Patient-related outcome measure (PROM) for assessing quality of life (QoL) in patients with alpha-1-antitrypsin deficiency (AATD): a systematic review protocol

K. Müller[1], H. Knüttel[2], T. Greulich[3], F. Lammert[4], P. Strnad[5], C. F. Vogelmeier[3], M. Wilkens[6], R. Bals[7], M. Koller[1]

[1]Center for Clinical Studies, University Hospital Regensburg, Regensburg, Germany
[2]University Library, University of Regensburg, Regensburg, Germany
[3]Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Marburg, Germany
[4]Department of Medicine II, Saarland University Medical Center, Homburg, Germany
[5]Department of Internal Medicine III, University Hospital Rheinisch-Westfälisch Technische Hochschule, Aachen, Germany
[6]Gesellschaft für Alpha-1-Antitrypsin-Mangel Erkrankte e.V., Gernsheim, Germany
[7]Department of Pulmonary, Allergology and Critical Care Medicine, University of Saarland, Homburg, Germany

Corresponding author:
Michael Koller
Franz-Josef-Strauß-Allee 11
93053 Regensburg
michael.koller@ukr.de
++49 941 944 5630

Contributions

MK is the guarantor of this review. KM, MK, and HK drafted the manuscript. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. HK developed the search strategy in cooperation with KM and MK. KM and MK provided statistical expertise. RB, TG, FL, PS, CFV, and MW provided expertise on alpha-1-antitrypsin deficiency. All authors read, provided feedback, and approved the final manuscript.

Registration

The systematic review on patient-related outcome measures (PROM) for assessing quality of life (QoL) in patients with alpha-1-antitrypsin deficiency (AATD) was registered at PROSPERO (CRD 42021265360).

Support

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Rationale

Alpha-1-antitrypsin deficiency (AATD) is a hereditary disease, which may encompass rare severe forms (such as PiZZ) but also common mild genotypes (such as PiMZ) [1]. AATD is associated with a higher risk of developing chronic obstructive pulmonary disease (COPD), emphysema, chronic liver disease, ANCA-positive vasculitis and panniculitis [1,2].

The treatment of AATD is focused on the specific organ manifestation. Lung disease is an early-onset form of COPD as well as emphysema and is treated similarly to the non-deficient form. In addition, patients may also receive augmentation therapy consisting of weekly infusions of purified AAT. For liver disease, no specific treatment has been approved so far, and study data are even scarcer.

There is increasing awareness and acceptance that patient-related outcomes (PROs) are an essential component of a well-designed clinical study [3]. The umbrella term PRO includes all kinds of variables and outcomes that may be directly reported by patients, such as quality of life, satisfaction with care, preferences, somatic symptoms, or well-being [4]. Quality of life (QoL) is the most encompassing concept and commonly defined as a multidimensional construct covering subjective well-being and behavioral capacities in the psychological, social, and somatic domains [5].

PROs are assessed via questionnaires filled in by patients, either in paper/pencil format or by means of an electronic device (e.g., smartphone or tablet). PRO measures (PROMs) used in clinical studies undergo a rigorous and methodologically refined developmental process including psychometric testing and validation [6].

To our knowledge, no accepted and validated measurement approach yet exists that addresses QoL issues of patients with AATD, and our aim is to fill this gap.

Objectives

This systematic review of PROMs for measuring QoL in patients with AATD is the first step in a multiple-phase project termed “Design of a patient-related outcome (PRO) instrument for assessing quality of life in patients with alpha-1-antitrypsin deficiency”. The overall aim of this project is to design and validate PROMs for use in clinical practice and research of patients with AATD.

In principle, we are open to an assessment approach that is based on a single PROM specifically developed for AATD patients covering lung-specific as well as liver-specific

symptoms. If such a questionnaire is not available in the literature, a modular approach should be considered that covers generic aspects of QoL relevant for all AATD patients as well as specific symptom questionnaires related to either lung or liver manifestations [6]. In any event, the current project is conducted in accordance with guidelines in this research area [3,7–10].

The systematic review and the resulting selection process follow a stepwise process:

Step 1

The present systematic review constitutes step 1. The aim of this review is to explore the current state of PROMs used in patients with AATD. Such exploration may include PROMs specifically developed for patients with AATD as well as generic PROMs employed in the context of AATD studies. Furthermore, PROMs may be relevant that address symptoms and signs connected with the sequelae of AATD, in particular chronic obstructive pulmonary disease (COPD) or chronic liver disease.

