

1 TITLE: Outcome Measures Used in Pulmonary Rehabilitation in Patients With Acute
2 Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review

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14 measurement

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19 **Background.** Conflicting results about the effects of community-based pulmonary
20 rehabilitation in acute exacerbations of chronic obstructive pulmonary disease (AECOPD)
21 exist, possibly because the variety of outcome measures used and the lack of appropriate
22 measurement properties hinder the development of pulmonary rehabilitation guidelines.

23 **Purpose.** The purpose of this study was to identify and review the measurement properties of
24 patient-reported outcome measures (PROMs) and clinical outcome measures of AECOPD that
25 are used in pulmonary rehabilitation and that can be easily applied in a community setting.

26 **Data Sources.** PubMed, Web of Science, Scopus, and CINAHL were searched up to July 1,
27 2016.

28 **Study Selection.** Phase 1 identified outcome measures used in pulmonary rehabilitation for
29 AECOPD. Phase 2 reviewed the measurement properties of the identified outcome measures.

30 **Data Extraction.** One reviewer extracted the data and 2 reviewers independently assessed the
31 methodological quality of the studies and the measurement properties of the outcome
32 measures by using the Consensus-Based Standards for the Selection of Health Status
33 Measurement Instruments (COSMIN) recommendations.

34 **Data Synthesis.** Twenty-three PROMs and 18 clinical outcome measures were found. The
35 outcome measures most used were the St George Respiratory Questionnaire (n = 15/37
36 studies) and the 6-minute walk test (n = 21/37 studies). Thirty-two studies described the
37 measurement properties of 22 PROMs and 7 clinical outcome measures. The methodological
38 quality of the studies was mostly poor, and the measurement properties were mostly
39 indeterminate. The outcome measure exhibiting more robust properties was the COPD
40 Assessment Test.

41 **Limitations.** A number of studies were published without the validated search strategy used
42 and were included *a posteriori*; the fact that 3 studies presented combined results for patients
43 who were stable and patients with exacerbation, affected the conclusions that can be drawn.

44 **Conclusions.** A large variety of outcome measures have been used; however, studies on their
45 measurement properties are needed to enhance the understanding of community pulmonary
46 rehabilitation for AECOPD.

47

48 Chronic obstructive pulmonary disease (COPD) is frequently punctuated by acute
49 exacerbations (AECOPD).¹ Currently, more than 80% of these events are recommended to be
50 managed within the community since it can shorten the length of hospital stays and/or avoid
51 hospital admittance.²

52

53 Pulmonary rehabilitation is a well-established, evidenced-based intervention, possible to be
54 applied within the community (ie, in nonspecialized community health services, in
55 community centers, or at the patient's home)³⁻⁶ and with potential to prevent and decrease the
56 harmful effects of acute exacerbations.⁷ Costs associated with AECOPD in the United States
57 are estimated in \$7100 per patient/per exacerbation⁸ and recent economic studies have shown
58 that, compared with usual care, community-based pulmonary rehabilitation provides cost
59 savings of \$1098 per patient.⁹

60

61 Nevertheless, conflicting results regarding the clinical effects of pulmonary rehabilitation in
62 AECOPD have been reported^{10,11} and less than 10% of patients discharged from AECOPD are
63 being referred for pulmonary rehabilitation¹² thus, its implementation is not a common
64 practice. This inconsistency among studies may occur due to the wide variety of outcomes
65 and outcome measures used and/or due to the lack of appropriate measurement properties (ie,
66 reliability, validity and responsiveness) of the outcome measures used in exacerbation
67 periods. It is known that the measurement properties of any outcome measure are population
68 specific¹³ and that patients at distinct phases of their chronic disease (stable/exacerbation)
69 differ in the physiologic and ventilatory mechanisms of their lungs.¹⁴ Therefore, it can be
70 hypothesized that instrument measurement properties will also vary in stable and exacerbation
71 periods.

72

73 Nevertheless, studies involving pulmonary rehabilitation in patients with AECOPD have been
74 choosing their outcome measures based on the measurement properties established for stable
75 patients with COPD,^{15,16} which may hinder the development of pulmonary rehabilitation
76 guidelines and lead instead to publication of recommendations which lack rigorous
77 underpinning evidence in exacerbation periods.

78

79 Additionally, attending to patient's level of fragility during exacerbations, the specificities of
80 implementing a pulmonary rehabilitation program in a nonspecialized center and some
81 practical issues, such as the need for specific equipment and sufficient space and time required
82 to complete testing, especially when more than 1 test at baseline is required, may also
83 influence the selection of the outcome measure.¹⁷

84

85 Thus, the 2 aims of this systematic review were to identify patient-reported outcome measures
86 (PROMs) and clinical (non-patient-reported) outcome measures that are used to assess the
87 effects of pulmonary rehabilitation interventions in patients with AECOPD and that can be
88 easily applied in the community (ie, not expensive, not invasive, and quickly implemented)
89 and to synthesize/evaluate their measurement properties.

90

91 **Methods**

92 This systematic review (PROSPERO registration no. CRD42015023736) was conducted in 2
93 phases. Phase 1 identified outcome measures used to assess outcomes of pulmonary
94 rehabilitation interventions in patients with AECOPD and that can be easily applied in
95 community-based practice. Phase 2 aimed to assess the measurement properties of the
96 identified outcome measures.

97 **Phase 1: Measures Used in Pulmonary Rehabilitation**

98 **Data sources and searches.** The effects of pulmonary rehabilitation interventions in patients
99 with AECOPD have been largely reviewed,^{10,11,18-21} thus a first search limited to literature
100 reviews was conducted from May to June 2016 in PubMed, Web of Knowledge, Scopus, and
101 CINAHL. The original papers included in these reviews were extracted and searched for the
102 outcome measures.

103

104 The latest available literature review on this theme was dated from 2012 and thus, a second
105 search using the same keywords and databases but limited to original studies published from
106 2010 to June 2016 was also performed to identify all outcome measures most recently used by
107 physiotherapists. An interval of 2 years until the most recent review in the theme seemed
108 appropriate, as studies indicate that time from submission to publication can go up to 2
109 years.²² In both searches, the reference lists of the identified studies were scanned for other
110 potential eligible studies. Additionally, a weekly update was conducted until July 2016. The
111 full search strategy can be found in eAppendix 1 (available at: <https://academic.oup.com/ptj>).

