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Interface management concepts in health care for rare diseases in Germany: A study protocol for a mixed-methods study to develop best practice recommendations

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Interface management concepts in health care for rare diseases in Germany: A study protocol for a mixed-methods study to develop best practice recommendations

Laura Inhestern[1], David Zybarth[1], Ramona Otto[1], Maja Brandt[1], Martin Härter[1], Corinna Bergelt[1]

[1]Department *of Medical Psychology, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany*

Corresponding Author:

Laura Inhestern, M.Sc., PhD

Department of Medical Psychology
University Medical Center Hamburg-Eppendorf
Martinistr. 52, W26
20246 Hamburg, Germany
Phone: +49(0)40 7410 – 57684
Email: l.inhestern@uke.de

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ABSTRACT

Introduction: Patients and families affected by a rare disease are burdened in multiple ways. Functional interface management can unburden patients or relatives from the need to be solely accountable for the navigation through the health care system. This study aims at providing a systematic assessment of interface management concepts in the care of rare diseases and at developing best practice recommendations for interface management.

Methods and Analysis: We will conduct a mixed-methods study with three phases. In phase 1, we will develop a tool to assess existing concepts of interface management for rare diseases. The tool will be applied in a telephone survey with representatives of centers or clinics for rare diseases and cooperating practitioners. Based on these results, we will select 4-6 interface management concepts, which will be evaluated extensively in phase 2. For the evaluation, we will conduct semi-structured interviews with practitioners cooperating with centers or clinics for rare diseases, a survey including patients or parents/legal guardians from the selected centers or clinics and semi-structured interviews with patients or parents/legal guardians. The final phase of the study will be an integration of results from phase 1 and 2 to develop best practice recommendations for interface management in health care of rare diseases. In a concluding expert workshop recommendations will be presented and consented.

Ethics and dissemination: The study was approved by the Local Psychological Ethics Committee of the Center for Psychosocial Medicine of the University Medical Center Hamburg-Eppendorf (LPEK-0062). The findings of our study will be presented on national and international conferences and published in scientific, peer-reviewed journals. To assure that centers for rare diseases get access to the study results, centers are invited to send a representative to a final expert workshop in Phase 3. Moreover, an executive summary will be provided and send to relevant stakeholders.

Trial registration: German Clinical Trials Register (ID: DRKS00020488)

KEY WORDS

quality in health care, organization of health services, genetics, qualitative study

STRENGHTS AND LIMITATIONS OF THIS STUDY

- Based on three study phases, including qualitative and quantitative methods as well as the perspective of representatives of centers or clinics for rare diseases, practitioners and patients allow a rigorous development of best practice recommendations for interface management.

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- The results will allow health care providers to improve their interface management and, hence, to improve the journey through the health care system for patients with rare diseases and their relatives.
- Since we aim at including all centers for rare diseases in Germany, we will depend on their commitment for participation. Moreover, we expect a selection bias and, in parts, we may receive socially desirable answers from practitioners and centers or clinics for rare diseases.

INTRODUCTION

Currently about 30 million people in the European Union [1] and about 2.4-5 million people in Germany [2] are affected by one of about 6.000 to 8.000 known rare diseases [1]. Besides physical and mental constraints, living with a rare disease can be associated with social consequences such as stigma or financial drawbacks [3, 4]. Moreover, individuals with rare diseases can experience difficulties in their health care [5]. Due to lack of knowledge (e.g. in general practitioners and the general population) and inefficient diagnostic ways, it can take several years until patients receive the accurate diagnosis [6]. After diagnosis, receiving health care might be difficult in the home-area of the patients and patients often need travel far to get access to appropriate treatment and care [7, 8]. Recent studies show, that more difficulties regarding a smooth flow through the health care system is associated with a reduced quality of life [9].

Due to the high burden of these patients, in 2009 the EU released several recommendations for its member states to improve the situation of individuals with rare diseases and national action plans have been announced [10]. The German National Plan of Action for People with Rare Diseases was published in 2013 and comprises 52 proposed actions [11], includinga model of care delivery based on centers for rare diseases to structure and aggregate competencies. The national plan of action recommends centers for rare diseases on three levels based on the spectrum of their service (A-, B-, C-centers) [11]. Type A-centers are defined as reference centers offering a non-disease specific structure, including patient guides or interdisciplinary case conferences. Type A-centers serve as referral centers for patients with unclear diagnosis and comprise at least two B-centers. Moreover, type A-centers should provide education for undergraduate medical students and conduct clinical research. Type B-centers are centers of expertise for specific disease groups integrated into a hospital setting and delivering inpatient and outpatient care. Type C-centers are cooperating specialised clinics delivering care for

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specific disease groups. So far, no formal accreditation or certification body for centers of rare diseases has been implemented, but centers define themselves as A- or B-centers according to the catalogue of requirements from the national plan of action.

Currently, there are about 32 centers for rare diseases registered in the *se-atlas*, a platform for mapping health care providers for individuals with rare diseases in Germany [12]. Most of these centers comprise more than two B-centers. However, not all are designated as A-centers.

In health care of rare diseases, generic integrated care models to structure the paths of the patients through the health care system are missing and follow-up care outside the centers for rare diseases can be insufficient. At the same time, integrated care is particularly important in rare diseases due to the delays in diagnosis and, if diagnosed, highly specialized demands with regard to treatment and monitoring [13]. In a sophisticated and highly specialized health care system, quality of care depends on the management of interfaces and may be impaired by deficits in communication and information transfer [14]. Intersectional communication and coordination is mandatory to enable continuity of disease management and to alleviate patients' or relatives' burden of being accountable for navigating through the health care system [15, 16]. Approaches for interface management range from implementation of health information technologies, care coordinators, one-stop-clinics to standard operation procedures [13, 17-19]. Integrated care models for single rare diseases have been established [18], but the shared experiences of individuals with rare diseases concerning medical and psychosocial consequences and with the health care system call for overall best practice recommendations.

