



Treatment Trials in Young Patients with Chronic Obstructive Pulmonary Disease and Pre-Chronic Obstructive Pulmonary Disease Patients

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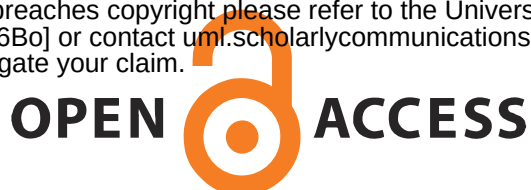
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**TREATMENT TRIALS IN PRE-COPD AND YOUNG COPD: TIME TO MOVE
 FORWARD**

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71

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73

74 **ABSTRACT**

75

76 Chronic Obstructive Pulmonary Disease is the end-result of a series of dynamic and cumulative
77 gene-environment interactions over a lifetime. The evolving understanding of COPD biology
78 provides novel opportunities for prevention, early diagnosis, and intervention. To advance these
79 concepts we propose therapeutic trials in two major groups of subjects: those “young”
80 individuals with COPD and those with pre-COPD. Given that lungs grow to about 20 years of
81 age and begin to age at approximately 50 years, we consider “young” COPD those patients in the
82 age range of 20-50 years. Pre-COPD relates to individuals of any age who have respiratory
83 symptoms with or without structural and/or functional abnormalities, in the absence of airflow
84 limitation, and who may develop persistent airflow limitation over time. We exclude from the
85 current discussion infants and adolescents because of their unique physiological context and
86 COPD in older adults given their representation in prior randomized clinical trials (RCTs). We
87 highlight the need of RCTs focused on young COPD or Pre-COPD patients to reduce disease
88 progression, providing innovative approaches to identifying and engaging potential study
89 subjects. We detail approaches to RCTs design including potential outcomes such as lung
90 function, patient reported outcomes, exacerbations, lung imaging, mortality, and composite
91 endpoints. We critically review study design components such as statistical powering and
92 analysis, duration of study treatment, and formats to trial structure including platform, basket,
93 and umbrella trials. We provide a call to action for treatment RCTs in (1) young adults with
94 COPD and (2) those with pre-COPD at any age.

95

96 INTRODUCTION

97

98 Chronic Obstructive Pulmonary Disease (COPD) is a major global public health problem.

99 Conventionally believed to be a self-inflicted disease due to tobacco smoking that affects the
100 elderly (1), recent research has shown that COPD is the end-result of a series of dynamic and
101 cumulative gene-environment interactions over the lifetime, that go beyond smoking (2), can
102 begin early in life (in-utero, infancy and/or adolescence) (3-6), and result in varying lung
103 function trajectories (trajectome), several of which lead to COPD in adulthood (7-9) (**Figure 1**).
104 This new understanding of COPD provides novel opportunities for prevention, early diagnosis,
105 and intervention (10). This state-of-the-art review seeks to **launch a call to action to**
106 **investigators, funding agencies, industry, and regulators to initiate treatment trials in (1)**
107 **young adults with COPD and (2) those with pre-COPD, this is those with respiratory**
108 **symptoms, abnormal imaging and/or lung function without evidence of airflow limitation**
109 **who may (or may not) develop COPD with time (11, 12).**

110

111 NOSOLOGY

112

113 A first, key step to this end is to avoid nosological confusion. Accordingly, we propose to adopt
114 the following terminology (Table 1).

115

116 COPD

117

118 As defined by GOLD, COPD is a disease “*characterized by persistent respiratory symptoms and*
119 *airflow limitation that is due to airway and/or alveolar abnormalities usually caused by*
120 *significant exposure to noxious particles or gases and influenced by host factors including*
121 *abnormal lung development*”(13).

122

123 Early COPD

124

125 According to the Merriam-Webster dictionary, “early” means “near the beginning of a process.”

126 Because COPD can start early in life (3-5), and generally takes a long time to manifest clinically

127 (8), defining whether someone suffers “early” COPD is difficult (14). Some studies have used
128 “mild” airflow limitation as a surrogate for “early” disease (15). This assumption would be
129 correct if all patients started their journey from a normal peak lung function in early adulthood
130 and COPD would have progressed similarly in all of them. Alas, this assumption is incorrect
131 (**Figure 1**) (8). “Mild” (like moderate or severe) airflow limitation can occur at any age (**Figure**
132 **1**) and only describes the “severity” of airflow limitation. Therefore, we propose that “mild”
133 should not be used to identify “early” COPD. Likewise, we recognize that mild airflow limitation
134 may not always be COPD, at least according to the current definition of airway diseases. Finally,
135 a biological “early”, related to the initial mechanisms that eventually lead to COPD, should be
136 differentiated from a clinical “early,” which reflects the initial perception of symptoms,
137 functional limitation and/or structural abnormalities noted (16). Accordingly, we propose to use
138 the term “early COPD” only to discuss “biological early.”

