across Diseases	The Z-Project will oversee the other projects with respect to adherence to the common methodology. The Z-Project will pool data from the individual projects to identify networks of interacting symptoms and mechanisms of symptom persistence across projects and diseases.	Prof. Dr. Antonia Zapf, PhD	Department of Medical Biometry and Epidemiology, UKE

* Co-applicants: **P2:** PD Dr. Viola Andresen, MD; Prof Dr. Yvonne Nestoriuc, PhD; **P6** and **Z-Project:** Prof. Dr. Bernd Löwe, MD; UKE = Universitätsklinikum Hamburg-Eppendorf (University Medical Centre Hamburg-Eppendorf, Hamburg, Germany)

Table 2: Risk factors, mechanisms, and outcomes investigated by the SOMACROSS research unit

Predisposing, triggering and maintaining /aggravating factors	Single constructs	Instrument	Items	Months		
				0	6	12
Risk factors and mechanisms (assessed via self-report / laboratory test)						
Sociodemographic factors	Gender, age, nationality, heights, weights, marital status, migration status, current housing situation, insurance, education, occupational status, health care utilization	Single items	19	X	X	X
Psychosocial factors	Adverse childhood experiences	Adverse Childhood Experiences Questionnaire (ACE-D)	10	X		
	Personality: neuroticism	Big Five Inventory -10 (BFI-10)	10	X		
	Negative affectivity	Positive and Negative Affectivity Schedule (PANAS)	20	X		
	Life stressors	Perceived Stress Scale (PSS-10)	10	X		
	Perceived stigmatization	Single items	2	X		
Cognitive-perceptual and emotional mechanisms	Somatosensory amplification	Somatosensory Amplification Scale (SSAS)	10	X	X	X
	Catastrophizing	Coping Strategies Questionnaire - Catastrophizing Subscale (CSQ-CAT)	6	X	X	X
	Treatment expectations	Treatment Expectation Questionnaire (TEX-Q)	15	X	X	X
	Expectation of symptom severity	Numeric Rating Scale	1	X	X	X
	Expectation of symptom burden	Numeric Rating Scale	1	X	X	X
	Expectation of coping with symptoms	Numeric Rating Scale	1	X	X	X
	Psychological burden related to somatic symptoms or associated health concerns	Somatic Symptom Disorder – B Criteria Scale (SSD-12)	12	X	X	X
	Illness-related worries	Whiteley-Index Short Version (WI-7)	7	X	X	X
	Symptom perception	Illness perception questionnaire (B-IPQ)	8	X	X	X
	Anxiety	Generalized Anxiety Disorder-7 (GAD-7)	7	X	X	X
	Depression	Patient Health Questionnaire-9 (PHQ-9)	9	X	X	X
	Alexithymia	Toronto Alexithymia Scale (TAS-20)	20	X		
	Emotion regulation	Emotion Regulation Questionnaire (ERQ)	10	X		
Behavioral factors	Physical inactivity	International Physical Activity Questionnaire (IPAQ-SF)	7	X	X	X
Biomedical and treatment-related factors	(Prior) organic disease / comorbidity	Self-Administered Comorbidity Questionnaire (SCQ)	16	X		
	Medication adherence	Medication Adherence Report Scale (MARS-D)	5	X		
	Side effects	Numeric Rating Scale	1	X	X	X
	Treatment experiences	Numeric Rating Scale	2	X	X	X
	Systemic inflammation, markers of central sensitization (P1 to P5)	C-reactive protein (CRP)		X		
		Interleukin 6 (IL-6)		X		
		Tumor necrosis factor (TNF)		X		
	Duration of disease	Single interview questions	2	X		
	Medication	Single interview question	1	X	X	X
Outcome variables (assessed via self-report / diagnostic interview)						
Primary outcome: somatic symptoms	Somatic symptom burden	Patient Health Questionnaire-15 (PHQ-15)	15	X	X	X
	Symptom intensity	EURONET-SOMA Numeric Rating Scale	1	X	X	X
Secondary outcomes: functioning	Symptom interference	EURONET-SOMA Numeric Rating Scale	1	X	X	X
	Symptom related disability	Pain Disability Index – adapted (PDI)	7	X	X	X
	Health-related quality of life	Short Form Health Survey (SF-12)	12	X	X	X
Diagnosis of somatic symptom disorder (DSM-5)	Diagnostic classification	Structured Clinical Interview for the DSM-5 (SCID)	18	X		X
TOTAL (self-report items)			**266**			

