Comparative efficacy of different exercise interventions in chronic non-specific low back pain: protocol of a systematic review and network meta-analysis

Dennis Anheyer, Petra Klose, Anna Katharina Koch, Heidemarie Haller, Gustav Dobos, Holger Cramer

ABSTRACT
Introduction Chronic non-specific low back pain is a major public health problem. Evidence supports the effectiveness of exercise as an intervention. Due to a paucity of direct comparisons of different exercise categories, medical guidelines were unable to make specific recommendations regarding the type of exercise working best in improving chronic low back pain. This network meta-analysis (NMA) of randomised controlled trials aims to investigate the comparative efficacy of different exercise interventions in patients with chronic non-specific low back pain.

Methods and analysis MEDLINE, Scopus, Cochrane Central Register of Controlled Trials, Physiotherapy Evidence Database, SPORTDiscus, Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform search portal were searched on November 2019 and without language restrictions. The search will be updated after data analysis. Studies on adults with non-specific low back pain of at least 12 weeks duration comparing exercise to either no specific intervention (ie, no treatment, wait-list or usual care at the treating physician’s discretion) and/or functionally inert interventions (ie, sham or attention control interventions) will be eligible. Pain intensity and back-specific disability are defined as primary outcomes. Secondary outcomes will include health-related physical and mental quality of life, work disability, frequency of analgesic use and adverse events. All outcomes will be analysed short-term, intermediate-term and long-term. Data will be extracted independently by two review authors. Risk of bias will be assessed using the recommendations by the Cochrane Back and Neck Group and be based on an adaptation of the Cochrane Risk of Bias tool.

Ethics and dissemination This NMA will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) checklist. The results will be presented in peer-reviewed journals, implemented in existing national and international guidelines and will be presented to health care providers and decision makers. The planned completion date of the study is 1 July 2021.

PROSPERO registration number CRD42020151472.

Strengths and limitations of this study
► This network meta-analysis (NMA) will investigate the comparative efficacy of different types of exercise in order to offer an evidence-based synthesis that will integrate the actual recommendations, balancing values and preferences of patients and stakeholders.
► Evidence that can be drawn from a NMA is limited and can only be interpreted with caution.
► To avoid heterogeneity and inconsistency the definition of nodes (grouping of interventions) needs careful consideration.
► The interpretation of evidence from indirect comparisons is limited.
► Evidence drawn from ranking analysis is limited.

INTRODUCTION
With a lifetime prevalence of about 75%, low back pain is a major public health problem. Up to 30% of the population experience such pain per year. In 2015, more than 530 million people were suffering from low back pain worldwide (7211 per 100,000 persons), which indicates an increase of 17.3% (16.5%-18.2%) from 2005 to 2015. With more than 60 million disability-adjusted life years in 2015, low back pain has become one of the leading causes of disability worldwide, placing a major burden on individuals and healthcare system.

Current evidence supports the effectiveness of exercise as an intervention for chronic non-specific low back pain. Exercise generally seems to decrease pain and to improve function and quality of life in this patient population. Exercise is regarded as a primary intervention for chronic non-specific low back pain in most international medical guidelines. However, exercise is
an umbrella term for a very heterogeneous field of interventions with various mechanisms of action.\textsuperscript{10} Nevertheless, different categories of exercise have shown at least some effectiveness for low back pain.\textsuperscript{11–14} Due to a paucity of direct comparisons of different exercise categories, medical guidelines were unable to make specific recommendations regarding which type of exercise works best in improving chronic low back pain.\textsuperscript{9} Medical guidelines thus recommend basing the choice between different types of exercise on availability and the patients’ and therapists’ preferences rather than evidence.\textsuperscript{9}

For example, the National Institute for Health and Care Excellence (NICE) guideline NG59 about low back pain and sciatica\textsuperscript{8} states that ‘the Guideline Development Group found it difficult to tease out which type of exercise modality was effective’. The guideline’s authors agreed that it would be useful to recommend an intervention that the person with back pain would be likely to participate in and that promotes self-management.