112 **Study selection.** Selection of studies was performed by 1 reviewer (A.L.O.) and checked by a
113 second reviewer (A.S.M.). After removing duplicates, 1 reviewer (A.L.O.) performed the
114 initial screening of articles based on type of publication and relevance for the scope of the
115 review. Selection of studies checked by a second reviewer (A.S.M.).

116

117 First, title and abstract were screened, and if the articles were considered relevant, full text
118 was analyzed. Studies were included if they met the following 3 criteria: aimed to assess
119 pulmonary rehabilitation or one of its components; assessed patients with an AECOPD within
120 3 weeks of the onset as this is the mean time needed for recovery^{2,23,24}; and were written in
121 English, Spanish, French, or Portuguese. Studies were excluded if they were conducted in

122 animals; patients requiring emergency intubation, intensive care unit management, and/or
123 mechanical ventilation; patients with compromised neurological status or hemodynamic
124 instability; patients performing self-management programs only; and patients assessed only
125 after discharge for AECOPD. Book chapters, abstracts of communications or meetings, letters
126 to the editor, commentaries to studies, unpublished work and study protocols were excluded.

127

128 **Data extraction.** Data extraction focused on PROMs and clinical outcome measures used to
129 assess pulmonary rehabilitation interventions and that can be easily applied in community-
130 based practice. Thus, data regarding measures not suitable for this setting (eg, arterial blood
131 gases, cardiopulmonary exercise testing, body plethysmography studies, sputum weight and
132 analysis; penetration index of inhaled radioparticles and hospital length of stay) were not
133 extracted. Data extracted were: outcomes, outcome measures, patient characteristics (ie, age
134 and percentage of predicted forced expiratory volume in 1 second (FEV₁) at stability or in
135 acute exacerbation), treatment setting, time from AECOPD to intervention and duration of
136 intervention.

137

138 **Phase 2: Properties of Measures**

139 **Data sources and searches.** A systematic electronic literature search was conducted from
140 June to July 2016 on PubMed, Web of Science, Scopus, and CINAHL. A validated sensitive
141 search filter (sensitivity = 97.4%; precision = 4.4%) for finding studies on measurement
142 properties of outcome measures was used.²⁵ Only outcome measures included in phase 1 were
143 searched in phase 2, however, if new outcome measures feasible to be used in community
144 practice emerged from the search, they were also included. Reference lists of the identified

145 studies were scanned for other potential eligible studies and a weekly update was conducted
146 until September 2016. The full search strategy can be found in eAppendix 2 (available at:
147 <https://academic.oup.com/ptj>).

148

149 **Study selection.** Selection of studies was performed by 1 reviewer (A.L.O.) and checked by a
150 second reviewer (A.S.M.). Inclusion and exclusion criteria were as in phase 1. Additionally,
151 studies were included if information was reported regarding 1 or more measurement
152 properties (ie, reliability – internal consistency, reliability, measurement error; validity –
153 content validity, construct validity and criterion validity, responsiveness and interpretability).
154 Studies were excluded if reported on measurement properties of outcome measures not
155 feasible to use in community-based pulmonary rehabilitation programs, separated items of an
156 outcome measure and did not included the full measure.

157

158 **Data extraction and quality assessment.** Data was extracted by 1 reviewer (A.L.O.) using 2
159 standardized tables, one for PROMs and another for clinical outcome measures. Data
160 extracted were: outcome, outcome measure, author and year of publication, measurement
161 property assessed, quality of the study, quality of the measurement property and costs.

162

163 Two independent reviewers (A.L.O. and A.S.M.) evaluated the quality of the included studies
164 using the Consensus-Based Standards for the Selection of Health Status Measurement
165 Instruments (COSMIN) checklist (ie, poor, fair, good, excellent).²⁶ A consensus method was
166 used to solve disagreements between reviewers.

167

168 The quality of the outcome measures reported was determined using the rating system for
169 measurement properties proposed by Terwee et al.²⁷ For each measurement property a
170 criterion is defined for positive, negative and indeterminate rating.

171

172 **Data synthesis and analysis.** Data on PROMs and clinical outcome measures were separately
173 analyzed. For each measurement property (ie, reliability, validity, responsiveness and
174 interpretability), a synthesis of the quality of the study, using the COSMIN criteria,²⁶ and of
175 the quality outcome measure, using the system of Terwee et al,²⁷ was performed.

176

177 The consistency of the quality assessment performed by the 2 reviewers was explored with an
178 interrater agreement analysis using the Cohen kappa for each box of the COSMIN criteria.
179 The Cohen kappa value ranges from 0 to 1 and can be categorized as slight (< 0.2), fair (0.21–
180 0.4), moderate (0.41–0.6), substantial (0.61–0.8), or almost perfect (> 0.81) agreement.²⁸

181

182 **Results**

183 **Phase 1: Measures Used in Pulmonary Rehabilitation**

184 **Study selection.** A total of 220 literature reviews were found. After duplicates were removed
185 (n = 66) and exclusions were made on the basis of abstract and title screenings (n = 22), 132
186 full texts were screened and 15 literature reviews that reported on pulmonary rehabilitation
187 interventions in patients with AECOPD were included. Additionally, 24 original studies
188 included in the 15 reviews were extracted and searched for outcome measures not reported in
189 the reviews.

190

191 The search conducted for original studies published after 2010 retrieved 257 original studies.
192 After duplicates were removed (n = 134) and exclusions were made on the basis of abstract
193 and title screenings (n = 23), 100 full texts were screened and 13 original studies were
194 included. Thus, a total of 37 original studies were searched for outcome measures. A flow
195 diagram concerning the literature reviews and original studies search and reasons for studies
196 exclusions can be found in the Figure.

197

198 **Study characteristics.** The 37 studies included were conducted in 19 different countries. A
199 steady increase in the number of studies investigating pulmonary rehabilitation in patients
200 with AECOPD was observed, with only 7 papers published from 1964 to 2000 and 37 by
201 2016. Most studies were randomized control trials (n = 31)^{15,16,29-57} conducted with inpatients
202 (n = 27),^{15,16,29,30,33,35,37-41,43,45-48,51-61} followed by hospital outpatient departments (n =
203 6),^{15,37,38,42,44,49} inpatients plus patients' homes (n = 3),^{31,32,50} community settings (n = 3),^{34,62,63}
204 and patients' homes (n = 1)³⁶ (Tabs. 1 and 2).