The national plan of action has recommended to initiate a survey among practitioners and centers for rare diseases to identify relevant aspects to ensure cooperation (proposed action 17) [11].

Corresponding to this recommendation, our study focuses on concepts for interface management particularly between centers for rare diseases and practitioners in health care in Germany. The overall aim of our study is the development of best practice recommendations for interface management in health care of rare disease based on two steps: Firstly the systematic analysis of existing concepts for interface management including the identification of strengths and limitations and secondly the evaluation of the acceptance and feasibility of applied concepts. Specific research questions are:

- Which approaches and solutions exist in the literature and current health care for patients suffering from rare diseases regarding the interface management between primary and specialist care?

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- How do representatives of centers for rare diseases, general practitioners (GPs), specialists and affected patients or parents/legal guardians evaluate existing approaches and concepts regarding their acceptance, feasibility and benefit?
- Which improvements to minimize interface problems do representatives of centers for rare diseases and practitioners (GPs and specialists) as well as affected patients or parents/legal guardians suggest?

METHODS AND ANALYSIS

This study protocol is written according the SPIRIT guidelines and addresses applicable recommended items for clinical trial protocols [20].

Study setting

The study will be conducted at the Department of Medical Psychology of the University Medical Center Hamburg-Eppendorf in Germany. The study is conducted in collaboration with the German National Alliance for Chronic Rare Diseases (ACHSE e.V.), the Martin Zeitz Center for Rare Diseases (center for rare diseases of the University Medical Center Hamburg-Eppendorf) and the Department of Pediatrics of the University Medical Center Hamburg-Eppendorf.

Study design

The study will be conducted in three phases (Figure 1): Phase 1 comprises a comprehensive inventory of existing concepts regarding interface management in health care of rare diseases will be carried out. In phase 2 a differentiated evaluation of selected existing best practice concepts of interface management will be conducted. And finally, based on the first to steps, specific recommendations for the implementation of a Best-Practice-Model of interface management will be developed.

Key element of the project is a multi-perspective analysis of the existing interface management concepts in centers for rare diseases in Germany. The study applies a mixed-methods-design which includes quantitative as well as qualitative data collection.

Phase 1: Analysis of existing concepts of interface management for rare diseases

With regard to the analysis of existing concepts of interface management for rare diseases, we focus on the interface from primary health care to centers for rare diseases and back to primary health care.

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We aim at including A-centers and B-centers for rare diseases. Pediatric and adult health care as well as patients with a diagnosed or an undiagnosed rare disease respectively will be separately analysed in order to identify possible differences.

The analysis of existing concepts will be conducted using a stepwise approach:

Step 1: Systematic research

a. A systematic online search of the online presence of the centers for rare diseases in Germany will be conducted to identify instruments and questionnaires concerning interface management that are online available. Additionally, a web-based research concerning interface management tools in medical care in general or chronic diseases will be performed.
b. A systematic research of international scientific publications concerning interface management in the medical care of rare diseases will be conducted (e.g. PubMed and other databases) to identify and analyze concepts, that may not have been implemented in Germany.

Step 2: Expert workshop

The centers for rare diseases will be invited to send 1 or 2 representatives for an expert workshop. The workshop will aim at exchanging experiences, gathering interface problems and possible solutions. In order to validly include the patient´s perspective, the alliance for chronically rare diseases (ACHSE e.V.) is asked to send 3 to 4 representatives as well. Furthermore, 2 to 3 representatives the National Action League for People with Rare Diseases (NAMSE) nd of the Federal Ministry of Health will be invited to participate.

Step 3: On-site visitations

4 to 6 centers for rare diseases will be visited by the project team to assess the implementation of interface management approaches. The visited centers should represent the different regions of Germany. The method of on-site visitations was chosen based on the assumption that specific aspects and problems of interface management cannot be adequately represented by written report or telephone surveys.

Step 4: Development of an assessment tool for interface management

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Based on the results of step 1 to 3 (literature and online research; results of expert workshop as well as on-site visitations) a structured assessment tool to evaluate the interface management in rare diseases will be developed and finalized by expert consensus.

Step 5: Telephone survey of all centers of expertise for rare diseases and practitioners

All centers of expertise in rare diseases listed in the *se-atlas* will be invited for participation in a telephone survey using the developed and consented assessment tool.

In those centers that have a coordination site, the coordinator will be asked to participate and additionally, to provide information on 3-4 centers of expertise for a specific rare disease or disease group (B-centers). In centers without coordination site, 3 to 4 B-centers will be randomly selected and interviewed.

Per center of rare diseases at least 3 interviews should be conducted. All in all about n=100 structured interviews should be conducted with representatives of A- and B-centers. Each interviewee will be asked to name cooperating practitioners who will be invited to participate in an interview. Overall, the final sample should comprise about n=60 practitioners. Since interface management might differ between pediatric and adult care as well as between diagnosed and undiagnosed diseases, these aspects will be assessed and considered additionally.

Step 6: Selection of concepts

Based on the results from steps 1 to 5, we will select 4 to 6 concepts for interface management for further evaluation from the perspective of practitioners and individuals with rare diseases. Selection criteria will be based on the telephone survey results on acceptance, feasibility and benefit of the concepts from the practitioners' perspective.

Phase 2: Evaluation of selected interface management concepts

To evaluate 4-6 selected interface management concepts, we will include the perspective of patients with rare diseases or their parents/legal guardians as well as the perspective of practitioners who refer patients and cooperate with selected centers.