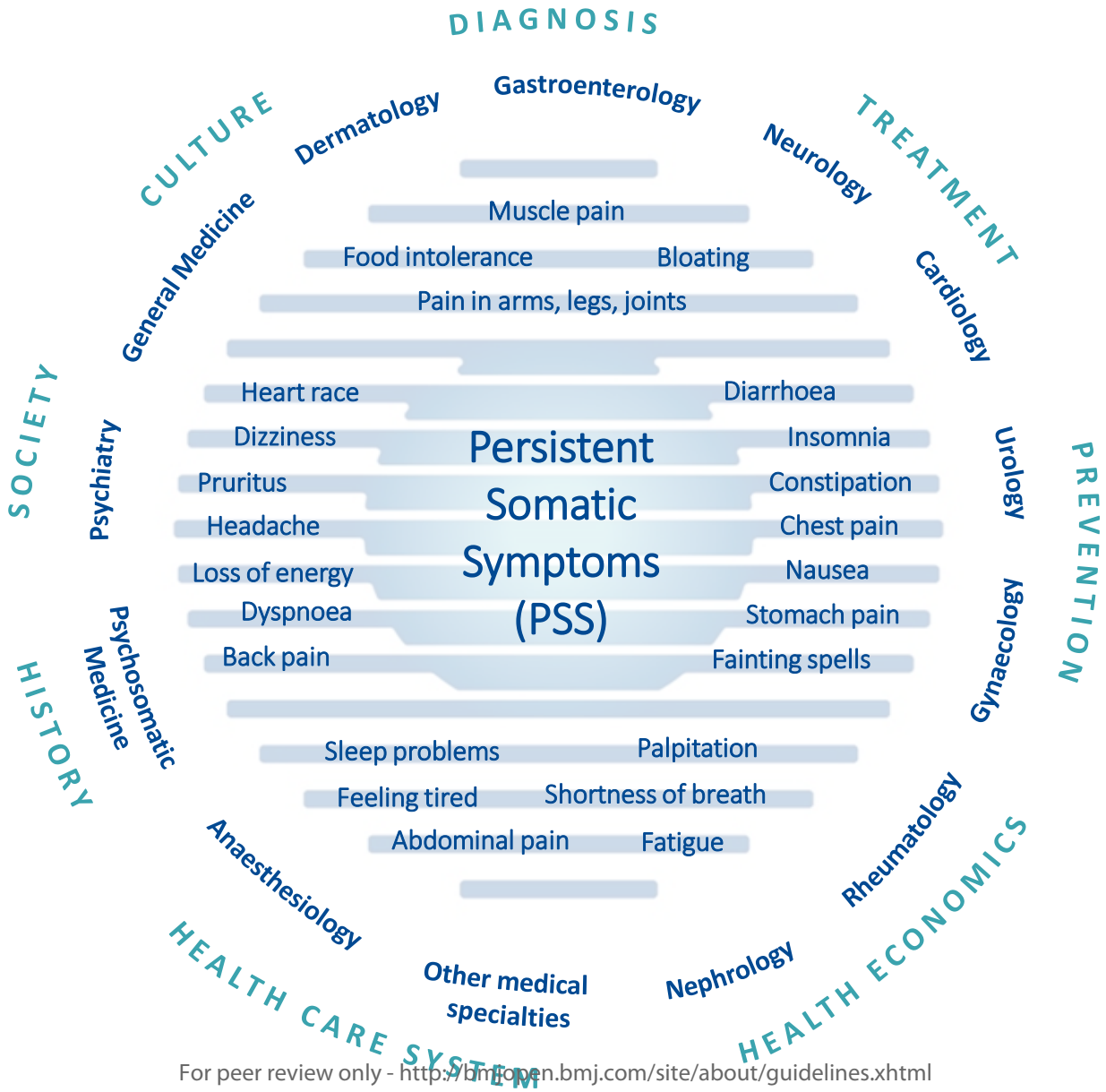
FIGURE LEGENDS