139

140 **COPD in young subjects**

141

142 The term “young” directly relates to the age of the subject and may seem straightforward and
143 confusion less. However, to some extent, “young” is also a value judgment that depends on the
144 age of the observer and the part of the globe where the individual lives, as life expectancy varies
145 greatly in different parts of the world. For the discussion that follows, given that lung growth and
146 development reach its peak at around 20-25 years of age and begin to decline at 45-50 years (17),
147 we propose to operationally consider “young” patients with COPD as those included in an *age*
148 *range of 20-50 years* (**Figure 1**). In population-based studies these younger individuals have a
149 higher prevalence of prior asthma diagnosis (18). It is anticipated that in young patients with
150 COPD preventive measures and pharmacological interventions may result in better outcomes
151 than in older patients (10, 19, 20) and may slow down disease progression (10). Importantly, this
152 age range can include patients who never achieved normal peak lung function in early adulthood
153 and/or those with early accelerated lung function decline (**Figure 1**) which may have different
154 underlying mechanisms (i.e., endotypes (21)) and may therefore require different therapeutic
155 interventions (5, 22, 23).

156

157 **Pre-COPD**

158 The term pre-COPD has been recently proposed to identify individuals of *any age* who have
159 respiratory symptoms with/without structural and/or functional abnormalities, in the absence of
160 airflow limitation ($FEV_1/FVC \geq 0.7$), and who may (or may not) develop persistent airflow
161 limitation (i.e., COPD) over time (11, 12). This term includes a heterogeneous population of
162 patients. So far, several subtypes of pre-COPD have been reported. The best studied one includes
163 patients with non-obstructive chronic bronchitis (**NOCB**), in whom symptoms are associated with
164 significant morbidity regardless of whether they ultimately progress to airflow limitation (11).
165 Other, less well studied, subtypes of pre-COPD are subjects without airflow limitation who have
166 emphysema detected with computed tomography (**CT**) (24), individuals with Preserved Ratio
167 Impaired Spirometry (**PRISm** – post-bronchodilator $FEV_1 < 80\%$ predicted and $FEV_1/FVC \geq$
168 0.70) (25), and subjects with low diffusing capacity for carbon monoxide (DLCO) (26) or rapid
169 FEV_1 decline (27). The natural history and potential response to treatment these heterogenous
170 conditions is unknown.

171

172 **Disease activity vs. disease progression**

173

174 These two terms are related but not synonymous. Disease “*activity*” relates to the level of
175 activation of the pathobiological processes that cause the disease (14), whereas disease
176 “*progression*” refers to a deterioration over time in an objective marker of pathology, such as by
177 computed tomography, or function. The relationship between disease “activity” and disease
178 “progression” in COPD remains unclear. Disease activity is probably a necessary but insufficient
179 condition for disease progression. For instance, a given patient may suffer frequent exacerbations
180 (a clinical surrogate marker of an “active” disease”) without a clear deterioration in lung function
181 (a marker of disease “progression”). We currently lack validated biomarkers to identify whether
182 or not specific endotypes are “active” in COPD (28) and, as a result, disease “activity” in COPD
183 is often estimated *post-hoc* by evidence of disease “progression” (29). Of note, however, in older
184 patients with moderate-severe COPD, persistent systemic inflammation has been associated with
185 increased all-cause mortality and exacerbation frequency (30), and the use of inflammometry and
186 multi-dimensional assessment to guide treatment improved several patient related outcomes
187 (**PROs**) at three months in a small pilot randomized controlled trials (**RCT**) (31). Whether these
188 limited preliminary data apply to younger patients is unknown. Likewise, patients with milder

189 airflow limitation appear to progress (in terms of FEV₁ decline) faster than those with more
190 severe airflow limitation (32) so identifying biomarkers of disease activity associated with
191 different lung function trajectories (**Figure 1**) would be of great value (33, 34). In any case,
192 future treatment trials in young patients should ideally target individuals at risk of disease
193 progression based on validated biomarkers of disease activity.

194

195 **Primary, secondary, and tertiary prevention**

196

197 Primary prevention aims at preventing a disease before it occurs by eliminating exposures to risk
198 factors and/or increasing resistance to it should exposure occur. Primary prevention of COPD is
199 key in children and adolescents (**Figure 1**) but likely relates more to public health measures than
200 to therapeutic interventions, although we acknowledge that boosting “catch-up” of impaired lung
201 function in early life may deserve specific investigation (8, 24, 35, 36). Secondary prevention
202 aims to reduce progression once disease has already manifested. This is, precisely, the goal of
203 this call for action for treatment trials in young patients. Finally, tertiary prevention aims at
204 reducing the impact of an ongoing illness, has been more frequently considered in the setting of
205 COPD in older patients, and has been extensively investigated in previous RCTs.

206

207 **TREATMENT TRIALS IN YOUNG COPD AND PRE-COPD PATIENTS**

208

209 The discussion that follows focuses on treatment trials in young (20-50 years of age) adults with
210 COPD or Pre-COPD (any age). These trials are needed as young patients with COPD or pre-
211 COPD may already suffer a significant burden of disease (37, 38). In these patients, treatment
212 cannot be neglected, although the scientific evidence supporting the best therapeutic alternatives
213 has not been generated. In addition, it is likely that a therapeutic intervention in younger
214 individuals with the drugs currently available, before advanced tissue destruction, multimorbidity
215 and effects of ageing become clinically relevant, may be more effective (10) and may
216 reduce/arrest disease progression. Finally, the combination of primary and secondary preventive
217 measures aimed at avoiding all those factors associated with low lung function in different age
218 bins with appropriate, evidence-based, treatment of younger COPD patients, has the potential to

219 reduce the societal burden of disease, promote respiratory health and, eventually the
220 development of COPD (39).