Interviews with general or specialized practitioners

The selected centers will be asked to name 10-15 cooperating general or specialized practitioners (target per center n=10, total: n=50). Identified practitioners will be invited to participate in an interview

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study on their experiences with the interface concept of the respective center for rare diseases. The interview guideline will address acceptance and benefits of interface concepts, the compatibility with medical practice and treatment processes, barriers and facilitators for the management of interfaces in medical care and suggestions for improvement.

Survey of patients with rare diseases/relatives

The selected centers will be asked to invite patients or parents/legal guardians of patients currently or formerly treated in the center to participate in a cross-sectional survey (target per center n=60, total: n=300). The survey will comprise a questionnaire covering questions on the experiences on the interface management as well as existing and validated instruments on patient satisfaction and satisfaction with health care. Additionally, relevant data regarding disease and health care history will be collected.

Survey participants will be invited to also participate in a semi-structured interview (target per center n=10, total: n=50 interviews). The interviews will follow a guideline covering questions on the experiences of interface management and health care provision, barriers and facilitators for the management of interfaces in health care and suggestions for improvement.

Data analysis

All interviews will be conducted via telephone. The interviews will be recorded and transcribed verbatim and will be analysed by qualitative content analysis based on the approach of Mayring [21]. Material will be coded using an inductive procedure. Categories obtained will be discussed by two separate researches in order to augment validity and reliability of the coding guideline. Unclear category assignments are discussed till a consensus is reached. The analysis will be performed with the software program MaxQDA.

Quantitative data will be analysed using descriptive statistics. Mean and standard deviation will be reported for continuous data and frequencies and percentages for categorical data. Differences between patients and parents/legal guardians treated in different centers will be analysed using group comparisons (chi^{2-}, U- or t-tests, depending on scale level). Outcomes will be patient satisfaction with health care as well as disease and health care related burden. If applicable, disease related parameters such as time until confirmed diagnosis or duration of hospital stays will also be included in the comparisons. To determine potential health care related predictors of patients'/relatives' burden or

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patient satisfaction multiple regression analyses will be applied. All statistical analyses will be performed using the software program SPSS.

Evaluation of not yet implemented interface management concepts

If in Step 6 of Phase 1 an interface management concepts is chosen, which has not been implemented until the time of our study, this concept will be evaluated using a qualitative approach based on expert interviews. We will invite experts in the field of health care provision in rare diseases (centers for rare diseases, NAMSE, ACHSE e.V., target n=10) to participate in an interview. The interview guideline will be developed according to the guideline for the primary and specialized health care providers in the evaluation of the selected interface management concepts.

Phase 3: Integration of results and development of best practice recommendations for interface management in health care of rare diseases

The final phase of the study will be based on the results of phase 1 and 2 and a concluding expert workshop.

First, the quantitative and qualitative findings from practitioners' as well as patients' and parents/legal guardians' perspective will be integrated and aggregated. The findings will be presented in an expert workshop. Participants of the workshop in Phase 1 will be invited to participate (representatives from centers for rare diseases, ACHSE e.V. and NAMSE, Federal Ministry of Health). The aim of the workshop is to finalise and consent on explicit best practice recommendations for interface management in health care of rare disease.

Data management and monitoring

Members of the research team will continuously document data collection and manage the data collection at the different phases.

Questionnaires will be entered in a SPSS database by research assistants. To assure high quality data, double entry will take place for about 20% of the questionnaires and checked for mistakes. Data are only accessible to members of the research team.

Adverse events will be monitored, documented and the necessity of adaptation in the study process will be discussed within the research team.

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Patient and Public Involvement statement

Patient organisations are systematically involved in the study. The German National Alliance for Chronic Rare Diseases (ACHSE e.V.), the umbrella organisation of patient organisations, is a collaborator on the study. During the study phases I and III, representatives of the ACHSE e.V. will be invited to participate in the expert workshops. In phase II patients' perspective is systematically included and a crucial part of the evaluation ofthe interface management concepts.

ETHICS AND DISSEMINATION

Ethics approval and consent to participate

The study has been approved by the Local Psychological Ethics Committee of the Center for Psychosocial Medicine of the University Medical Center Hamburg-Eppendorf (LPEK-0062). All participants will receive detailed study information. Informed consent will be obtained from study participants prior to participation in the study.

Confidentiality

Data protection is assured by pseudonymisation using a unique code. The code list can only be decrypted by members of the research team and will be destroyed after the end of data collection. Access to study data will be restricted by authorised access only for members of the research team.

Competing interests

The authors declare that they have no competing interests.

Funding

The study is funded by the Federal Ministry of Health in Germany. Representatives of our funding source will be invited to participate in the expert workshops and will be informed about the selection of interface management concepts for evaluation. However, the funding source is not involved in the study design, the collection, analysis and interpretation of data and in writing the manuscript.

Availability of data and material

The research team will have full access to the dataset. Availability of these data will be restricted and data will not be publicly available. However, anonymized data will be available from the authors upon

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reasonable request and with permission of Local Psychological Ethics Committee (LPEK) and the data protection officer of the University Medical Center Hamburg-Eppendorf.

Dissemination

The findings of our study will be presented on national and international conferences and published in peer-reviewed scientific journals. To assure that centers for rare diseases get access to the study results, all centers are invited to send a representative to the final expert workshop in Phase 3. Moreover, an executive summary will be provided and send to all centers for rare diseases, all participating practitioners, ACHSE e.V. and NAMSE as well as other relevant professional societies, e.g. the German Society of Pediatrics and Adolescent Medicine.