205 **Outcomes and outcome measures.** Twenty-three PROMs and 18 clinical outcome measures
206 were identified. The most common patient-reported outcomes assessed were dyspnea (n = 24),
207 using the modified Borg Scale (mBorg)^{30,32,38,39,42,44,46,52-55,58,62,63} (n = 14), and health-related
208 quality of life (n = 23), using the St George Respiratory Questionnaire (SGRQ)<sup>16,34-37,39,42,44,49-
209 51,54,56,58,59</sup> (n = 15). The most common clinical outcomes assessed were functional exercise
210 capacity (n = 24), using the 6-minute walk test^{16,30-32,37,38,41,43,44,48,49,51-53,56,58,63} (n = 21), and
211 lung function (n = 13), using the FEV₁^{16,30,31,36,39,44,55,57,60,61} (n = 10). Other outcomes assessed
212 were anxiety and depression, fatigue, cough, physical activity, strength, activities of daily

213 living, lung function, peripheral blood gases, subjective airway clearance, and body
214 composition.

215

216 Tables 1 and 2 show the patient-reported and clinical outcomes and outcome measures
217 reported.

218

219 **Phase 2: Properties of Measures**

220 **Study selection.** The search for measurement properties identified 82 studies. After the
221 removal of duplicates, 41 studies were screened. During the title and abstract screening, 18
222 studies were excluded. The full text of 23 studies was assessed and another 15 studies were
223 excluded. Therefore, 8 original studies were selected. The search for relevant studies within
224 the reference lists retrieved 24 additional studies. Therefore, a total of 32 studies were
225 included in this review (Figure).

226

227 **Measurement properties.** The measurement properties of 22 PROMs used to assess 5
228 outcomes (ie, dyspnea [6 outcome measures], health-related quality of life [11 outcome
229 measures], health status [2 outcome measures], activities of daily living [2 outcome
230 measures], and general symptoms [1 outcome measure]) were reported by 26 of 32 studies.
231 The measurement properties of 7 clinical outcome measures used to assess 4 outcomes (ie,
232 oxygen saturation [1 outcome measure], lung function [4 outcome measures], body
233 composition [1 outcome measure], and physical activity [1 outcome measure]) were reported
234 in 8 of 32 studies.

235

236 The methodological quality of each study and the quality of the measurement properties of
237 each measure can be found in Tables 3 and 4. The agreement between the 2 independent
238 reviewers using the COSMIN quality assessment was substantial ($\kappa = 0.688$).

239

240 The characteristics of the included studies and synthesis of the results per outcome and
241 outcome measure can be found in eAppendix 3 (available at: <https://academic.oup.com/ptj>;
242 eTab. 1a and eTab. 1b).

243

244 **Quality and properties of PROMs.** Reliability was studied for 5 PROMs in 5 studies of fair
245 to excellent methodological quality (ie, SGRQ, Chronic Respiratory Diseases Questionnaire
246 [CRQ], Clinical COPD Questionnaire [CCQ], and COPD Assessment Test [CAT])^{64–68} and in
247 2 studies of poor methodological quality (ie, CCQ and Exacerbations of Chronic Pulmonary
248 Disease Tool–Patient-Reported Outcome [EXACT-PRO]).^{67,69} Studies were rated as poor
249 mainly because an analysis of the unidimensionality of the scale was not preformed.

250

251 Measurement properties presented positive results in all reliability categories assessed (ie,
252 internal consistency and test-retest; measurement error has not been assessed) and for all
253 outcome measures (Tab. 3).

254

255 Validity was studied for most PROMs, except for the mBorg, visual analog scale, Short-Form
256 6D, and Nottingham Health Profile, in 21 studies.^{64–84} Overall, the methodological quality of
257 the studies was rated from poor to fair, except for structural validity studied in the CRQ and
258 the CAT, which were rated excellent.^{64,65} For criterion validity, reasons for rating “poor” were

259 related with the inadequacy of the gold standard used as comparator. Regarding to construct
260 validity, weaknesses included lack of formulation of hypotheses and lack of description of the
261 comparator instrument.

262

263 Criterion validity was indeterminate in 5 studies (ie, modified Medical Research Council
264 [MRC], MRC, extended MRC, CCQ, COPD severity score, EuroQol 5D [EQ-5D], Breathing
265 Problems Questionnaire, London Chest Activities of Daily Living Scale [LCADL], and
266 Manchester Respiratory Activities of Daily Living Questionnaire)^{70,71,77,79,81} and positive in 1
267 study (ie, Global Initiative for Chronic Obstructive Lung Disease plus Symptom Severity
268 Index [GOLD + SSI]).⁸³ Structural validity presented positive results in 2 studies (ie, CRQ
269 and CAT).^{64,65} Construct validity, was indeterminate in 11 studies (ie, Baseline Dyspnea
270 Index and Transition Dyspnea Index [BDI/TDI], SGRQ, CRQ, CCQ, COPD severity score,
271 EQ-5D, Short-Form 6D, Measure Your Medical Outcome Profile, and Medical Outcomes
272 Study 6-Item General Health Survey, modified MRC, SGRQ, EXACT-PRO, and
273 LCADL)^{66,68-70,72,75,76,79,80,82}, negative in 2 studies (ie, SGRQ and CRQ)^{64,73}, and positive in 7
274 studies (ie, SGRQ, CRQ, CCQ, CAT, and Cough and Sputum Assessment
275 Questionnaire)^{65,67,74-76,78,84} (Tab. 3).

276

277 Responsiveness was studied for most PROMs, except for the modified MRC, MRC, extended
278 MRC, Breathing Problems Questionnaire, GOLD + SSI, Manchester Respiratory Activities of
279 Daily Living Questionnaire, and LCADL, in 19 studies of poor to fair methodological
280 quality.^{64,66-69,72-77,79,80,84-89} Common weaknesses of studies included lack of description of the
281 comparator instrument and inadequacy of design and statistical methods used.