221
222 Although the results of large multicenter RCTs have driven our current understanding and
223 management of COPD, they have historically faced a number of limitations (**Table 2**) (40-43).
224 These and other considerations may apply also to future treatment trials in young patients and
225 are discussed below.

226

227 **Case Finding/Recruitment**

228

229 In a recent, large epidemiological study in China, the prevalence of COPD in adults aged 20-49
230 years was 16.4% in males and 7.4% in females (**Figure 2**) (44), so finding and recruiting these
231 patients into an RCT may require a combined strategy. Although widespread population
232 spirometric screening has not been traditionally advocated (45), targeted case finding approaches
233 are promising (46). Indeed, there has been a recent proposal supporting the use of forced
234 spirometry in the general population (even in children and adolescents) as a marker of not only
235 respiratory diseases but global health (47). Symptom-based instruments (e.g., COPD-PS (48),
236 IPAG (49), COPD-Q (50), and LFQ (51)) and PROs questionnaires (e.g., CAT (52), CAPTURE
237 (53, 54) or CAT/CAAT (55)) were have been developed or adapted for case finding in patients
238 with established COPD. Their utility in young patients is unclear as most were developed and
239 tested in those over 40 years of age. Mucus hypersecretion can be better identified using the
240 symptoms component of the SGRQ or the phlegm question in the CAT rather than the Medical
241 Research Council (**MRC**) definition for chronic bronchitis (CB) (11, 56-59). Reduced physical
242 activity measured by daily accelerometer recordings is reduced in COPD patients detected by
243 spirometry screening (60), so PROs measuring physical activity (e.g. Clinical visit-PROactive
244 Physical Activity in COPD (C-PPAC) (61)) could potentially be used to identify these patients.
245 Primary care networks may be particularly crucial in identifying potential young patients from
246 electronic medical records (62), either by identifying patterns of risk factors, biomarkers, or in
247 identifying symptoms before COPD is diagnosed (63). Finally, public advertising campaigns via
248 traditional print or electronic media, social media campaigns and collaboration with non-profit
249 advocacy organizations can be useful aids to boost patient recruitment. The power of the patient-

250 led collaborative “Venture Philanthropy” effort by the Cystic Fibrosis Foundation (64)
251 transformed Cystic Fibrosis from a highly mortal disease in early life to a disease that can be
252 treated with precision (65). The COPD Foundation has recently launched a multidisciplinary
253 collaborative initiative, [COPD360Net](#), with the mission to support the development and adoption
254 of novel digital health tools, medical devices and therapeutics that treat COPD, prevent its
255 progression, and improve lives of patients with COPD and related chronic lung conditions at all
256 stages of disease (Supplemental **Figure 1**). COPD360Net is currently seeking partners to
257 conduct a collaborative platform trial in young patients with Pre-COPD and NOCB.
258

259 **Smoking exposure/status**

260
261 Previous RCTs in COPD have studied (older) current or former smokers. As prior studies
262 suggested that variation in smoking status impacted the range of lung function decline (66) and
263 mortality (67), previous history and current active smoking should be carefully monitored and
264 adjusted for in future therapeutic trials. This is particularly relevant as smoking cessation should
265 be encouraged given its beneficial effects (66, 68) and is facilitated by numerous interventions
266 (69). Notably, about a third of COPD patients around the world are never smokers (70) and many
267 other environmental risk factors are associated with low lung function through life. For example,
268 early studies of e-cigarette exposure has been suggested to result in altered pulmonary function
269 and structure (71, 72). Similarly, occupational exposure and air pollution (73, 74) have been
270 associated with respiratory disease and should be considered in study design, conduct and
271 analyses . It is imperative to study young never smokers with COPD (5, 35, 75-79) exposed or
272 not to other known (indoor pollution) or unknown environmental factors as well as those
273 impacted by abnormal lung development before the age of 20.
274

275 **Nonrespiratory medications**

276
277 It is possible that nonrespiratory medications may influence the development of COPD or its
278 complications. For example, it remains unclear if statin therapy can favorably influence
279 noncardiovascular complications of COPD (80). Preclinical data with metformin have suggested
280 improvement in the development of emphysema with cohort studies providing variable clinical

281 correlates (81, 82). It will be important during therapeutic trials to carefully record non-
282 respiratory medications.

283

284 **Outcome measures**

285

286 The outcome measure of any trial should be reproducible over time, have known
287 biological variability, be responsive to treatment, and be relevant to the targeted trait. In
288 young patients, the following ones could be considered.