DISCUSSION

The findings of our study will provide a systematic assessment of the current state of interface management in the context of rare diseases in Germany. A structured assessment tool to evaluate the interface management will be developed. The tool will focus on processes regarding the access to centers for rare diseases and information transfer to and from other health care providers. At the end of the study, consented best practice recommendations will allow health care institutions to improve their interface management and, hence, to improve the journey through the health care system for affected patients and their relatives.

Strengths and limitations

Since the assessment tool to measure interface management will be rigorously developed based on the expert workshops with representatives of both centers for rare diseases and representatives of patient organizations, important aspects from both perspectives will be represented in the tool.

Moreover, aiming at the inclusion of all centers for rare diseases in Germany, the study will provide a comprehensive assessment of interface management in centers for rare diseases in Germany. We will conduct an evaluation of the interface management in selected centers from the perspective of practitioners cooperating with the centers for rare diseases and patients or parents/legal guardians. This allows conclusions not only on the internal processes between health care providers but also on the impact on patients or parents/legal guardians themselves in their challenge to navigate through the health care system.

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Since we aim at including all centers for rare diseases, the study success will depend on their commitment for participation. It could be possible that we receive socially desirable answers, in particular from representatives of centers of rare diseases, since they may know about best practice processes but do not include them in their daily routines. The study design aims alleviating this possible bias by the inclusion of the perspective of referring primary care physicians as well as the perspective of the patient/parent/legal guardian in different study phases.

However, we might also experience a selection bias in the recruitment or willingness of participation in practitioners cooperating with the centers for rare diseases and patients/relatives, e.g. practitioners or patients with certain positive or explicitly negative experiences might be more likely to participate.

FIGURES

Figure 1: Flowchart of the study phases.

DECLARATIONS

Authors' contributions

CB and MH designed the study. LI, DZ, MB and RO were involved in the conception and design of the study. LI drafted the manuscript, which was modified and supplemented by all other authors. All authors are involved in the management and execution of the study. All authors were involved in revising the manuscript substantively, and read and approved the final manuscript.

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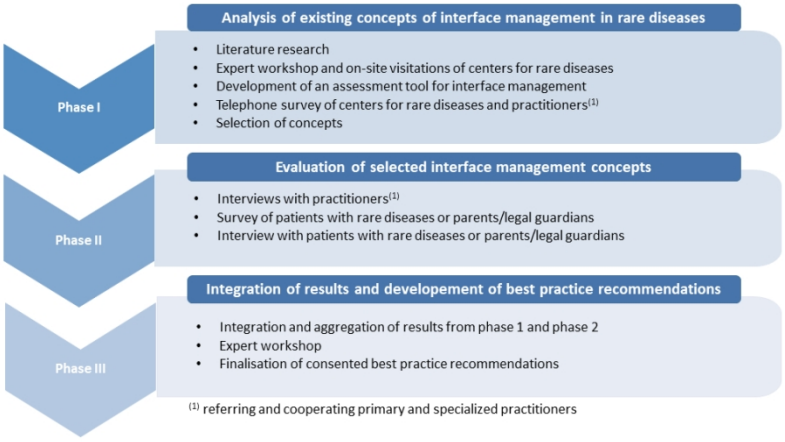

Flowchart of the study phases.

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

Section/item	Item No	Description	Reported on page
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	see study registration
Protocol version	3	Date and version identifier	Na
Funding	4	Sources and types of financial, material, and other support	10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 12
	5b	Name and contact information for the trial sponsor	10
	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	10
	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)	9
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	3-4
	6b	Explanation for choice of comparators	na
Objectives	7	Specific objectives or hypotheses	4-5

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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)	4
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	5
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)	5-9 (several study phases)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	na
	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)	na
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	na
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	na
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	5-9 (several study phases)
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)	Fig. 1,
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	5-9 (several study phases)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5-9 (several study phases)
Methods: Assignment of interventions (for controlled trials)			

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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	na
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	na
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	na
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	na
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	na
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	5-9 (several study phases)
	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	na
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	9
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	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8

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	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)	na
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	9
	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	na
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	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
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)	10
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	na
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	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
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	10/11

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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	na
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	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	na
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	not provided
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	na

*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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Interface management concepts in health care for rare diseases in Germany: A study protocol for a mixed-methods study to develop best practice recommendations

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Interface management concepts in health care for rare diseases in Germany: A study protocol for a mixed-methods study to develop best practice recommendations

Laura Inhestern[1], David Zybarth[1], Ramona Otto[1], Maja Brandt[1], Martin Härter[1], Corinna Bergelt[1]

[1]Department *of Medical Psychology, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany*

Corresponding Author:

Laura Inhestern, M.Sc., PhD

Department of Medical Psychology
University Medical Center Hamburg-Eppendorf
Martinistr. 52, W26
20246 Hamburg, Germany
Phone: +49(0)40 7410 – 57684
Email: l.inhestern@uke.de

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ABSTRACT

Introduction: Patients and families affected by a rare disease are burdened in multiple ways. Functional interface management can unburden patients or relatives from the need to be solely accountable for the navigation through the health care system. This study aims 1) at providing an assessment of approaches and interface management concepts in the care of rare diseases, 2) at evaluating selected existing approaches and concepts and 3) at developing best practice recommendations for interface management.

Methods and Analysis: We will conduct a mixed-methods study with three phases. In phase 1, we will develop a tool to assess existing concepts of interface management for rare diseases based on a literature search and an expert workshop. The tool will be applied in a telephone survey with representatives of centers or clinics of expertise for rare diseases (target: n=100) and cooperating practitioners (target: n=60). Based on the results of phase 1, we will select four to six centers of expertise with interface management concepts, which will be evaluated extensively in phase 2. For the evaluation, we will conduct semi-structured interviews with practitioners cooperating with centers or clinics for rare diseases (target: n=50), a paper based survey including patients or parents/legal guardians (total target: n=300) from the selected centers or clinics and semi-structured interviews with patients or parents/legal guardians (total target: n=50). The final phase of the study will be an integration of results from phase 1 and 2 to develop best practice recommendations for interface management in health care of rare diseases. In a concluding expert workshop recommendations will be presented and finalised.