Thus, the primary outcome of interest is to identify which PROMs have been used in patients with AATD. The secondary outcome is to summarize the psychometric properties of identified PROMs. The details of the work to be done in step 1 are described in this protocol.

Step 2

Step 2 will be conducted independently of and parallel to step 1 and aims to collect information about QoL issues of patients with AATD. Sources of information will be patient advocates and physicians of the study group with experience in or expert knowledge on AATD. This information may be collected via semi-structured questionnaires or focus groups [6].

Step 3

Based on the findings of steps 1 and 2, a list of AATD-relevant questionnaires will be prepared by the methodologists in charge of the project (KM and MK). Prioritizing/selection will be done in a standardized group process involving experts in AATD, methodologists, and representatives of patient organizations.

The selected PROM or PROMs will be subjected to validation studies to investigate the psychometric properties and feasibility in clinical practice, which will be specified in a separate protocol.

Methods

This systematic review protocol was developed according to PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines [11,12]. No ethical approval was needed. The systematic review protocol was registered with PROSPERO (CRD 42021265360).

Eligibility criteria

All PROMs that have been used in the context of studies with AATD patients are eligible for this review. Measures may include PROMs that have been specifically developed for AATD patients, generic PROMs such as the EuroQuality Group (EQ)-5D or the Short Form Health Survey (SF)-12, or PROMs that have been developed to assess lung- and liver-specific issues because lung and liver diseases are the most common clinical sequelae of AATD [2]. As AATD is a rare disease, the number of identified eligible PROMs and studies is expected to be low.

The term “study” is used in an encompassing manner in the present context and includes PROM validation studies, clinical studies that made use of PROMs, as well as reviews or position papers with relevance to PROMs.

Only studies in languages other than English and German that can be adequately translated by using Google Translate or DeepL Translator will be included.

Information sources

In order to be highly sensitive, we will use several search approaches. We will search

1. questionnaire databases: PROQOLID (Patient-reported Outcome and Quality of Life Instruments Database), Hogrefe Testzentrale, Open Test Archive, and Registry of scales and measures;
2. electronic bibliographic databases: MEDLINE (Ovid), Embase (Ovid), Science Citation Index Expanded & Social Sciences Citation Index (Web of Science), APA PsycInfo (EBSCOhost), CINAHL (EBSCOhost), COSMIN Database of Systematic Reviews, and Cochrane Library (Wiley);
3. web search engine: Google Scholar (first 100 results);
4. trial registers for ongoing and recently completed trials: ClinicalTrials.gov, WHO ICTRP, and EU CTR;
5. reference lists of included primary studies and relevant published reviews; and
6. authors’ personal files.

Search strategies

To begin with, questionnaire databases will be searched to detect AATD-specific PROMs. Only a single concept "AATD" will be used, which will be searched for with several synonyms, such as “AATD”, “α1-antitrypsin deficiency”, “alpha 1-antitrypsin deficiency”, “alpha-1 antitrypsin deficiency”, and “alpha-1-antitrypsin deficiency”.

The searches in the bibliographic databases and the web search engine will be carried out in accordance with the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) recommendations [9]. As our target population consists of patients with a rare disease, we do not expect many hits. Thus, in order to achieve a high search sensitivity, we deviate from COSMIN recommendations. Therefore, the filters for the type of study, type of instrument, and measurement properties recommended in the COSMIN guideline were not used to limit the search results. In addition, the filter includes PROMs that are known to be relevant in the present context.

Four concepts will be employed in the searches:

1. Population: AATD. The structure of the search was taken from a systematic review on the treatment of lung disease in AATD [13] with an addition of search terms for higher sensitivity.
2. Construct: Quality of Life. For optimal sensitivity, the search strategy of this search element is based on the filter "Quality of life (QoL)" by Vissers and de Vries [14], the filter "Patient reported outcome measures (PROMs)" by Jansma and de Vries [15], and additional search terms from the "PROM group construct & instrument type filter" by Mackintosh et al. [16]. None of these filters has been validated regarding recall and specificity.
3. AATD-specific PROMs: At the time of protocol development, the review team had no knowledge of any AATD-specific PROMs. However, this situation may change in later update searches; in this case, reports on these instruments will be searched for by the instrument name.
4. Generic or symptom-specific PROMs: The names of generic and symptom-specific PROMs that are known to have been applied to patients with AATD were included. This list will be amended for update searches, once new instruments are available.