289

290 *Lung function*

291

292 FEV₁ is a simple, relatively inexpensive, reproducible measure recognized as an outcome
293 measure by regulatory authorities, including the US Food and Drug Administration (**FDA**) and
294 the European Medicines Agency (**EMA**). Further, FEV₁ decline has been traditionally used as a
295 measure of disease progression in COPD (83). However, in young patients there are important
296 additional considerations. First, in these patients a reduced FEV₁ value may result from
297 abnormal lung development and/or early enhanced decline (**Figure 1**) (7) and, in the absence of
298 historic data, these two trajectories are difficult to define (7). Second, absolute decline in FEV₁ is
299 faster in patients with milder airflow limitation (32), who might be younger. If so, this may
300 facilitate studying the impact of interventions on FEV₁ decline in younger patients. Absolute
301 FEV₁ decline is also subject to bias from starting lung size which is influenced by factors such as
302 height and gender. **Table 3** enumerates the change in FEV₁ among RCTs targeting mild to
303 severe COPD patients with average ages 50-65. A systematic review of RCT suggests that a 5.0
304 ml/yr. reduction (95% CI 0.8-9.1 ml/yr.) has been suggested in the rate of FEV₁ decline in active
305 treatment arms compared with placebo (84). Arguably, younger individuals show faster FEV₁
306 decline (32) because they have more lung function left to lose, and this might make it easier to
307 study the impact of interventions on FEV₁ decline. However, a single FEV₁ measurement is not
308 a good predictor of the future FEV₁ trajectory and rapid FEV₁ decliners can only be identified in
309 retrospect (85, 86). Thus, it may be more pragmatic to enrich the study population using
310 surrogate markers of accelerated FEV₁ decline (87), including chronic mucus hypersecretion
311 (88), prior frequent exacerbations (32, 89), or imaging features as described below.

312
313 Longer trials extending beyond 3 years (the minimum currently required by Regulators) reduce
314 FEV₁ decline variability and, accordingly, the sample size required. **Table 3** highlights that trials
315 to evaluate rate of decline have generally been long in duration and that longer trials reduce
316 variability. The common approach to conduct a three year trial still requires a relatively large
317 sample. For example, if we assume a SD of 100 mL/yr. and wish to detect a difference of 12
318 mL/yr. approximately 1500/group are required to be 90% powered for $\alpha=0.05$. If instead SD
319 80mL/yr. and effect size of 15 mL/yr. are assumed, then this requirement for 90% power drops
320 to approximately 600/arm. The advantage of longer trials needs to be counterbalanced by the
321 challenge of retaining sufficient subjects and avoiding issues with biases introduced by
322 differential withdrawal. As such, it will be key to carefully and prospectively define the estimand
323 (90) that we are trying to estimate with consideration to how subjects who prematurely
324 discontinue the intervention and/or leave the trial will be handled. In any case, FEV₁ decline
325 should be measured in studies of young patients to characterize the population and to evaluate
326 potential disease modification. Other lung function measures, like novel spirometric parameters
327 (91-93), inspiratory capacity, body plethysmography (to quantify hyperinflation), oscillometry,
328 DLCO, may also deserve investigation in this population.

329

330 *Symptoms/Health status/PROs*

331

332 The CAT is likely to be the preferred option in most cases, irrespective of whether participants
333 have been recruited on the basis of mucus hypersecretion, breathlessness or exercise limitation as
334 its multi-dimensional nature will capture changes in each of these features. Unless study
335 participants are symptomatic, symptom scores, PROs and health-related quality of life (**HRQL**)
336 measures will not be able to detect improvement with interventions, as CAT score values <10 are
337 not associated with a noticeable effect on daily life (94). Yet, available evidence shows that
338 young patients are not asymptomatic (37) and that COPD patients with mild airflow obstruction
339 (not necessarily young) do have marginally elevated SGRQ and CAT scores (57, 58, 95, 96),
340 suggesting that there is potential for improvement. In fact, a trial in average age of 65 years-old
341 COPD patients with mild-moderate airflow limitation showed an effect on CAT scores (15), and
342 a subgroup analysis of the EMAX study (mean age 65 years) showed that magnitude of

343 symptomatic benefit of dual bronchodilator compared to monotherapy was similar in patients
344 with CAT scores ~10 or ~20 (97). Measures of physical activity (e.g., Daily-PROactive Physical
345 Activity in COPD (**D-PPAC**) (61) may also be considered. Bronchodilator trials in GOLD grade
346 1 patients showed variable results (98, 99). What constitutes a Minimal Clinically Important
347 Difference (MCID) in patients with low level of symptoms (100, 101), and whether therapeutic
348 interventions in these patients would have a large enough effect to be detected, is uncertain. In
349 summary, the optimum symptom score, PRO or HRQL measure to use in a particular trial will
350 depend on the inclusion criteria. Lastly, measures of health care utilization should also be
351 considered as relevant endpoints given their impact on patients and the health care system (102,
352 103).

353

354 *Exacerbations*

355

356 Exacerbations of COPD (**ECOPD**) remain a central, valid, and important tenet for the adequate
357 assessment of clinical disease and therapeutic needs, and for RCTs they represent an important
358 outcome measure (18, 102, 104, 105). Their prevalence and severity in young patients are still
359 not well defined but they do indeed occur (37). ECOPD in young individuals may be influenced
360 by symptom reporting. This, in turn, may be subject to individual variability in perception (106)
361 and, further prejudiced by societal and cultural norms for interpreting and reporting of
362 respiratory symptoms, as well as by local primary care set-up and its interface with tertiary
363 hospitals. We do not know if frequent ‘exacerbator’ phenotypes exist in young patients, so more
364 epidemiological work on this group would assist in developing interventional studies.