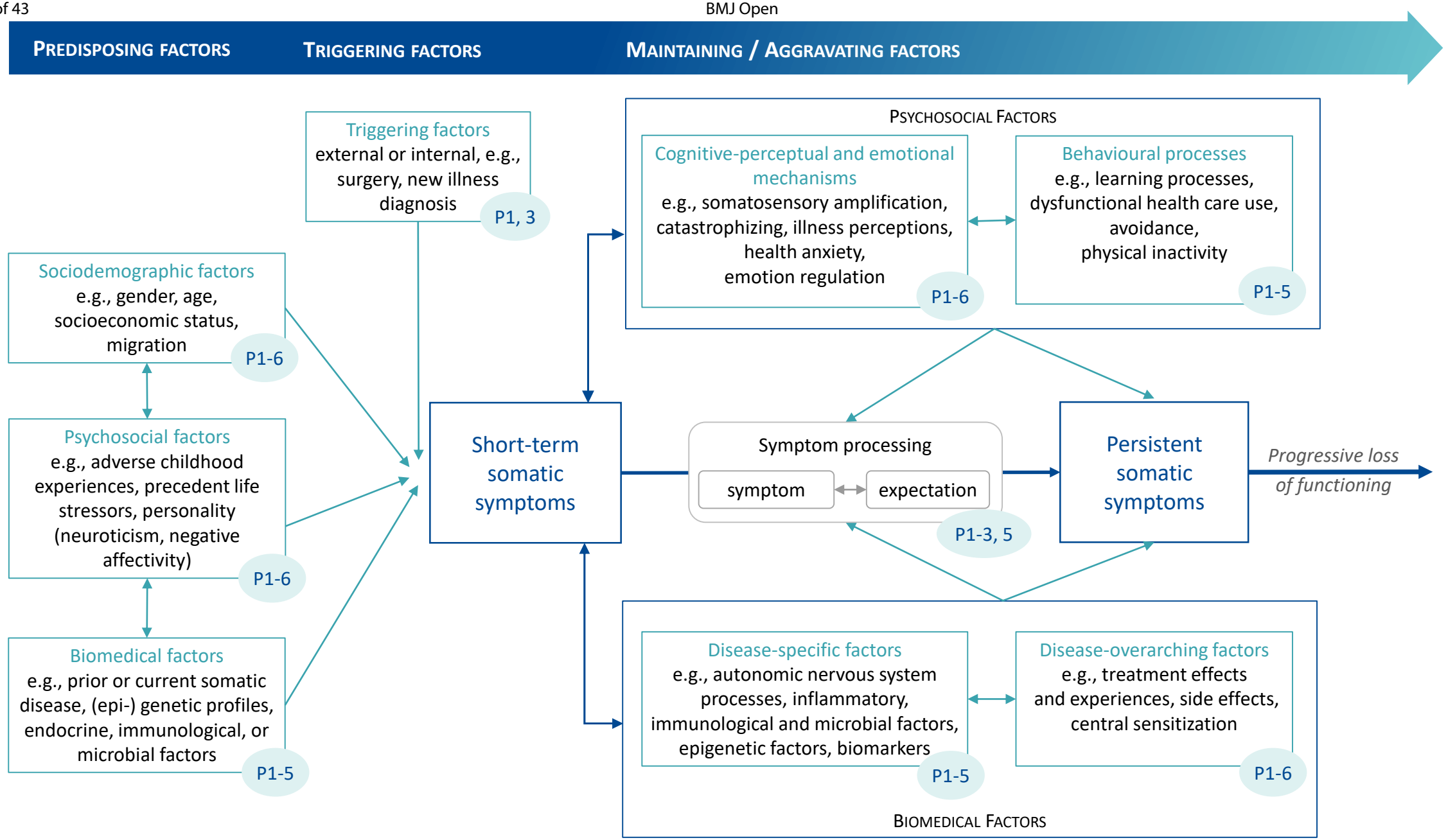
Figure 1. Relevance of Persistent Somatic Symptoms