These concepts were combined using Boolean operators to generate three subject-based search strategies for an overall highly sensitive search approach: (population AND construct) OR (AATD-specific PROMs) OR (generic PROMs AND population).

No limitations regarding study design, date, or language will be imposed during the search.

The search strategy was created by a librarian (HK) with expertise in searching for systematic reviews. A draft strategy for MEDLINE was developed with input from the project team (Supplement 1). In accordance with the guideline for Peer Review of Electronic Search Strategies (PRESS) [17], the search strategy was peer-reviewed by an independent librarian (BD). No revision of the search strategy was needed. The MEDLINE strategy will be adapted to the syntax and subject headings of the other databases.

Data management

All records identified in database searches will be compiled in Citavi (version 6 or higher). Duplicates will be removed. Review documentation will be compiled in the free web-tool Rayyan (www.rayyan.ai) and Microsoft Excel (version 2019 or higher). Review documentation in Rayyan will be stored on cloud services and automatically backed up daily. Review documentation, search results studies, and relevant PROMs will be saved and backed up on the institute's own data server. Data will only be accessed by the reviewers (KM and MK).

Study selection process

In the first stage of screening, two reviewers (KM and MK) will independently read the titles and abstracts of all studies identified by the search. The studies that meet the eligibility criteria will be included, and full texts will be obtained. If no full text of a study can be requested, the study will be excluded.

During the second stage of screening, the reviewers (KM and MK) will independently read the full texts of the remaining studies and remove any study that does not meet the eligibility criteria. The reviewers will seek additional information from study authors where necessary to resolve questions about eligibility. Disagreement regarding the eligibility of specific studies will be discussed by the reviewers and resolved by consent.

The number of studies at each stage of the search and reasons for excluding trials will be recorded. Neither of the two reviewers will be blinded to the journal titles or the study authors or the institutions.

Quality assessment of PROMs

The quality assessment will be in accordance with COSMIN recommendations [8,18,19], including the evaluation of the methodological quality of studies, the evaluation of measurement properties, as well as feasibility aspects of the identified PROMs. Both evaluations will be integrated into a best evidence synthesis.

The extraction of data will be based on tools provided by COSMIN (www.cosmin.nl). For the purpose of reaching the aim of the total project, we will extend the tools by including aspects such as disease-specific symptoms of AATD in the evaluation of content validity as well as evaluations of feasibility, interpretability, and suitability for additional health economic analysis of PROMs.

The extraction and evaluation of these aspects will be independently conducted by two reviewers (KM and MK). The reviewers will resolve any disagreements by discussion, involving a third review author (RB) where necessary.

PROM selection process

COSMIN recommends an order of the importance of measurement properties: 1. content validity, 2. internal structure (internal consistency and structural validity), and 3. remaining measurement properties (reliability, measurement error, hypotheses testing, cross cultural validity, criterion validity, and responsiveness) [8]. In accordance with COSMIN guidelines [8], PROMs with poor or unknown content validity will not be further considered in the selection process.

COSMIN recommendations have a strong focus on measurement properties of PROMs. However, this project follows a practical approach focusing on the feasibility in clinical routine and clinical studies. Thus, this project will include feasibility aspects and measurement properties that become apparent in the context of this review, measurement properties will be only one of a number of decision criteria.

We implement the following crucial and optional quality criteria to select appropriate PROMs:

Crucial quality criteria:

- adequate to cover generic aspects and/or disease-specific aspects for either lung or liver symptoms of patients with AATD,
- usability and shortness,
- dynamic range (coverage of symptoms of early and late disease), and
- availability in major international languages.

Optional quality criteria:

- proven psychometric properties (reliability, validity, sensitivity, and responsiveness to change), and
- suitability for additional health economic analysis (utilities).

Based on these criteria, appropriate PROMs will be selected in a standardized group process involving clinical experts in AATD, methodologists, and representatives of patient organizations.