282

283 Responsiveness was indeterminate in 14 studies (ie, SGRQ, CCQ, COPD severity score, EQ-
284 5D, Short-Form 6D, Nottingham Health Profile, Measure Your Medical Outcome Profile,
285 Medical Outcomes Study 6-Item General Health Survey, EXACT-PRO, Cough and Sputum
286 Assessment Questionnaire, mBorg, visual analog scale, and CCQ),^{66–69,73,75,77,79,80,84–87,89}
287 negative in 5 studies (ie, SGRQ, CRQ, CAT, and EQ-5D),^{64,72,74,75,79} and positive in 3 studies
288 (ie, BDI/TDI and CAT)^{72,76,88} (Tab. 3).

289

290 Interpretability was found in 2 studies which presented values of the minimal clinically
291 important difference (MCID) for the CRQ (MCID = 1.01)⁶⁴ and the CCQ (MCID = 0.44).⁶⁸

292

293 **Quality and properties of clinical measures.** Reliability was not studied for any of the
294 clinical outcome measures found (Tab. 4).

295

296 Validity was studied for all clinical outcome measures in 8 studies of fair to poor
297 methodological quality.^{70,72,90–95} For criterion validity, reasons for rating “poor” were related
298 with the inadequacy of the gold standard used as comparator, whereas for construct validity
299 reasons were related to the lack of formulation of hypotheses and the lack of description of the
300 comparator instrument.

301

302 Overall, measurement properties presented positive results for criterion validity assessed in 4
303 studies (ie, peripheral oxygen saturation [SpO₂], forced vital capacity, and computerized
304 respiratory sounds)^{70,90,93,94}; however, in 1 study assessing the FEV₁, criterion validity was
305 indeterminate.⁷⁰ Regarding to construct validity, indeterminate results were found in 2 studies

306 (ie, SpO₂, peak expiratory flow [PEF], FEV₁, and forced vital capacity)^{70,92} and positive
307 results in 3 studies (ie, SpO₂, PEF, and time spent in weight-bearing activities assessed with
308 an accelerometer)^{90,91,95} (Tab. 4).

309

310 Responsiveness was studied for the PEF and FEV₁ in 2 studies^{72,91} of fair and poor
311 methodological quality, respectively. The study was rated as poor because it did not describe
312 the measurement properties of the comparator instrument.

313

314 Responsiveness was rated positive for the PEF⁹¹ and indeterminate for the FEV₁⁷² (Tab. 4).

315

316 Interpretability was not studied for any of the clinical outcome measures found (Tab. 4).

317

318 **Discussion**

319 To our knowledge, this is the first systematic review to provide a comprehensive overview of
320 the measurement properties of the outcome measures most used in pulmonary rehabilitation
321 programs during AECOPD and that can be easily applied in a community setting. Twenty-
322 three PROMs and 18 clinical outcome measures were identified in intervention studies. The
323 most used measures were the St George Respiratory Questionnaire (n = 15/37) and the 6-
324 minute walk test (n = 21/37). Several measures have been used only in isolated studies (ie,
325 New York Heart Association Functional Classification, Activities of Daily Living Dyspnea
326 Scale, diaries, Functional Assessment of Chronic Illness Therapy, feeling thermometer,
327 mBorg fatigue, LCADL, 3-minute step test, 3-minute walk test, 2-minute step-in-place test,
328 FEV₁/forced vital capacity, computerized respiratory sounds, fat-free mass index, body mass

329 index, accelerometer, quadriceps twitch responses, and maximum inspiratory pressure).
330 Measurement properties were only synthesized for 22 PROMs and 7 clinical outcome
331 measures. The methodological quality of most studies was poor, and the results obtained for
332 the measurement properties were indeterminate. The PROMs and clinical outcome measures
333 exhibiting the most appropriate measurement properties were the CAT and SpO₂,
334 respectively.

335

336 The most used PROMs were the mBorg and the SGRQ. Dyspnea and health-related quality of
337 life have been reported as the outcomes that better reflect the overall impact of the disease⁹⁶
338 and, therefore their monitoring during AECOPD, with appropriate outcome measures, is
339 essential to guide health professionals on the most effective interventions. Nevertheless, the
340 measurement properties of the mBorg have been little reported and, when reported, in studies
341 of poor methodological quality. The BDI/TDI, although not commonly used, was the only
342 outcome measure which rated fair and positive for responsiveness on dyspnea. The SGRQ has
343 shown appropriate test retest reliability but inconclusive validity and responsiveness.

344 Although, the SGRQ has strong measurement properties in stable patients with COPD,^{24,97} it
345 reports to the past month, 3 months and 1 year. These inappropriate timeframes to assess
346 improvements from an AECOPD, which usually takes 1 to 3 weeks to be meaningful to
347 patients,^{23,98} might explain some of the divergent results found. Measurement properties of
348 CAT have been assessed in a reasonable number of studies of fair methodological
349 quality^{65,75,76,78,88} and positive results have been found. Therefore, the BDI/TDI and CAT may
350 be promising PROMs to assess the effectiveness of community-based pulmonary
351 rehabilitation in patients with AECOPD.

352

353 The most used clinical outcome measures were the FEV₁ and the 6-minute walk test.
354 However, the measurement properties of the FEV₁ were found in studies of poor
355 methodological quality and no studies were found reporting on the measurement properties of
356 the 6-minute walk test in patients with AECOPD which impaired conclusions regarding its
357 use. Similarly to exercise tolerance, no studies were found reporting on measurement
358 properties of muscle strength. Currently, it is known that the inflammatory effects of
359 AECOPD are not confined to the lungs but also impair peripheral muscle strength and
360 exercise tolerance.¹ Declines in these outcomes are independent predictors of hospitalizations
361 and mortality.^{99,100} Early rehabilitation may play a crucial role in preventing and reducing
362 losses in exercise capacity, muscle strength and musculoskeletal dysfunction,^{16,43} thus
363 possibly reverting this cascade of events. Nevertheless, there is the urgent need to establish
364 the measurement properties of clinical outcome measures for AECOPD to assess patients'
365 dysfunctions, plan interventions, and verify their effectiveness.