Ethics and dissemination: The study was approved by the Local Psychological Ethics Committee of the Center for Psychosocial Medicine of the University Medical Center Hamburg-Eppendorf (LPEK-0062). The findings of our study will be presented on national and international conferences and published in scientific, peer-reviewed journals. To assure that centers for rare diseases get access to the study results, centers are invited to send a representative to a final expert workshop in Phase 3. Moreover, an executive summary will be provided and send to relevant stakeholders.

Trial registration: German Clinical Trials Register (ID: DRKS00020488)

KEY WORDS

quality in health care, organization of health services, genetics, qualitative study

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STRENGHTS AND LIMITATIONS OF THIS STUDY

- Based on three study phases, including qualitative and quantitative methods as well as the perspective of representatives of centers or clinics for rare diseases, practitioners and patients allow a rigorous development of best practice recommendations for interface management.
- The results will allow health care providers to improve their interface management and, hence, to improve the journey through the health care system for patients with rare diseases and their relatives.
- Since we aim at including all centers for rare diseases in Germany, we will depend on their commitment for participation and we may have a selection bias, e.g. due to socially desirable of study participants.

INTRODUCTION

According to the European definition a disease is defined as rare, if five people or less in 10.000 people are diagnosed with this disease [1]. Currently about 30 million people in the European Union [1] and about 2.4-5 million people in Germany [2] are affected by one of about 6.000 to 8.000 known rare diseases [1].

Besides physical and mental constraints, living with a rare disease can be associated with social consequences such as stigma or financial drawbacks [3, 4]. Moreover, individuals with rare diseases can experience difficulties in their health care [5]. Due to lack of knowledge (e.g. in general practitioners and the general population) and inefficient diagnostic ways, it can take several years until patients receive the accurate diagnosis [6, 7]. After diagnosis, receiving health care might be difficult in the home-area of the patients and patients often need to travel far to get access to appropriate treatment and care [8, 9]. Patients with rare diseases report diverse health care needs, e.g. information on care facilities or psychological counselling [10]. Recent studies show, that more difficulties regarding a smooth flow through the health care system are associated with a reduced quality of life [11].

Due to the high burden of these patients, in 2009 the EU released several recommendations for its member states to improve the situation of individuals with rare diseases and national action plans have been announced [12]. The German National Plan of Action for People with Rare Diseases was published in 2013 and comprises 52 proposed actions [13], including a model of care delivery based on centers for rare diseases to structure and aggregate competencies. The national plan of action recommends

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centers for rare diseases on three levels based on the spectrum of their service (A-, B-, C-centers) (Table 1) [13].

Table 1. Description of centers for rare diseases [13]

Patient group	Structure	Tasks
Type A-center		
Patients with unclear diagnosis or undiagnosed disease	• Comprise at least three B-centers • Mostly located at university clinics	• Non-disease specific structure (e.g. coordinator, interdisciplinary case conferences) • Provision of education and teaching for undergraduate medical students • Clinical research and basic research acitivities
Type B-center		
Patients with diagnosed rare disease or clear suspected diagnosis	• Integration into hospital setting	• Provision of inpatient and outpatient multidisciplinary health care
Type C-centers		
Patients with diagnosed rare disease or clear suspected diagnosis allowing for health care nearby the patient's residence	• Specialised clinics or specialised practitioners	• Provision of outpatient care located nearby the patient's residence

So far, no formal accreditation or certification body for centers of rare diseases has been implemented, but centers define themselves as A- or B-centers according to the catalogue of requirements from the national plan of action.

Currently, there are about 32 centers for rare diseases registered in the *se-atlas*, a platform for mapping health care providers for individuals with rare diseases in Germany [14]. Most of these centers comprise more than three B-centers. However, not all are designated as A-centers.

In health care of rare diseases, generic integrated care models to structure the paths of the patients through the health care system are missing and follow-up care outside the centers for rare diseases can be insufficient. At the same time, integrated care is particularly important in rare diseases due to the delays in diagnosis and, if diagnosed, highly specialized demands with regard to treatment and monitoring [15]. In a sophisticated and highly specialized health care system, quality of care depends on the management of interfaces and may be impaired by deficits in communication and information transfer [16]. Interfaces in health care of rare diseases are e.g. center for rare diseases/primary health care provider, center for rare diseases/patient or center for rare diseases/specialised clinic [13]. To manage these interfaces, intersectional communication and coordination is mandatory to enable

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continuity of health care and to alleviate patients' or relatives' burden of being accountable for navigating through the health care system [17, 18]. Approaches for interface management range from implementation of health information technologies, care coordinators, one-stop-clinics to standard operation procedures [15, 19-21]. However, integrated care models have only been established for single rare diseases [20]. The field is rather scattered and overall guidelines including the shared experiences of individuals with rare diseases concerning medical and psychosocial consequences and best practice recommendations are missing.

The national plan of action has recommended to initiate a survey among practitioners and centers for rare diseases to identify relevant aspects to ensure cooperation (proposed action 17) [13].