Data

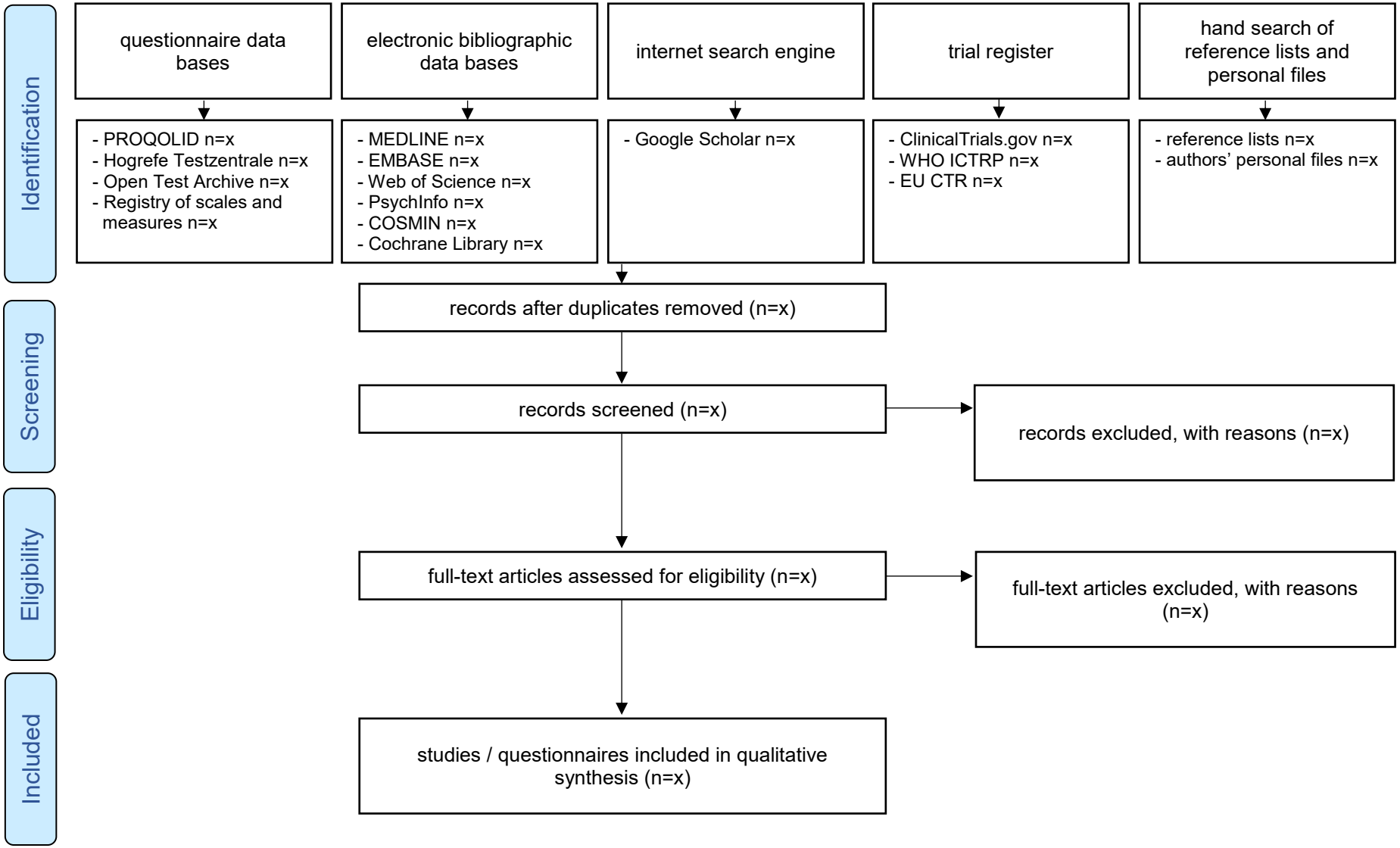
The searches will be reported according to the PRISMA-S guideline [20]. The number of studies at each stage of the search will be presented in a PRISMA flow diagram (Figure 1).

We will provide a narrative synthesis containing the frequency of PROMs and the evaluation of the methodological quality of included studies and identified PROMs.

Discussion

The present protocol is based on the state-of-the art methodology of library science in order to scrutinize, extract, and evaluate the current literature on PROMs with respect to a rare disease. The information gained from this review will enable the research group to select appropriate PROMs and study them in subsequent validation studies. Our ultimate aim is to come up with a measurement approach that is methodologically sound as well as practically feasible for both, clinical research and clinical practice. Most importantly, the large-scale implementation of such a measurement approach will strengthen the voice of patients suffering from AATD.

Figure 1 PRISMA flow diagram



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