366

367 This systematic review evidenced that the conflicting results of pulmonary rehabilitation
368 programs in patients with AECOPD^{10,15,16,50} may not be related to the quality of treatment but
369 with the lack of appropriateness of measurement proprieties of the outcome measures used.
370 Additionally, whilst the methodology of this review target only measures that could be
371 implemented in community settings (ie, simple and accessible measures), our results can also
372 be applicable to other clinical settings where these measures are available. Nevertheless, since
373 most AECOPD are recommended to be managed in the community and community-based
374 pulmonary rehabilitation might be a promising intervention for minimizing a patient's decline
375 and prevent recurrence, robust studies on the validity, reliability and responsiveness, as well
376 as on availability, cost and interpretability (ie, by establishing the MCID), of outcome

377 measures are urgently needed. These studies will contribute to clarify the role of community-
378 based pulmonary rehabilitation in patients with AECOPD.

379

380 **Study Limitations**

381 This study has some limitations that need to be acknowledged. Several relevant studies for
382 this systematic review^{67–69,71–73,75,77–79,81–83,85,86,88–95} were not found with the validated search
383 strategy used and were only included after searching through the reference lists of the
384 reviewed studies. Relevant studies may have fallen out of the search due the absence of
385 keywords related to measurement properties in their title, abstract or keywords, which
386 impaired the filter used to identify them. Adequate use of the Medical Subject Headings
387 (MESH) terms is warranted to identify the purpose of the studies and improve the quality of
388 the results found in future systematic reviews.

389

390 This systematic review has followed the COSMIN recommendations to assess the quality of
391 the included studies. The COSMIN was originally developed for health-related PROMs, such
392 as questionnaires,²⁶ and thus its validity, reliability and adequacy for assessing the
393 methodological quality of clinical studies and outcome measures, may be questioned.
394 Nonetheless, in the absence of a measure specifically designed to evaluate such studies and
395 outcome measures, the COSMIN is indicated as an adequate alternative tool.^{101,102}

396

397 The selection of studies was performed by 1 reviewer which could have caused bias in the
398 studies selection. This limitation has been mitigated by consulting a second reviewer when
399 uncertainties were found and by defining strict inclusion and exclusion criteria prior to studies
400 selection.

401

402 Finally, 3 of the studies included presented combined results of stable and exacerbated
403 patients with COPD^{69,73,74} which could have affected some of the conclusions established.
404 Nevertheless, the results of these studies have been considered within the universe of all
405 studies included, and thus we believe that any potential bias that could have been introduced
406 was diluted. Future studies should focus on patients with AECOPD only, so that
407 recommendations regarding its measurement properties can be established with confidence.

408

409 **Conclusions**

410 Although a large number of outcome measures easy to implement in a community-based
411 setting have been used to assess pulmonary rehabilitation in patients with AECOPD, their
412 measurement properties have been poorly studied. Given the wide availability of measures it
413 does not seem necessary to develop new outcome measures to be used in community-based
414 pulmonary rehabilitation of patients with AECOPD. Instead, studies following the COSMIN
415 standards to evaluate the measurement properties (ie, reliability, validity and responsiveness)
416 of the existing outcome measures are recommended. Such studies would contribute to clarify
417 the role of community-based pulmonary rehabilitation in patients with AECOPD and guide
418 the development of core outcome sets.

419

420 **Author Contributions**

421 Concept/idea/research design: A.L. Oliveira, A.S. Marques
422 Writing: A.L. Oliveira, A.S. Marques
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429 Consultation (including review of manuscript before submitting): A.L. Oliveira, A.S. Marques
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436

437 **Disclosures**

438 The authors completed the ICJME Form for Disclosure of Potential Conflicts of Interest. No
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739 **Table 1.**

740 Patient-Reported Outcomes Used in Pulmonary Rehabilitation of Patients With Acute Exacerbation (AE) of Chronic Obstructive Pulmonary
 741 Disease (COPD)^a

Outcome	Outcome Measure	Patient Characteristics					Intervention Setting	Intervention Timing	Intervention Duration
		No. of Patients	Age (y)	FEV _{1pp} (%)	FEV _{1ppAE} (%)	FEV _{1ppST} (%)			
Dyspnea	BDI/TDI ³⁰⁻³²	26-30	62.3-69		34.1-60		Inpatient and home	4-8 d after hospital presentation	11 d-18 mo
	VAS ^{35,60}	1-27	68.4-74	NS			Inpatient	At hospital presentation to 2 d after hospital presentation	45 min-2 mo
	Borg Scale ^{33,36,41}	26-110	61-75			35-42	Inpatient and home	At hospital presentation to hospital discharge	Until hospital discharge to 6 wk
	mBorg ^{30,32,38,39,42,44,46,52-55,58,62,63}	19-1,826	45-78.8		34.1-69.4	50.5-56	Inpatient, hospital outpatient department, and	At hospital presentation to 3 wk after discharge	60 min-19 mo

							community		
	MRC ^{36,39,49,52,59}	19–94	58.4–73.9		38–53.3	29–56	Inpatient, hospital outpatient department, and home	At hospital presentation to 2 wk after discharge	Until hospital discharge to 12 wk
	mMRC ^{15,38,44,48,51,63}	19–97	56.8–73.8 (mean)		35–69.4	37.3–44.4	Inpatient, hospital outpatient department, and community	At hospital presentation to 3 wk after discharge	Until hospital discharge to 12 wk
	NYHA ⁴¹	38	61	NS			Inpatient	As soon as stable	Until hospital discharge
	ADLDS ⁵²	94	69.2–73.9		38–39		Inpatient	2 d after hospital presentation	Until hospital discharge
HRQL	Diary ³²	26	64–69		34.9–37.5		Inpatient and home	4–7 d after admission	19 mo
	CRQ ^{15,31,32,34,37,38,42,52}	19–97	64–73.9		34.1–52	36.7–42.7	Inpatient, hospital outpatient department, community, and home	As soon as stable to 3.7 wk after hospital presentation	Until hospital discharge to 18 mo