365

366 *Lung Imaging*

367

368 Imaging biomarkers can be used both to identify individuals at high risk for disease progression
369 as well as endpoints in treatment trials in young patients. In particular, CT metrics of small
370 airway abnormality may be most helpful to enrich the study population with young patients at
371 higher risk for disease progression. Density-based metrics have the strongest supportive data for
372 reproducibility making them attractive as clinical endpoints, although they may be relevant only
373 for specific therapeutic interventions.

374 Several *airway abnormalities* on chest CT scans correlate with dyspnea, quality of life and
375 functional capacity, and predict lung function decline (**Supplemental Table 1**) (57, 107). Pi10, a
376 measure of the thickness of medium size airways, relates to incident COPD over 3-5 years (108,
377 109) and is sensitive to change over time (110), even over short follow-up periods (111).

378 Parametric response mapping (**PRM**) matches inspiratory and expiratory images to estimate non-
379 emphysematous gas trapping or functional small airways disease (**PRM^{fSAD}**) and also predicts
380 lung function decline (112, 113). The normal density E to I Ratio, another measure of gas
381 trapping due to small airway disease, is also associated with FEV₁ decline (114). Total airway
382 count correlates with the number of terminal bronchioles on micro-CT (115) and is associated
383 with FEV₁ decline, especially in those with mild to moderate disease (116). Airway fractal
384 dimension (**AFD**), a measure of the complexity of airway branching, is lower in patients with
385 more severe airflow limitation and is also associated with FEV₁ decline (117). Finally, the
386 airway surface area to volume ratio reflects a combination of airway loss and airway narrowing,
387 is associated with FEV₁ decline, and can be used to phenotype individuals into those with
388 predominant loss vs. narrowing of airways (118, 119).

389
390 Density-based measures of emphysema are also associated with lung function decline (120, 121)
391 and mortality (117, 119, 122-125). CT emphysema progresses over time, particularly in current
392 smokers (126, 127). The lung density metric is already in use in α -1 antitrypsin deficiency, a
393 known cause of COPD in the young, as primary endpoint to assess the impact of interventions
394 targeting attenuation of disease progression (128, 129). The correlation between emphysema and
395 lung function is weaker compared to metrics of small airway abnormality (130, 131), but the
396 reproducibility for PRM emphysema (**PRM^{Emph}**) is higher (132). This can allow a smaller sample
397 size in RCTs (133). Finally, both **PRM^{Emph}** and **PRM^{fSAD}** have histologic validation with human
398 lung tissue (134). Studies using CT measures of lung *biomechanics* suggest that once
399 emphysema is initiated, mechano-transduction can accelerate further development of
400 emphysema; hence CT indices that assess alterations in lung biomechanics have been associated
401 with FEV₁ decline and BODE (125, 135). Qualitative assessment of mucus plugs on chest CT
402 has been associated with ECOPD (136).

403

404 Other imaging techniques also hold promise. For instance, polarized gas MRI can identify
405 abnormalities in diffusion and ventilation, which may precede the development of clinically
406 overt disease (137) .

407

408 *Mortality*

409

410 Several issues need consideration in relation to mortality as a potential outcome in future studies
411 of young patients. First, the comparison of death rates in major COPD trials in the 2000s (40, 43)
412 and 2010s (138) shows that, fortunately, the risk of mortality in COPD is decreasing and may
413 hopefully continue to decrease in the near future. Second, life expectancy varies widely across
414 the world, so geographical variations will have to be considered in any future study in young
415 patients. Finally, death rates are substantially lower in younger (20-50 years) than older COPD
416 patients included in previous studies (40, 43, 138), and this may have a direct impact on sample
417 size estimation. For instance, in the United States in 2017 the death rate in the 35-54 age group
418 was about 300 per 100,000 persons (139). If we hypothesize that COPD may increase this risk
419 two- or three-fold, estimated deaths in a population of young patients would be in the range of
420 600 to 900 deaths per 100,000 in a given year. Then, if a given therapeutic intervention was to
421 reduce mortality in these patients by 30% (likely an optimistic estimation), an RCT with
422 mortality as a primary endpoint would require recruiting about 80,000 patients, significantly
423 more than those recruited in TORCH, UPLIFT and SUMMIT, which randomized from 6,000 to
424 16,000 patients (40, 43, 138). These considerations make mortality an unlikely useful outcome
425 measure in future treatment trials in young patients.