Corresponding to this recommendation, our study focuses on concepts for interface management particularly between centers for rare diseases and practitioners in health care in Germany. The overall aim of our study is the development of best practice recommendations for interface management in health care of rare disease based on two steps: Firstly the systematic analysis of existing concepts for interface management including the identification of strengths and limitations and secondly the evaluation of the acceptance and feasibility of applied concepts. Specific research questions are:

- Which approaches and solutions exist in the literature and current health care for patients suffering from rare diseases regarding the interface management between primary and specialist care?
- How do representatives of centers for rare diseases, general practitioners (GPs), specialists and affected patients or parents/legal guardians evaluate existing approaches and concepts regarding their acceptance, feasibility and benefit?
- Which improvements to minimize interface problems do representatives of centers for rare diseases and practitioners (GPs and specialists) as well as affected patients or parents/legal guardians suggest?

METHODS AND ANALYSIS

This study protocol is written according the SPIRIT guidelines and addresses applicable recommended items for clinical trial protocols [22].

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Study setting

The study will be conducted at the Department of Medical Psychology of the University Medical Center Hamburg-Eppendorf in Germany. The study is conducted in collaboration with the German National Alliance for Chronic Rare Diseases (ACHSE e.V.), the Martin Zeitz Center for Rare Diseases (center for rare diseases of the University Medical Center Hamburg-Eppendorf) and the Department of Pediatrics of the University Medical Center Hamburg-Eppendorf.

Study design

The study will be conducted in three phases (Figure 1): Phase 1 comprises a comprehensive inventory of existing concepts regarding interface management in health care of rare diseases. This phase will allow an insight and overview how health care and interfaces are currently managed in centers for rare diseases. In phase 2 a differentiated evaluation of selected existing best practice concepts of interface management will be conducted. Including the patients and practitioners' perspectives will provide important information on how the interfaces are working according to their experiences. And finally, based on the first two steps, specific recommendations for the implementation of a Best-Practice-Model of interface management will be developed.

Key element of the project is a multi-perspective analysis of the existing interface management concepts in centers for rare diseases in Germany. The study applies a mixed-methods-design which includes quantitative as well as qualitative data collection.

Phase 1: Collation of existing concepts of interface management for rare diseases

With regard to the collation of existing concepts of interface management for rare diseases, we focus on the interface from primary health care to centers for rare diseases and back to primary health care (e.g. strategies or workflow to link between different centers and primary health care providers). We aim at including A-centers and B-centers for rare diseases. Pediatric and adult health care as well as patients with a diagnosed or an undiagnosed rare disease respectively will be separately analysed in order to identify possible differences. Duration of phase 1 will be approximately twelve months.

The analysis of existing concepts will be conducted using a stepwise approach:

Step 1: Systematic search

a. A systematic search of the online presence of the centers for rare diseases in Germany will be conducted to identify instruments and questionnaires concerning interface management that are

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available on the websites of the centers. Additionally, an online search concerning interface management tools in medical care in general or chronic diseases will be performed.

b. A systematic search of international scientific publications concerning interface management in the medical care of rare diseases will be conducted (e.g. PubMed and other databases) to identify and analyze concepts, that may not have been implemented in Germany. Pubmed database will be searched using the search terms on interface management, care coordination, integrated care or intersectional communication and rare disease, orphan disease or undiagnosed disease. No limitations with regard to time will be adopted. References of relevant literature will be searched for additional studies.

Step 2: Expert workshop

The centers for rare diseases will be invited to send one or two representatives for an expert workshop. The workshop will aim at exchanging experiences, gathering interface problems and possible solutions. In order to validly include the patient´s perspective, the alliance for chronically rare diseases (ACHSE e.V.) will be asked to send three to four representatives as well. Furthermore, two to three representatives the National Action League for People with Rare Diseases (NAMSE) and of the Federal Ministry of Health will be invited to participate.

Step 3: On-site visitations

Four to six centers for rare diseases will be visited by the project team to assess the implementation of interface management approaches. The visited centers should represent the different regions of Germany. The method of on-site visitations is chosen based on the assumption that specific aspects and problems of interface management may not be adequately represented by written report or telephone surveys.

Step 4: Development of an assessment tool for interface management

Results of step one to three (literature and online search; results of expert workshop as well as on-site visitations) will be collated by the study team and relevant domains for interface management will be identified. Items covering the domains will be formulated by the study team and a first draft of a structured assessment tool to evaluate the interface management in rare diseases will be developed. The assessment tool will be sent to the participants of the expert workshop and their feedback will be

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obtained. After adjustments based on the feedback, the assessment tool will be presented to three to five experts, discussed and finalized by expert consensus.

Step 5: Telephone survey of all centers of expertise for rare diseases and practitioners

All centers of expertise in rare diseases in Germany listed on a website collating all centers for rare diseases (*se-atlas)* will be invited for participation in a telephone survey using the developed and consented assessment tool. The telephone survey aims at investigating the interface management of the centers of expertise for rare diseases and to identify concepts, if applied in the centers.

In those centers that have a coordination site, the coordinator will be asked to participate and additionally, to provide information on three to four centers of expertise for a specific rare disease or disease group (B-centers). In centers without coordination site, three to four B-centers will be randomly selected and surveyed.

Per center of rare diseases at least three participants should be surveyed. All in all about n=100 representatives of A- and B-centers should participate. Each participant will be asked to name cooperating practitioners who also will be invited to participate in the survey. Overall, the final sample should comprise about n=60 practitioners.

Step 6: Selection of concepts

Based on the scoring results from the telephone survey using the developed assessment tool (step 5), we will select four to six centers for rare diseases for further evaluation from the perspective of practitioners and individuals with rare diseases. Selection criteria will be based on the survey results on the description of interface management of the centers for rare diseases and on acceptance, feasibility and benefit of the concepts from the practitioners' perspective. Those centers with an established and working concept and structures to manage interfaces (e.g. between sectors or between center and patient) will be selected for study phase 2.