SGRQ ^{16,34-37,39,42,44,49-51,54,56,58,59}	19-1,826	58.4-78.8		35.6-56.1	29-56	Inpatient, hospital outpatient department, community, and home	As soon as stable to 2 wk after hospital presentation	Until hospital discharge to 12 wk
SF-36 ^{34,38,44}	24-97	69.6-73.8		35-56.1	36.7-41.7	Inpatient, hospital outpatient department, and community	After discharge to 3 wk after hospital presentation	8 wk
EQ-5D ^{36,42,55,56}	16-526	65-73.7		52	38-42	Inpatient, hospital outpatient department, and home	As soon as stable to 1 wk after hospital discharge	Until hospital discharge to 8 wk
CAT ^{52,61}	11-94	69.2-78		34-39		Inpatient	1-2 days after hospital presentation	2 d to until hospital discharge
FACIT fatigue ⁵⁹	19	71			29	Inpatient	Immediately at hospital presentation	6 wk
Feeling thermometer ¹⁵	19	67.5			42.7	Inpatient or hospital outpatient department	2 wk after hospital presentation	12 wk

Anxiety and depression	HADS ^{38,55}	49–97	69.7–73.7	35–41			Inpatient and hospital outpatient department	As soon as stable to immediately after discharge	Until hospital discharge to 8 wk
Fatigue	mBorg ⁴²	60	65–67	52			Hospital outpatient department	1 wk after discharge	8 wk
Sputum	VAS sputum ^{53,61}	11–61	68–78		34–39		Inpatient	As soon as stable	2–4 d
General symptoms	BCSS ^{51,56,61,62}	11–90	56.8–78		34–69.4	37.3–44.4	Inpatient and community	At hospital presentation to 72 h after hospital presentation	60 min to until hospital discharge
ADL	Barthel Index ^{33,57}	21–110	68–75		45.1–46.1	35–38	Inpatient	At hospital presentation to 72 h after hospital presentation	Until hospital discharge
	LCADL ⁵⁴	44	77.4–78.8		41.8–41.4		Inpatient	As soon as stable	8–9 d
Composite measure	BODE Index ^{38,48,51,52}	50–97	65.1–73.9		35–39	37.3–44.4	Inpatient and hospital outpatient department	At hospital presentation to 2 d after hospital presentation	Until hospital discharge to 8 wk

742 ^aADL = activities of daily living; ADLDS = Activity of Daily Living Dyspnea Scale; AE = acute exacerbation; BCSS = Breathlessness, Cough,
743 and Sputum Scale; BDI/TDI = Baseline Dyspnea Index and Transition Dyspnea Index; BODE = body mass index, airflow obstruction, dyspnea,
744 and exercise capacity; CAT = COPD Assessment Test; CRQ = Chronic Respiratory Disease Questionnaire; EQ-5D = EuroQol 5D; FACIT =
745 Functional Assessment of Chronic Illness Therapy; FEV_{1pp} = percentage predicted forced expiratory volume in 1 s; HADS = Hospital Anxiety
746 and Depression Scale; HRQL = Health-Related Quality of Life; LCADL = London Chest Activities of Daily Living Scale; mBorg = modified
747 Borg Scale; MRC = Medical Research Council; mMRC = modified MRC; NS = not stated; NYHA = New York Heart Association Functional
748 Classification; SF-36 = Short Form (36-Item) Health Survey; SGRQ = St George Respiratory Questionnaire; ST = stable; VAS = visual analog
749 scale.
750

751 **Table 2.**

752 Clinical Outcomes Used in Pulmonary Rehabilitation of Patients With Acute Exacerbation (AE) of Chronic Obstructive Pulmonary Disease
 753 (COPD)^a
 754

Outcome	Outcome Measure	Patient Characteristics					Intervention Setting	Intervention Timing	Intervention Duration
		No. of Patients	Age (y)	FEV _{1p}	FEV _{1ppA}	FEV _{1ppS}			
Functional exercise capacity	6MWT ^{16,30–32,37,38,41,43,44,48,49,51–53,56,58,63}	28–1,826	61–73.9		34.1–69.4	50.5	Inpatient, hospital outpatient department, community, and home	At hospital presentation to 3 wk after discharge	4 d–18 mo
	ISWT ^{34,36,42,50}	26–196	65–71.1		52	36.7–51.9	Inpatient, hospital outpatient department, community, and home	Immediately to 10 d after discharge	6–8 wk
	ESWT ^{42,47,50}	20–196	65–70.1		52	39.8–51.9	Inpatient, hospital outpatient department, and home	At hospital presentation to 1 wk after discharge	Until hospital discharge to 8 wk

	3-min step test ³⁶	26	65– 67			38–42	Home	Immediately after discharge	6 wk
	3-min walk test ⁵⁷	21	68– 73.6		45.1–46.1		Inpatient	48 h after hospital presentation	Until hospital discharge
	2-minute step-in-place test ⁵⁵	49	72.4 – 73.7		39–41		Inpatient	As soon as stable	Until hospital discharge
Oxygen saturation	SpO ₂ ^{30,38–40,52,55,56,60,62}	1–526	56.8 – 73.9		35–69.4	52–56	Inpatient, hospital outpatient department, and community	At hospital presentation to 8 d after hospital presentation	45 min–8 wk
Lung function	FEV ₁ ^{16,30,31,36,39,44,55,57,60,61}	1–60	62.3 –78		34–56.1	38–56	Inpatient, hospital outpatient department, and home	At hospital presentation to 3 wk after hospital discharge	45 min–18 mo
	FVC ^{30,31,36,39,61}	11–59	62.3 –78		34–39	38–56	Inpatient and home	At hospital presentation to immediately after hospital discharge	2 d–18 mo

	FEV ₁ /FVC ³⁹	59	70.2			57.9–64.4	Inpatient	At hospital presentation	7 d
	PEF ^{40,41}	38–45	61	NS			Inpatient	At hospital presentation	Until hospital discharge
	CRS ⁶²	19	56.8		69.4		Community	Within 48 to 72 h after hospital presentation	3 wk
Body composition	Fat-free mass index ⁴²	60	65–67		52		Hospital outpatient department	1 wk after hospital discharge	8 wk
	BMI ⁵¹	90	67.8–69.5		35.9–35.6	37.3–44.4	Inpatient	2 d after hospital presentation	Until hospital discharge
Physical activity	Accelerometer ¹⁶	29	67.8–64.1		39.1–41.7		Inpatient	3 d after hospital presentation	At least 3 sessions
Strength	MVIC ^{16,36,42,43,45,47,50,54,55,57}	11–196	65–78.8		39.1–52	38–51.9	Inpatient, hospital outpatient department, and home	At hospital presentation to 1 wk after hospital discharge	7 d–8 wk
	TwQ ⁴²	60	65–67		52		Hospital outpatient	1 wk after hospital	8 wk

							department	discharge	
	MIP ³⁰	28	62.3 – 65.6		38		Inpatient	6–8 d after hospital presentation	11 d