426

427 *Composite endpoints*

428

429 A composite endpoint combines different individual endpoints to increase the frequency of
430 events, allowing RCTs to be conducted with fewer participants and/or to be shorter. A composite
431 endpoint also enables different aspects of a disease to be evaluated together, potentially
432 providing a broader view of the impact of a therapeutic intervention and can be used to reduce
433 bias caused by subjects who prematurely discontinue. The components of a composite endpoint
434 need to be carefully selected to be sufficiently independent and of similar clinical relevance. The

435 frequency of each component should ideally be similar, so that more frequently occurring
436 component(s) do not dominate. Alternatively, each component can be weighted differently. For
437 instance, in COPD trials in older patients with severe COPD, although ECOPD is likely more
438 frequent than death both could be components of a potential composite endpoint. In contrast, the
439 lesser anticipated mortality of young patients suggests that such a composite endpoint may be
440 even more dominated by ECOPD, even if these events are less prevalent than in older COPD
441 patients. *Post-hoc* analysis of data from the UPLIFT trial of 5,992 patients with COPD
442 randomized to receive tiotropium *vs.* usual care, studied over 4 years showed that a composite
443 index consisting of death, respiratory failure, hospitalized exacerbations, and trial dropout due to
444 COPD worsening could reduce the number of patients needed to achieve a significant outcome
445 by half (140).

446
447 The clinically important deterioration (**CID**) composite endpoint, which combines worsening of
448 PROs and FEV₁ with ECOPD, was designed for short COPD clinical trials (141) and several
449 studies showed significant treatment differences (142-144). Further, longer studies demonstrated
450 that CID events during the first 6 months of the study predict later mortality (145-147),
451 suggesting that pharmacological interventions that modify CID frequency in short term trials
452 may have longer term benefits. The use of CID in studies in young patients needs to consider
453 several aspects. It is unclear if the MCID threshold values determined in older patients (4-unit
454 worsening for SGRQ and 100 ml decrease for FEV₁) are valid in younger patients (141).
455 Likewise, the frequency and variability of CID components varies between cohorts with different
456 characteristics, so they need to be established in a cohort of young patients, as they dictate the
457 sample size calculations of future studies. In summary, CID provides a framework for a potential
458 composite endpoint in young patients, but methodology work is needed to identify the most
459 appropriate components and define appropriate MCID thresholds. Other potential composite
460 endpoints to consider in this population include the Early Clinically Important Improvement
461 (ECII) (148) and COPDCompEx (see above) (149). An alternative to using a composite endpoint
462 would be to jointly model the relevant endpoints that indicate deterioration (150), an approach
463 that has been utilized in oncology trials (151).

464

465

466 **Treatable traits, endotypes and biomarkers**

467 As COPD is complex and heterogeneous, its clinical management requires a personalized
468 approach. To this end, a management strategy based on treatable traits (TTs) has been proposed
469 (152). TTs can be recognized based on their clinical characteristics (i.e., phenotypes) and/or
470 through validated biomarkers of specific pathobiological mechanisms (i.e., endotypes) in the
471 pulmonary, extra-pulmonary, and behavioral/environmental domains (152). TTs can coexist,
472 interact, and change with time (spontaneously, or as a result of treatment) in the same patient
473 (152). Because management guided by TTs can improve clinical outcomes (31), the design of
474 future treatment trials in young patients needs to consider their presence or absence. Likewise, it
475 should be noted that endotypes may vary with age, so they may differ in young and older COPD
476 patients and improved understanding derived from ongoing research in young individuals may
477 inform future treatment guidelines.

478
479 A promising biological marker is circulating eosinophils. RCTs in moderate to very severe
480 COPD patients have shown that higher blood eosinophil counts at baseline are associated with
481 greater benefits from inhaled corticosteroids (ICS) (153). This biomarker is now used in clinical
482 practice to guide ICS use in patients with a history of exacerbations (154). Bronchoscopy and
483 sputum studies in COPD patients have demonstrated that higher blood eosinophil counts are
484 associated with increased lung eosinophil numbers and a profile of T2 inflammation, providing
485 an explanation for the differential ICS effect (155, 156). Furthermore, lower blood and sputum
486 eosinophils are associated with greater presence of proteobacteria (157, 158), with increased
487 bacterial infections and pneumonia observed in these individuals (159). Clinical trials in younger
488 COPD patients may be able to utilize blood eosinophil counts to select subgroups with distinct
489 inflammation and microbiome profiles, and there may be considerable potential for ICS or other
490 interventions targeting T2 inflammation in younger COPD patients with higher eosinophil
491 counts. It is hoped that with improved understanding of the biological underpinnings behind
492 COPD in young individuals or those with pre-COPD therapeutic approaches to be tested will be
493 targeted to specific TTs.

494

495 **Type of intervention**

496 Pharmacological interventions are likely to be central in treatment trials of young adults with
497 COPD, but other types of intervention may also be considered, alone or in combination with
498 drug interventions. For instance, smoking cessation measures will have to be incorporated in any
499 study design, even to get the approval of IRBs. Likewise, promotion of healthy lifestyle
500 (exercise, diet, sleep, inhalational substance avoidance) will have to be considered as well.

501

502 **Placebo or comparator**

503

504 Approved treatments for COPD do not have a lower age limit but the scientific evidence
505 supporting them has been generated in older populations. Thus, young patients are often treated
506 without evidence for their effectiveness in COPD. As there are no specific approved treatments
507 for COPD in young patients there is no age specific standard of care comparator. On the other
508 hand, many currently available treatments are used in younger asthmatics, and the use of a
509 placebo may prove challenging depending on the agent being tested.