Phase 2: Evaluation of selected centers with regard to their interface management concepts

To evaluate the four to six centers with regard to their interface management concepts selected in phase 1, we will include the perspective of patients with rare diseases or their parents/legal guardians as well as the perspective of practitioners who refer patients and cooperate with selected centers. We will assess the experiences on interface management and collaboration with the centers for rare diseases

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and how it could be improved according to their needs from practitioners' and patients' perspectives. Duration of phase 2 will be approximately 10 months.

Interviews with general or specialized practitioners

The selected centers will be asked to name 10-15 cooperating general or specialized practitioners (target per center n=10, total: n=50). Identified practitioners will be invited to participate in a semi-structured interview on their experiences with the interface concept of the respective center for rare diseases. The interview guideline will address acceptance and benefits of interface concepts, the compatibility with medical practice and treatment processes, barriers and facilitators for the management of interfaces in medical care and suggestions for improvement.

Survey of patients with rare diseases/relatives

The selected centers will be asked to invite patients or parents/legal guardians of patients currently or formerly treated in the center to participate in a cross-sectional survey (target per center n=60, total: n=300). The survey will comprise a questionnaire covering questions on the experiences on the interface management as well as existing and validated instruments on patient satisfaction, satisfaction with health care, psychosocial burden, quality of life and needs/unmet needs. Additionally, relevant data regarding disease and health care history will be collected.

Survey participants will be invited to also participate in a semi-structured interview (target per center n=10, total: n=50 interviews). The interviews will follow a guideline covering questions on the experiences of interface management and health care provision, barriers and facilitators for the management of interfaces in health care and suggestions for improvement.

Data analysis

All interviews will be conducted via telephone. The interviews will be recorded and transcribed verbatim and will be analysed by qualitative content analysis based on the approach of Mayring [23]. Material will be coded using an inductive procedure. Categories obtained will be discussed by two separate researches in order to augment validity and reliability of the coding guideline. Unclear category assignments are discussed till a consensus is reached. The analysis will be performed with the software program MaxQDA.

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Quantitative data will be analysed using descriptive statistics to describe the study samples. Mean and standard deviation will be reported for continuous data and frequencies and percentages for categorical data. Differences between patients and parents/legal guardians treated in different centers will be analysed using group comparisons (chi^{2}-, U- or t-tests, depending on scale level). Outcomes will be patient satisfaction with health care as well as disease and health care related burden. If applicable, disease related parameters such as time until confirmed diagnosis or duration of hospital stays will also be included in the comparisons. To determine potential health care related predictors of patients'/relatives' burden or patient satisfaction multiple regression analyses will be applied. All statistical analyses will be performed using the software program SPSS.

Qualitative and quantitative data will be synthesized after separate analyses of quantitative and qualitative data. The results on interface management will be related to each other and examined with regard to convergence, complementarity and discrepancy. Qualitative data may allow a further exploration of quantitative findings, increase understanding and support interpretation of results [24].

Evaluation of not yet implemented interface management concepts

If in Step 6 of Phase 1 an interface management concepts is chosen, which has not been implemented until the time of our study, this concept will be evaluated using a qualitative approach based on expert interviews. We will invite experts in the field of health care provision in rare diseases (centers for rare diseases, NAMSE, ACHSE e.V., target n=10) to participate in an interview. The interview guideline will be developed according to the guideline for the primary and specialized health care providers in the evaluation of the selected interface management concepts.

Phase 3: Integration of results and development of best practice recommendations for interface management in health care of rare diseases

The final phase of the study will be based on the results of phase 1 and 2 and a concluding expert workshop. Study phase 3 will approximately take two months.

The results of study phase 1 (survey with representatives of the centers for rare diseases) and phase 2 (interviews with primary health care providers, survey and interviews with patients) will be integrated and aggregated. The findings will be aggregated by the study team and best practice recommendations will be drafted.

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The recommendations will be presented to experts in the field of rare diseases (e.g. patient representatives, representatives from the centers of expertise, ACHSE e.V. and NAMSE, Federal Ministry of Health) and discussed in an expert workshop. The aim of the workshop is to finalise and consent on explicit best practice recommendations for interface management in health care of rare disease based on the considerations of the discussion.

Data management and monitoring

Members of the research team will continuously document data collection and manage the data collection at the different phases.

Questionnaires will be entered in a SPSS database by research assistants. To assure high quality data, double entry will take place for about 20% of the questionnaires and checked for mistakes. Data will only be accessible to members of the research team.

Adverse events will be monitored, documented and the necessity of adaptation in the study process will be discussed within the research team.

Patient and Public Involvement statement

Patient organisations are systematically involved in the study. The German National Alliance for Chronic Rare Diseases (ACHSE e.V.), the umbrella organisation of patient organisations, is a collaborator on the study. During the study phases 1 and 3, representatives of the ACHSE e.V. will be invited to participate in the expert workshops. In phase 2 patients' perspective is systematically included and a crucial part of the evaluation ofthe interface management concepts.

ETHICS AND DISSEMINATION

Ethics approval and consent to participate

The study has been approved by the Local Psychological Ethics Committee of the Center for Psychosocial Medicine of the University Medical Center Hamburg-Eppendorf (LPEK-0062). All participants will receive detailed study information. Informed consent will be obtained from study participants prior to participation in the study.

Confidentiality

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Data protection is assured by pseudonymisation using a unique code. The code list can only be decrypted by members of the research team and will be destroyed after the end of data collection. Access to study data will be restricted by authorised access only for members of the research team.