755 ^a6MWT = 6-min walk test; AE = acute exacerbation; BMI = body mass index; CRS = computerized respiratory sounds; ESWT = endurance
756 shuttle walk test; FEV₁ = forced expiratory volume in 1 s; FEV_{1pp} = percentage predicted FEV₁; FVC = forced vital capacity; ISWT =
757 incremental shuttle walk test; MIP = maximum inspiratory pressure; MVIC = maximal voluntary isometric contraction; NS = not stated; PEF =
758 peak expiratory flow; SpO₂ = peripheral oxygen saturation; ST = stable; TwQ = quadriceps twitch responses.

759

760 **Table 3.**

761 Consensus-Based Standards for the Selection of Health Status Measurement Instruments (COSMIN) Evaluation, Quality of the Measurement
 762 Property, and Cost of Patient-Reported Outcomes^a

Outcome	Outcome Measure	Study	Reliability		Validity			Responsiveness	Cost
			Internal Consistency	Test-Retest	Criterion Validity	Structural Validity	Construct Validity (Hypothesis Testing)		
Dyspnea	mBorg	Kendrick et al, 2000 ⁸⁵						Poor/?	Free
	VAS	Lemasson et al, 2007 ⁸⁶						Poor/?	Free
	mMRC	Güray et al, 2007 ⁷⁰			Poor/?		Poor/?		Free
	MRC	Steer et al, 2012 ⁷¹			Poor/?				Free
	eMRC	Steer et al, 2012 ⁷¹			Poor/?				No information
	BDI/TDI	Aaron et al, 2002 ⁷²					Poor/?	Fair/+	Not free for commercial use
HRQL	SGRQ	Doll et al, 2003 ⁷³					Fair/-	Poor/?	Free
		Bourbeau et al, 2004 ⁷⁴					Fair/+	Fair/-	
		Menn et al, 2010 ⁸⁷						Poor/?	
		Katsoulas et al, 2010 ⁶⁶		Fair/+			Good/?	Poor/?	
		Jones et al, 2012 ⁷⁵					Poor/?	Poor/?	
		Tu et al, 2014 ⁷⁶					Poor/?		
	CRQ	Bourbeau et al, 2004 ⁷⁴					Fair/+	Fair/-	Not free
		Tsai et al,	Excellent/+			Excellent/	Poor/-	Fair/-	

		2008 ⁶⁴				+			
		Aaron et al, 2002 ⁷²					Poor/?	Fair/-	
	CCQ	Trappenburg et al, 2010 ⁷⁷			Fair/?			Poor/?	Not free
		Antoniou et al, 2014 ⁶⁷	Poor/+	Fair/+			Fair/+	Poor/?	
		Kocks et al, 2006 ⁶⁸					Poor/?	Poor/?	
	CAT	Jones et al, 2009 ⁶⁵	Excellent/+			Excellent/+	Fair/+		Not free for commercial use
		Jones et al, 2011 ⁷⁸					Fair/+		
		Jones et al 2012 ⁷⁵					Fair/+	Poor/-	
		Mackay et al, 2012 ⁸⁸						Fair/+	
		Tu et al, 2014 ⁷⁶					Poor/+	Fair/+	
	COPDSS	Miravittles et al, 2011 ⁷⁹			Fair/?		Poor/?	Poor/?	Free
	EQ-5D	Menn et al, 2010 ⁸⁷						Poor/?	Not free for clinical and commercial use
		Goossens et al, 2011 ⁸⁹						Poor/?	
		Miravittles et al, 2011 ⁷⁹			Fair/?		Poor/?	Fair/-	
		Paterson et al, 2000 ⁸⁰					Poor/?	Poor/?	
	SF-6D	Menn et al, 2010 ⁸⁷						Poor/?	Not free for commercial use
	BPQ	Yohannes et al, 2005 ⁸¹			Poor/?				Not free for commercial use
	NHP	Doll et al, 2003 ⁷³						Poor/?	Not free; copyright held by Galen Research
	MYMOP	Paterson et al, 2000 ⁸⁰					Poor/?	Poor/?	Free

	MOS-6A	Paterson et al, 2000 ⁸⁰					Poor/?	Poor/?	Free
Health status	EXACT-PRO	Leidy et al, 2014 ⁸²					Poor/?		Not free for commercial use
		Leidy et al, 2011 ⁶⁹	Poor/+				Poor/?	Poor/?	
	GOLD + SSI	Hutchinson et al, 2010 ⁸³			Poor/+				Free
ADL	MRADL	Yohannes et al, 2005 ⁸¹			Poor/?				Not free for commercial use
	LCADL	Miravittles et al, 2011 ⁷⁹			Fair/?		Poor/?		Free
General symptoms	CASA-Q	Monz et al, 2010 ⁸⁴					Poor/+	Poor/?	No information

763 ^aADL = activities of daily living; BDI/TDI = Baseline Dyspnea Index and Transition Dyspnea Index; BPQ = Breathing Problems Questionnaire; CASA-Q = Cough and Sputum
764 Assessment Questionnaire; CAT = COPD [Chronic Obstructive Pulmonary Disease] Assessment Test; CCQ = Clinical COPD Questionnaire; COPDSS = COPD severity score;
765 CRQ = Chronic Respiratory Disease Questionnaire; eMRC = extended Medical Research Council (MRC); EQ-5D = EuroQol 5D; EXACT-PRO = Exacerbations of Chronic
766 Pulmonary Disease Tool–Patient-Reported Outcome; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HRQL = Health-Related Quality of Life; LCADL = London
767 Chest Activities of Daily Living Scale; mBorg = modified Borg Scale; mMRC = modified MRC; MOS-6A = Medical Outcomes Study 6-Item General Health Survey; MRADL =
768 Manchester Respiratory Activities of Daily Living Questionnaire; MYMOP = Measure Your Medical Outcome Profile; NHP = Nottingham Health Profile; SF-6D = Short-Form 6D;
769 SGRQ = St George Respiratory Questionnaire; SSI = Symptom Severity Index; VAS = visual analog scale; + = positive; - = negative; ? = indeterminate.