The 2017 German National Disease Management Guideline for Non-Specific Low Back Pain\textsuperscript{9} states that exercise therapy is more effective than usual care or passive treatment options.\textsuperscript{15} Strengthening the muscles and stabilisation reduces the symptoms and enable the patient to return to work more quickly.\textsuperscript{16, 17} However, evidence is lacking for what type of exercise is the most effective. Hence, in absence of a precise recommendation on which type of exercise is to be used in clinical practice, the health professionals can decide the type of treatment based on their preferences and/or patients and stakeholder preferences and condition severity. Consequently, all kinds of sport, physical activity, training and so on are recommended and patient’s preferences and fitness are considered the main selection criteria.\textsuperscript{9}

The 2017 Clinical Guideline of the American College of Physicians\textsuperscript{18} gives three recommendations. Recommendation 2 is: ‘For patients with chronic low back pain, clinicians and patients should initially select nonpharmacologic treatment with exercise, […] tai chi, yoga, motor control exercise, progressive relaxation […]. (Grade: strong recommendation)’. The guideline authors confirm that there are ‘no clear differences between different exercise regimens’.\textsuperscript{18}

A network meta-analysis (NMA) is needed to investigate the comparative efficacy of different types of exercise in order to base recommendations on evidence and preferences rather than preferences alone. To fill this gap, we will perform an NMA of randomised controlled trials (RCTs) to investigate the comparative efficacy of different exercise interventions compared with no specific intervention or functionally inert interventions on pain intensity and back-specific disability in patients with chronic non-specific low back pain.

Thus, this NMA will inform clinical practice to make the best possible choices for treating chronic non-specific low back pain. It will further inform future research as it will identify research gaps and demonstrate where further high-quality research is needed.

### Patient and public involvement

This review protocol was developed in a consensus process between clinical experts, methodological experts and patient advocates. The review’s stakeholder advisory board comprised a general practitioner and full professor of general medicine with longstanding experiences regarding the needs, preferences and capabilities of patients with chronic non-specific low back pain. Further, patient advocates of Germany’s biggest and most important pain related patient associations participated in the study development: the director of the German Patient Association Ankylosing Spondylitis and a patient advocate of one of Germany’s biggest patient associations for pain (‘SchmerzLOS e.V.’). The patient representative was chosen because he also served as the main patient representative in the recently updated German National Disease Management Guideline non-specific for Low Back Pain (‘Nationale VersorgungsLeitlinie unspezifischer Kreuzschmerz’) which also exclusively focused on non-specific forms of low back pain\textsuperscript{9} and because there is no national patient organisation for patients with non-specific low back pain. The stakeholder board was involved in all levels of the protocol development such as choice of eligible patient groups, exercise categories, comparators, and especially regarding patient-relevant outcomes.

The results of this NMA will help to inform patients and their healthcare providers about the comparative efficacy and safety of different types of exercise in order to enable informed shared decision-making. Future patients will thus directly benefit from the results of this review.

### METHODS AND ANALYSIS

This protocol is reported in compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement.\textsuperscript{19} The full NMA will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses_NMA checklist.\textsuperscript{10}

### Eligibility criteria

**Population**

This NMA will focus on patients with chronic non-specific low back pain.\textsuperscript{20} Studies on adults (at least 18 years) of all genders with non-specific low back pain of at least 12 weeks duration will be eligible.\textsuperscript{21} Studies including patients with low back pain caused by specific pathologies (eg, herniated discs, fractures, ankylosing spondylitis, spondyloarthritides, infections, neoplasms or metastases) or conditions (eg, pregnancy) will be excluded as will studies that focus exclusively on acute exacerbations of chronic low back pain.\textsuperscript{19} Studies on patients with sciatica or radicular symptoms will only be eligible if they were diagnosed with non-specific low back pain. Studies including patients with a mixture of non-specific and specific low back pain will only be eligible if data on those two patient groups are presented separately.
Interventions
Studies on exercise interventions will be eligible. Exercise interventions will be defined as structured interventions planned, prescribed and delivered by a health professional that include conducting specific activities, movements, postures (or both). Studies on exercise on a one-to-one basis or in a group environment will be eligible. Studies including unstructured self-management or simple advice to stay physically active will be excluded. Studies on exercise combined with another non-exercise intervention (such as multimodal pain treatment) will also be excluded. For the purpose of this review, NICE categories for different categories of exercise were adopted:

1. Biomechanical exercise: this category of exercise is primarily directed at altering or improving spinal mechanics and includes muscle strengthening, stretching, range of motion exercise, motor control exercise (eg, spinal stabilisation exercises, core stability programmes and Pilates) or programmes addressing specific movement patterns or problems (eg, McKenzie exercise, including directional preference exercises, and the Feldenkrais method).

2. Aerobic exercise: this category of exercise is primarily directed at improving cardiovascular fitness and endurance. This category includes walking, jogging, running, cycling, swimming for example.

3. Mind-body exercise: this category of exercise comprises a combined physical, mental and spiritual focus. This type often includes a focus on breathing and a meditative state of mind besides movement or body positioning. Also referred to as meditative movement. Examples include the various forms of Yoga and Tai Chi.

4. Mixed modality exercise: an umbrella category for exercise interventions that incorporate a combination of any of the previous three categories.

A description of the interventions based on an abbreviated form of the Template for intervention description and replication (TIDieR) checklist will be found in the supplement.

Comparators
Studies comparing exercise to either no specific intervention (ie, no treatment, wait-list or usual care at the treating physician’s discretion and according to NICE guideline and the American College of Physicians guideline) and/or functionally inert interventions (ie, sham or attention control interventions) will be eligible. Studies comparing one exercise type as defined above to another exercise type will also be eligible.

Outcomes
In line with the recommendations by Deyo et al., the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), the Cochrane Back and Neck Group and patient advocates, the following outcomes were chosen as primary outcomes:

1. Pain intensity (eg, as measured by the visual analogue scale for pain).

2. Back-specific disability (eg, as measured by the Roland-Morris Disability Questionnaire).

Secondary outcomes will include:

1. Health-related quality of life (eg, as measured on the 36-item Short Form).

   a. Physical quality of life.

   b. Mental quality of life.

2. Work disability.

3. Frequency of analgesic use or the number of medications used.

4. Adverse events.

   All outcomes will be assessed at short-term (less than 3 months from randomisation), intermediate-term (3–12 months from randomisation) and long-term (more than 12 months from randomisation) time points.

Design of primary studies
This NMA will only include RCTs. In order to include only trials that will be at least minimally clinically relevant, only trials with at least short-term follow-up (4 weeks from randomisation or longer) will be eligible.

Information sources and search strategy
Based on NICE guidelines and the search strategy used by the Cochrane Back and Neck Group, the following electronic databases will be searched without language or time restrictions:

1. MEDLINE.

2. Scopus.

3. Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library).

4. Physiotherapy Evidence Database.

5. SPORTDiscus.

The complete search strategy for MEDLINE is shown in table 1.

Additionally, the following trial registries will be searched for all prospectively registered and ongoing trials:


It will be tried to identify further studies from reference lists of identified relevant trials or reviews. A copy of the full article will be obtained for each reference reporting a potentially eligible trial. Where this is not possible, attempts will be made to contact authors for them to provide additional information. We will search for grey literature in online (http://www.opengrey.eu/).

Based on prior systematic reviews and guidelines, a total of about 150 eligible primary studies are expected.