510

511 **Statistical power**

512 Due to the relative lack of data on outcome measures in young patients, statistical power
513 calculations will rely on information from observational cohorts (such as Early COPD in UK,
514 ECLIPSE, COPDGene or SOURCE in the US, CADSET in Europe (160) and TRAIT in Japan
515 (161)) and consortia that include a proportion of young patients (**Table 5**), electronic medical
516 records, and/or blinded sample size reassessment/adaptive approaches and better define clinical
517 trials duration. Likewise, the expected treatment effect sizes are not well established, although
518 the expectation is that treatment differences might be greater in younger patients with
519 (presumably) milder airflow limitation.

520

521 **Platform trials**

522

523 There is increasing interest in developing innovative approaches to enhance efficiency of clinical
524 trials while testing numerous questions at the same time; master protocols such as umbrella
525 (multiple targeted therapies in the context of a single disease), basket (study a single targeted

526 therapy in the context of multiple diseases or disease subtypes), and platform (multiple targeted
527 therapies in the context of a single disease in a perpetual manner) trials are such an approach
528 (162). Given potentially heterogeneity in patient populations platform trials may reflect a
529 potential alternative to consider as they can invoke adaptive designs where progress is
530 periodically re-assessed, and participants are reallocated from ineffective treatments to contribute
531 to the overall outcome (163). Master protocol approaches, including platform trials, have been
532 principally used in oncology (64) but have seen a tremendous increase in the setting of the
533 COVID-19 pandemic (164). An initial exploratory study in young patients could be done using a
534 master protocol design, which offers the advantage of evaluating multiple therapies (162). This
535 approach would benefit from collaborations among multiple stakeholders, successfully used in
536 the COVID-19 era (165), including industry partners and regulatory agencies.

537

538 **Maintaining participant commitment in long clinical trials**

539

540 Younger patients with COPD may be less motivated to participate in RCTs, as they are likely to
541 be employed, caring for a young family, unlikely to be symptom-limited and more likely to
542 relocate. Hence, developing a strong relationship with participants will be key as will be
543 conducting trials through mechanisms that have broad geographic reaches. Although the primary
544 outcome assessments are likely to be clinic-based, the use of digital health technology for interim
545 assessments, monitoring trial medication adherence, and digital trial communication may aid.
546 Regular participants contact to review symptoms, provide updates on trial progress, and
547 appropriate subject compensation will be important to reduce dropouts during follow up. Many
548 outcomes can be followed using appropriately anonymized electronic medical records that
549 enhance the quality of the data and assess an intervention's cost-effectiveness.

550

551 **Future Steps**

552

553 It is clear that earlier intervention in younger patients with COPD or those at risk with pre-COPD
554 will be a crucial next paradigm in the management of this impactful disorder. The most critical
555 next steps now involve the design and development of specific RCTs in individuals with young

556 COPD and pre-COPD. **Table 5** enumerates potential issues and approaches to consider in their
557 design.

558

559 **CONCLUSIONS**

560

561 Designing treatment trials in young patients and pre-COPD patients is complex. However, the
562 barriers mentioned herein can be overcome, and the potential rewards in terms of knowledge and
563 improved health by conducting successful trials are likely substantial. Now is the time to refine
564 an approach to a collaborative initiative to modify the course of the 3rd leading cause of death in
565 the world and a significant cause of morbidity globally. This requires commitment from Industry
566 and Government funders and partnerships among diverse international stakeholders to implement
567 platform trials utilizing harmonized methodology and standard outcome measures that will
568 generate robust data. These can be integrated to develop evidence-based personalized preventive
569 and therapeutic interventions that modify disease progression based on risk factors and/or
570 treatable traits (152). Working together and acting earlier in young patients and patients with pre-
571 COPD (10) can reduce the global burden of COPD (39).

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1195

1196 **Table 1. Nosology used in this review. For further explanations, see text.**

1197

Term	Definition
Early COPD	<i>Biological</i> term that indicates that the disease is near its beginning (at any age); requires validated <i>biomarkers</i> to be identified/quantified in clinical practice.
Mild COPD	<i>Functional</i> term that indicates that the disease is associated with mild airflow limitation (at any age)
Young COPD	<i>Age-dependent</i> term that identifies a subpopulation of patients with COPD (FEV1/FVC<0.7) between 20-50 years of age (independent of the severity of airflow limitation present)
Pre-COPD	<i>Individuals</i> (of any age) who present chronic respiratory symptoms, with or without structural and/or functional abnormalities, in the absence of airflow limitation (FEV1/FVC>0.7) who may (or may not) develop persistent airflow limitation (i.e., COPD) over time
Disease activity	<i>Biological</i> term that relates to the level of activation of the pathobiological processes (endotypes) that cause the disease. It can ideally be identified and quantified by validated biomarkers (currently lacking in COPD)
Disease progression	<i>Clinical</i> term that refers to a progressive deterioration in an objective marker of pathology or lung function
Primary prevention	Aimed at preventing the disease <i>before it occurs</i> by eliminating exposures to risk factors and/or increasing resistance to disease should exposure occur
Secondary prevention	Aimed at reducing the impact of a disease that <i>has already occurred</i> by diagnosing and treating it as soon as possible to halt or slow its progress
Tertiary prevention	Aimed at <i>mitigating the impact</i> of an ongoing illness