770

771 **Table 4.**

772 Consensus-Based Standards for the Selection of Health Status Measurement Instruments (COSMIN) Evaluation, Quality of the Measurement
 773 Property, and Cost of Clinical Outcomes^a

Outcome	Outcome Measure	Study	Reliability		Validity		Responsiveness	Cost
			Internal Consistency	Test-Retest	Criterion Validity	Construct Validity (Hypothesis Testing)		
Oxygen saturation	SpO ₂ (%)	Güryay et al, 2007 ⁷⁰			Fair/+	Poor/?		Not free
		Kelly et al, 2001 ⁹⁰			Fair/+	Poor/+		
Lung function	PEF (pp)	Emerman et al, 1996 ⁹¹				Poor/+	Fair/+	Not free
		Güryay et al, 2007 ⁷⁰				Poor/?		
	FEV ₁ (pp or L)	Güryay et al, 2007 ⁷⁰			Poor/?	Poor/?		Not free
		Aaron et al, 2002 ⁷²					Poor/?	
		White et al, 2005 ⁹²				Poor/?		
	FVC (pp)	Güryay et al, 2007 ⁷⁰				Poor/?		Not free
CRS	Morillo et al, 2013 ⁹³			Fair/+			Not free	
Body composition	BMI (kg/m ²)	Tsimogianni et al, 2009 ⁹⁴			Poor/+			Free
Physical activity	Time spent in weight-bearing activities (min)	Pitta et al, 2006 ⁹⁵				Poor/+		Not free

774 ^aBMI = body mass index; CRS = computerized respiratory sounds; FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; PEF = peak expiratory flow; pp =
 775 percentage of predicted normal value; SpO₂ = peripheral oxygen saturation; + = positive; - = negative; ? = indeterminate.

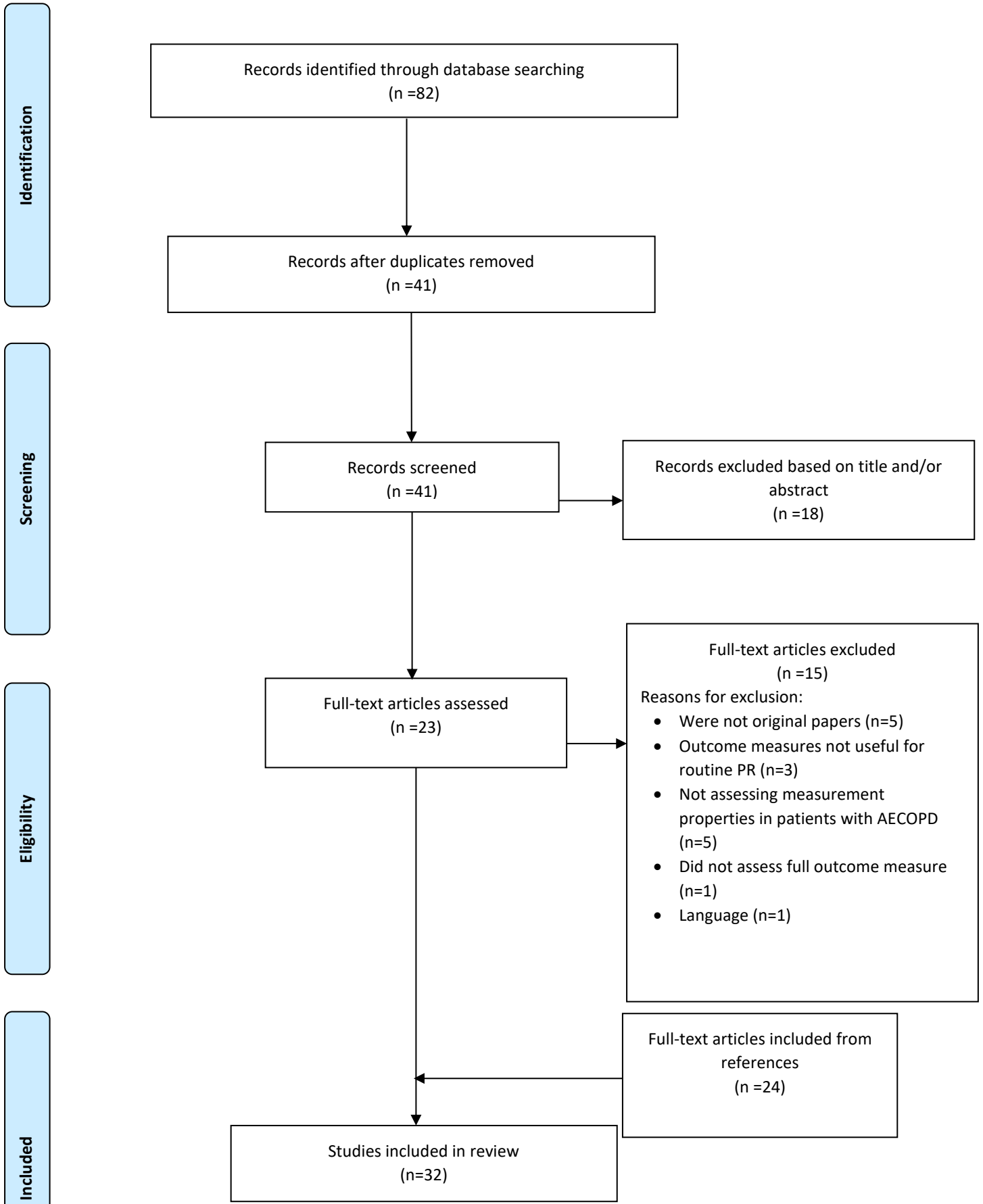


Figure.

Flow diagram of the studies assessing the measurement proprieties of the outcome measures used in the pulmonary rehabilitation (PR) of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) (phase 2).