Data extraction
Data will be extracted independently by two review authors. Disagreements will be dissolved by discussion. If this is impossible, a third author will be approached. If necessary, additional information will be obtained from the study authors. The data extraction form will
Open access

Table 1  Complete search strategy for Medline

<table>
<thead>
<tr>
<th>Search 1.1—population search terms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lower back pain population (Search 1.1)</td>
</tr>
<tr>
<td>2</td>
<td>Excluded study designs and publication types (Search 1.2)</td>
</tr>
<tr>
<td>3</td>
<td>1 not 2</td>
</tr>
<tr>
<td>4</td>
<td>exp exercise/</td>
</tr>
<tr>
<td>5</td>
<td>exp exercise therapy/</td>
</tr>
<tr>
<td>6</td>
<td>exp &quot;physical education and training&quot;/</td>
</tr>
<tr>
<td>7</td>
<td>(stretch* adj3 (active* or passive* or relax* or static* or dynamic* or gentil* or ballistic* or force* or isometric or technique* or exercis* or therapi*)),ti,ab.</td>
</tr>
<tr>
<td>8</td>
<td>(aerobic* adj (exercise* or train* or therapi*)),ti,ab.</td>
</tr>
<tr>
<td>9</td>
<td>(corrective* or biomechanic*) adj (exercise* or train* or therapi*)),ti,ab.</td>
</tr>
<tr>
<td>10</td>
<td>(biomechanic* adj (method* or course*)),ti,ab.</td>
</tr>
<tr>
<td>11</td>
<td>(strength* or stabil* or program* or train* or therapi* or technique* or treat*) adj3 exercise*),ti,ab.</td>
</tr>
<tr>
<td>12</td>
<td>(fitness* adj3 (program* or train* or therapi*)),ti,ab.</td>
</tr>
<tr>
<td>13</td>
<td>(tai ji or tai chi or taichi or taijiquan),ti,ab.</td>
</tr>
<tr>
<td>14</td>
<td>(qi gong or ch'i k#ng or ch'i g#ng or chi k#ng or chi g#ng or qi k#ng or qi g#ng),ti,ab.</td>
</tr>
<tr>
<td>15</td>
<td>core stability,ti,ab.</td>
</tr>
<tr>
<td>16</td>
<td>yoga/</td>
</tr>
<tr>
<td>17</td>
<td>tai ji/</td>
</tr>
<tr>
<td>18</td>
<td>exercise movement techniques/</td>
</tr>
<tr>
<td>19</td>
<td>exp hydrotherapy/</td>
</tr>
<tr>
<td>20</td>
<td>exp balneotherap/</td>
</tr>
<tr>
<td>21</td>
<td>(water* or bath* or pool or pools or shower* or underwater* or spa or spas or aqua*) adj2 (exercise* or train* or therapi* or treat* or manag*),ti,ab.</td>
</tr>
<tr>
<td>22</td>
<td>(hydrotherap* or hydro-therap*),ti,ab.</td>
</tr>
<tr>
<td>23</td>
<td>posture/</td>
</tr>
<tr>
<td>24</td>
<td>postural balance/</td>
</tr>
<tr>
<td>25</td>
<td>sciatica/</td>
</tr>
<tr>
<td>26</td>
<td>radiculopathy/</td>
</tr>
<tr>
<td>27</td>
<td>alexander technique*,ti,ab.</td>
</tr>
<tr>
<td>28</td>
<td>or/4–29</td>
</tr>
<tr>
<td>29</td>
<td>Study filters RCT(Search 1.3)</td>
</tr>
<tr>
<td>30</td>
<td>3 and 30 and 31</td>
</tr>
</tbody>
</table>

Search 1.2—search terms for excluded study designs and publication types

The following study designs and publication types will be removed from retrieved results using the NOT operator.

<table>
<thead>
<tr>
<th>Search 1.2—search terms for excluded study designs and publication types</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>11</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>13</td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>16</td>
</tr>
<tr>
<td>17</td>
</tr>
<tr>
<td>18</td>
</tr>
</tbody>
</table>

Search 1.3—randomised controlled trials search terms

<table>
<thead>
<tr>
<th>Search 1.3—randomised controlled trials search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
</tbody>
</table>

be developed a priori and pilot tested in a representative sample of the studies to be reviewed; if necessary, the form will be adapted. Data will be extracted on
methods, participants, interventions and control interventions, outcomes and results. For studies with more than one publication, the first publication will be considered as the primary reference, but data will be extracted from all publications. Post-treatment assessments will be extracted and analysed. If only change from baseline data is reported, authors will be contacted.