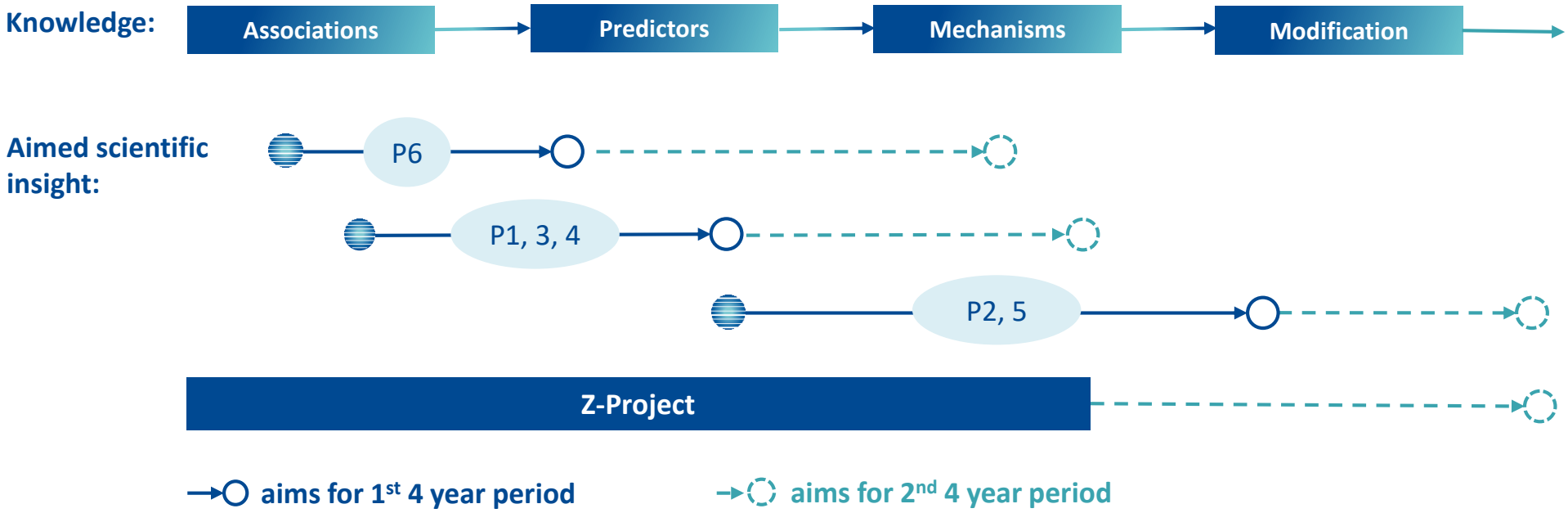
Figure 2. Working model of the SOMACROSS research unit: Risk factors and mechanisms for somatic symptom persistence as investigated by the individual projects (blue numbers indicate projects investigating the respective factors)