Dissemination

The findings of our study will be presented on national and international conferences and published in peer-reviewed scientific journals. To assure that centers for rare diseases get access to the study results, all centers are invited to send a representative to the final expert workshop in Phase 3. Moreover, an executive summary will be provided and send to all centers for rare diseases, all participating practitioners and NAMSE as well as other relevant professional societies, e.g. the German Society of Pediatrics and Adolescent Medicine. To make the results accessible and available to affected patients and families, an executive summary will be sent to ACHSE e.V. to distribute it to their member patient organizations.

DISCUSSION

The findings of our study will provide a systematic assessment of the current state of interface management in the context of rare diseases in Germany. A structured assessment tool to evaluate the interface management will be developed. The tool will focus on processes regarding the access to centers for rare diseases and information transfer to and from other health care providers. At the end of the study, consented best practice recommendations will allow health care institutions to improve their interface management and, hence, to improve the journey through the health care system for affected patients and their relatives.

Strengths and limitations

One strengths of the presented study is the rigorous development of the assessment tool to measure interface management based on the expert workshops with representatives of both centers for rare diseases and representatives of patient organizations. Important aspects from both perspectives will be represented in the tool.

Moreover, aiming at the inclusion of all centers for rare diseases in Germany, the study will provide a comprehensive assessment of interface management in centers for rare diseases in Germany. We will conduct an evaluation of the interface management in selected centers from the perspective of

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practitioners cooperating with the centers for rare diseases and patients or parents/legal guardians. This allows conclusions not only on the internal processes between health care providers but also on the impact on patients or parents/legal guardians themselves in their challenge to navigate through the health care system, which can be considered as another strength of the study.

One major limitation of the study is, that the study success will depend on the commitment for participation of centers for rare diseases. It could be possible that we receive socially desirable answers, in particular from representatives of centers of rare diseases, since they may know about best practice processes but do not include them in their daily routines. The study design aims alleviating this possible bias by the inclusion of the perspective of referring primary care physicians as well as the perspective of the patient/parent/legal guardian in different study phases. However, we might also experience a selection bias in the recruitment or willingness of participation in practitioners cooperating with the centers for rare diseases and patients/relatives, e.g. practitioners or patients with certain positive or explicitly negative experiences might be more likely to participate.

Another limitation is the method of expert workshops in phase 1 and phase 3. Participants will need to commit to participate and there may be a limited reliability (e.g. selection/participation bias). At the same time, this method allows the inclusion of patient experts and health care experts in the development of recommendations for interface management.

Against the background of internationally different health care services, our findings may be relevant specifically for Germany. Still, difficulties in health care provision for patients with rare diseases are experienced across countries [25, 26]. Therefore, the results of our study and certain recommendations based on our findings may be relevant internationally.

FIGURES

Figure 1: Flowchart of the study phases.

DECLARATIONS

Contributorship statement

CB and MH designed the study. LI, DZ, MB and RO were involved in the conception and design of the study. LI drafted the manuscript, which was modified and supplemented by all other authors. All authors

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are involved in the management and execution of the study. All authors were involved in revising the manuscript substantively, and read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Funding

The study is funded by the Federal Ministry of Health (Bundesministerium für Gesundheit) in Germany. Representatives of our funding source will be invited to participate in the expert workshops and will be informed about the selection of interface management concepts for evaluation. However, the funding source is not involved in the study design, the collection, analysis and interpretation of data and in writing the manuscript.

Data sharing statement

The research team will have full access to the dataset. Availability of these data will be restricted and data will not be publicly available. However, anonymized data will be available from the authors upon reasonable request and with permission of Local Psychological Ethics Committee (LPEK) and the data protection officer of the University Medical Center Hamburg-Eppendorf.

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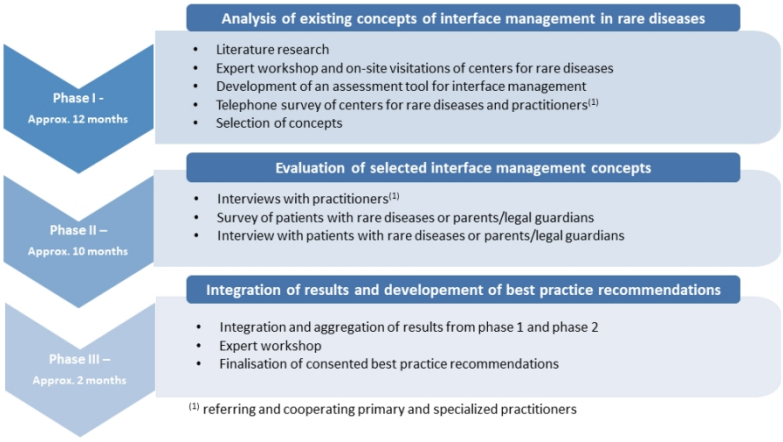

Flowchart of the study phases.

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

Section/item	Item No	Description	Reported on page
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	2
	2b	All items from the World Health Organization Trial Registration Data Set	see study registration
Protocol version	3	Date and version identifier	Na
Funding	4	Sources and types of financial, material, and other support	10
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 12
	5b	Name and contact information for the trial sponsor	10
	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	10
	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)	9
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	3-4
	6b	Explanation for choice of comparators	na
Objectives	7	Specific objectives or hypotheses	4-5

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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)	4
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	5
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)	5-9 (several study phases)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	na
	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)	na
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	na
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	na
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	5-9 (several study phases)
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)	Fig. 1,
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	5-9 (several study phases)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5-9 (several study phases)
Methods: Assignment of interventions (for controlled trials)			

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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	na
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	na
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	na
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	na
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	na
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	5-9 (several study phases)
	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	na
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	9
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	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8

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	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)	na
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	9
	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	na
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	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
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)	10
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	na
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	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
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	10/11

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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	na
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	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	na
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	not provided
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	na

*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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