Risk of bias in individual studies
Two review authors will assess risk of bias independently. Disagreements will be handled as outlined above. Risk of bias will be assessed using the recommendations by the Cochrane Back and Neck Group and be based on an adaptation of the Cochrane Risk of Bias tool. Risk of bias is assessed on 13 items from 6 domains: selection bias (adequate random sequence generation, allocation concealment, group similarity at baseline), performance bias (blinding of participants, blinding of personnel/providers, similar cointerventions, acceptable compliance), attrition bias (acceptable drop-out rate, intention-to-treat analysis), detection bias (blinding of outcome assessors, similar timing of outcome assessment), reporting bias (no selective outcome reporting) and other bias. Each item is rated as either low risk of bias if requirements are adequately fulfilled, high risk of bias if requirements are not adequately fulfilled or unclear risk of bias if data provided are insufficient for a judgement.

Data analysis
According to NICE guidelines and recommendations by Cochrane, this NMA will be planned and calculated based on a Bayesian approach. After making model-based choices, further diagnostic processes must be undertaken to verify if the model was appropriate. These approaches must assess heterogeneity and inconsistency, two assumptions underlying any NMA that are highly influential to the results. First, a pairwise meta-analysis will be performed by using R software, V.3.3 (R Foundation for Statistical Computing, Vienna, Austria. https://cran.r-project.org) to check for consistency and to evaluate statistical heterogeneity. Therefore, \( \tau^2 \) and \( I^2 \) statistics will be applied to quantify the extent of between-trial heterogeneity and variability. To test their stability, the results of the random-effects model will be compared with that of the fixed-effects model. ORs with 95% CIs will be calculated for dichotomous variables, while mean difference (MD) with 95% CI will be estimated for continuous variables.

Where different instruments were used to measure the same outcome, standardised MDs and their 95% CIs will be calculated and re-expressed as MDs by multiplying them by the pooled SD of the baseline scores, either from available epidemiological studies or from the largest related RCT using the same measurement instrument. Pain, back-specific disability and quality of life will be re-expressed on an 11-point numerical rating scale, the Roland-Morris Disability Questionnaire and the SF-36, respectively.

Second, NMA will be conducted using a Bayesian Markov Chain Monte Carlo (MCMC) framework and fitted in R V.3.3 software (https://cran.r-project.org/src/base/R-3/) via the gemtc V.0.82 package.

Network geometry
In a first step of the NMA the geometry of the expected treatment network will be evaluated. Therefore, a graphical network diagram will be created and explored. Comparison-adjusted funnel plots will be applied to visually assess the presence of small-study effects in the network. Funnel plots in an NMA account for the fact that studies evaluate treatment effects for different comparisons.

Heterogeneity
Assessment of the statistical heterogeneity in the entire network will be based on the magnitude of the common \( \tau^2 \) estimated from the NMA models.

Prior selection, model fit and inconsistency
Decisions about priors will be based on geometry, asymmetry and heterogeneity of the treatment network. Additionally recommendations made by Copas and Shi will be taken into account. To check whether a model’s fit is satisfactory, the posterior mean residual deviance will be calculated. Furthermore, we will compare fixed-effect and random-effect models using the deviance information criterion. Consistency will be evaluated by comparing the model fit from a consistency model with that from an unrelated mean effect model and by comparing direct evidence from pairwise meta-analysis with indirect evidence using the node-split approach.

Data synthesis
Statistical inference will be based on 150 000 iterations of MCMC after a 50 000 iterations burn-in period by running four chains simultaneously. The distributions of the parameter will be summarised by their median (OR or MD) and 95% credible intervals (CrIs). Additionally, trace plots and Brooks-Gelman-Rubin diagnostic plots will be used to assess convergence. A Gaussian model will be used for continuous variables and a Bernoulli model will be used for dichotomous variables.