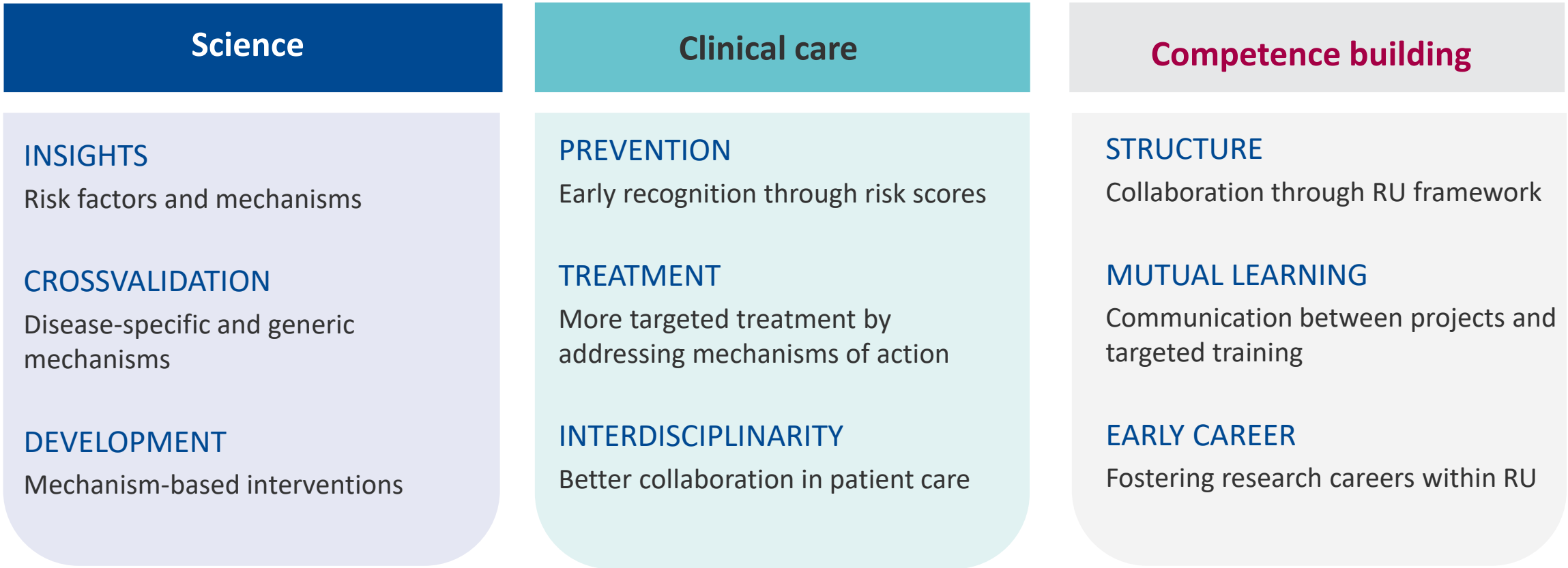
Figure 3. Projects 1-6 (P1-6): From current state of knowledge to aims of scientific insight

Figure 4. Steps forward through the SOMACROSS research unit






Knowledge:
Associations
Predictors
Mechanisms
Modification
Aimed scientific insight:
P6
P1, 3, 4
P2, 5
Z-Project
aims for 1st 4 year period
aims for 2nd 4 year period


Science
INSIGHTS
Risk factors and mechanisms
CROSSVALIDATION
Disease-specific and generic mechanisms
DEVELOPMENT
Mechanism-based interventions
Clinical care
PREVENTION
Early recognition through risk scores
TREATMENT
More targeted treatment by addressing mechanisms of action
INTERDISCIPLINARITY
Better collaboration in patient care
Competence building
STRUCTURE
Collaboration through RU framework
MUTUAL LEARNING
Communication between projects and targeted training
EARLY CAREER
Fostering research careers within RU

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	N/A – individual studies of research unit will be registered before start of recruitment (not this overall description of the research unit)
	2b	All items from the World Health Organization Trial Registration Data Set	N/A see above
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	21
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-13
	6b	Explanation for choice of comparators	9-13
Objectives	7	Specific objectives or hypotheses	13-14
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	14-18
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	14-15
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	15-16
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N/A – this is an overall study protocol for a research unit, not for an interventional study

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A – described in individual study protocols of SOMACROSS research unit
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A – see above
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A – see above
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	N/A – see above
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18 – described in individual study protocols of SOMACROSS research unit
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A – see above
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A – described in individual study protocols of SOMACROSS research unit

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A – see above
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A – see above
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A – see above
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A – see above
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-17, Table 2
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A – described in individual study protocols of SOMACROSS research unit
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18 – described in individual study protocols of SOMACROSS research unit
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A – see above
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A – see above
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A – see above
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A – see above
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A – see above
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18 – described in individual study protocols of SOMACROSS research unit

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	N/A – see above
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A – see above
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	N/A – see above
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18 – described in individual study protocols of SOMACROSS research unit
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A – proband insurance was concluded
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19-20
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19-20

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	15, 19 – described in detail in individual study protocols of SOMACROSS research unit
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	17– described in detail in individual study protocols of SOMACROSS research unit

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.