Posterior rank probability estimation
To support the decision-making process, the rank probability for every treatment option is estimated in a secondary analysis. In addition to the rank probabilities the surface under the cumulative rank curve will be estimated. Due to a risk that the ranking probabilities are falsely highlighted as clinically meaningful, while the treatment effects are statistically non-significant or very small, they will only be interpreted against the background of their respective 95% CrIs.

Handling of missing data will be conducted according to the Cochrane Handbook for Systematic Reviews.
The clinical relevance of MDs will be assessed by comparing them against established minimal clinically important differences for the respective measurement instrument.

Subgroup and sensitivity analyses
Based on Cochrane methodology and the recommendations of the review's stakeholder advisory board, subgroup analyses will be conducted for:
1. Type of participants: less than 65 years of age versus 65 years or older.
2. Type of delivery: home exercise versus supervised group exercise versus supervised individual exercise.
3. Intervention dose/intensity: total intervention time below 150 min per week versus above 150 min per week. Sensitivity analyses will be conducted for:
   1. Studies with low versus high or unclear risk of selection bias.
   2. Studies with low versus high or unclear risk of detection bias.
   3. Studies with low versus high or unclear risk of attrition bias.
   4. Studies whose exercise interventions used warm-up exercises versus no warm-up exercises.

Given that analgesics use is a highly relevant effect modifier in low back pain research, a meta-regression will be performed to investigate the influence of analgesics use on study results. The following subgroup analyses will be carried out:
1. Data on analgesics and other cointerventions use are available versus data on analgesics use only.
2. Analgesics and other cointerventions use was allowed versus analgesics and other cointerventions use was prohibited.
3. Analgesics and other cointerventions use were comparable between groups versus analgesics and other cointerventions use differed between groups.

Quality of evidence
Based on the methodological quality and the confidence in the results, the quality of evidence from direct comparisons will be graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) recommendations and their extension for network meta-analyses as:
1. High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

The quality of evidence will be downgraded due to concerns regarding risk of bias, inconsistency, indirectness, imprecision and publication bias.

The rating of quality of evidence from indirect comparisons will be based on the lower quality rating of the two direct comparisons, which are used in the indirect comparison (ie, A vs C and B vs C for the indirect comparison A vs B). The quality of indirect comparisons might further be downgraded due to intransitivity (differences between trials on interventions that are indirectly compared).

If both direct and indirect evidence is available for a specific comparison, the higher quality rating will be used to rate the quality of evidence of the NMA.

ETHICS AND DISSEMINATION
In order to make the results of this NMA as widely available within the scientific community as possible, it is planned to publish the results in a high-ranked peer-reviewed medical journal that grants immediate open access. It is further intended to present the results on international scientific conferences and meetings.

We expect that the trial results will be transferred to routine medical practice after scientific evidence-based publication. The applicants will enhance the dialogue between physicians and physical therapists and have established an expert network and provide information for researchers and patients (conferences, meetings, internet and consultation). Furthermore, after receiving approval from the sponsor of the study, a press release will be issued covering key aspects of the meta-analysis results. A press conference may also be considered in this context. Articles summarising the findings and implications of this meta-analysis will be submitted to journals targeting general physicians, clinical specialists, physical therapists and/or patients.

The results of the trial will be implemented in existing national and international guidelines and will be presented to healthcare providers and decision makers.

According to German guidelines, no ethical approval is needed as analyses are secondary analyses and all data were de-identified and analysed anonymously.

The planned completion date of the study is 1 July 2021.

Contributors
DA, PK and HC designed the systematic review protocol. HH, AKK and GD reviewed and revised the first draft. All authors read and approved the final manuscript.

Funding
This study is supported by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung; BMBF; grant number 01KG1905).

Competing interests
None declared.

Patient and public involvement
Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication
Not required.

Provenance and peer review
Not commissioned; externally peer reviewed.

Open access
This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially,
and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Anna Katharina Koch http://orcid.org/0000-0002-2565-8744
Heidemarie Haller http://orcid.org/0000-0001-7973-4071

REFERENCES