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1199

1200 **Table 2. Historical factors complicating randomized controlled trials in COPD.**

- 1201
- 1202 1. Definition of the disease and its severity has been primarily focused on a single parameter
 - 1203 (spirometry)
 - 1204 2. The paucity of regulatory accepted "qualified" intermediate efficacy endpoints and
 - 1205 validated biomarkers
 - 1206 3. The non-normal distribution of important trial outcomes
 - 1207 4. Differing patterns of disease progression
 - 1208 5. Slow FEV₁ decline which is further compounded by dropout or death amongst the sickest
 - 1209 6. Disease heterogeneity: described as different phenotypes and endotypes (e.g.,
 - 1210 emphysema, airways disease, lung microbiome, neutrophilic vs. eosinophilic
 - 1211 inflammation, aberrant tissue repair)
 - 1212 7. Variability of endpoints and their confounders, e.g., washout of background medications,
 - 1213 diurnal variation, seasonal effect

1214

1215

1 **Table 3: Rate of FEV₁ Decline (mL/yr.) Study Results**

Study	Length (years)	N	Mean FEV ₁ (%)	Mean Age	Active	Placebo	Difference (95% CI)	Estimated Effective SD	Implied N/group for 90% power to detect ² :	
									12 mL/yr. Difference	15 mL/yr. Difference
SUMMIT (138)	1-4 ¹	16485	60	65	38	46	-8 (-15, -1)	154	3462	2216
Zhou et al (15)	2	841	78	64	29	51	-22 (-37, -6)	110	1766	1131
Copenhagen CLS (166)	3	290	86	59	45	42	3 (-13, 19)	69	695	445
EUROSCOPE (167)	3	1277	77	52	57	69	-12 NS	UNK		
TORCH (168)	3	6112	44	65	42/43/39	55	-16 (-25, -8)	113	1864	1193
BRONCUS (169)	3	523	57	62	56	47	8 (-10, 25)	97	1374	879
ISOLDE (170)	3	751	50	64	50	59	-9 (-3, 20)	76	843	540
Lung Health Study II (171)	3.5 - 4.5 ¹	1116	68	56	44	47	-3 (-11, 5)	70	716	458
UPLIFT (40, 172)	4	5993	48	65	40	42	-2 (-6, 2)	72	757	485
Lung Health Study I (68)	5	5887	78	48	30	66	-31 UNK	57	475	304

2 ¹ Variable length follow-up

3 NS – not stated; UNK - unknown

4

1 **Table 4: Partnerships that may enable treatment trials in young patients.**
 2

Organization	Contribution
Professional organizations	Individuals at risk based on occupational exposure (e.g., firefighters, veterans, farm workers)
Primary care providers	Identify individuals at risk based on symptoms and risk (or early life events)
Birth cohorts (population based) with long longitudinal follow-up	Risk predictors, biomarkers, participants
Population based cohorts with longitudinal follow-up	Risk predictors, biomarkers
Pharmaceutical Industry	Partner on Platform trials, shared risk
International scientific multidisciplinary team	Collaborate on trial design and implementation
Patient Advocacy Groups	Coordinate platform trials

3

4

1 **Table 5: Future Steps in the design and conduct of intervention studies of young patients**
 2 **with COPD or those at risk with Pre-COPD.**
 3

	Young COPD	Pre-COPD
Potential Outcomes to explore	<ul style="list-style-type: none"> • Rate of FEV₁ decline • Time to first COPD exacerbation 	<ul style="list-style-type: none"> • Time to onset of COPD • Time to worsening in CAT (1 point) or SGRQ (4 points)
Study duration	<ul style="list-style-type: none"> • Three years 	<ul style="list-style-type: none"> • Three to five years
Interim analysis at 6 -12 months (to assess dropping therapy arms and/or extending trial duration/increase sample size)	<ul style="list-style-type: none"> • Rate of FEV₁ decline • Time to first COPD exacerbation • CAT change • Composite outcomes* 	<ul style="list-style-type: none"> • Rate of FEV₁ decline • CAT change • E-RS: COPD • Others (Impulse Oscillometry and/or Lung Imaging: airways disease parameters; HCRU Events; CompEx COPD) • Composite outcomes*
Potential Intervention Arms	Currently approved medications for COPD	Currently approved medications for COPD as well as novel agents capable of modifying disease progression
Placebo control	No (as these are currently approved medications for airflow limitation with no age limits)	Yes (since these medications are not approved for this indication)
Study Population as per the definition in the text (plus some other potential characteristics to consider in the study design to enrich the population studied)	<ul style="list-style-type: none"> • CAT score >10 • A Respiratory HCRU event in 2 of the past 3 years • Biomarker enrichment[†] 	<ul style="list-style-type: none"> • Individuals with NOCB symptoms as defined using the CAT or SGRQ • A Respiratory HCRU event in the past 24 months • Subjects with rapid FEV₁ decline • Biomarker enrichment[†]

4 ¹ Variable length follow-up

5 NS – not stated; UNK – unknown

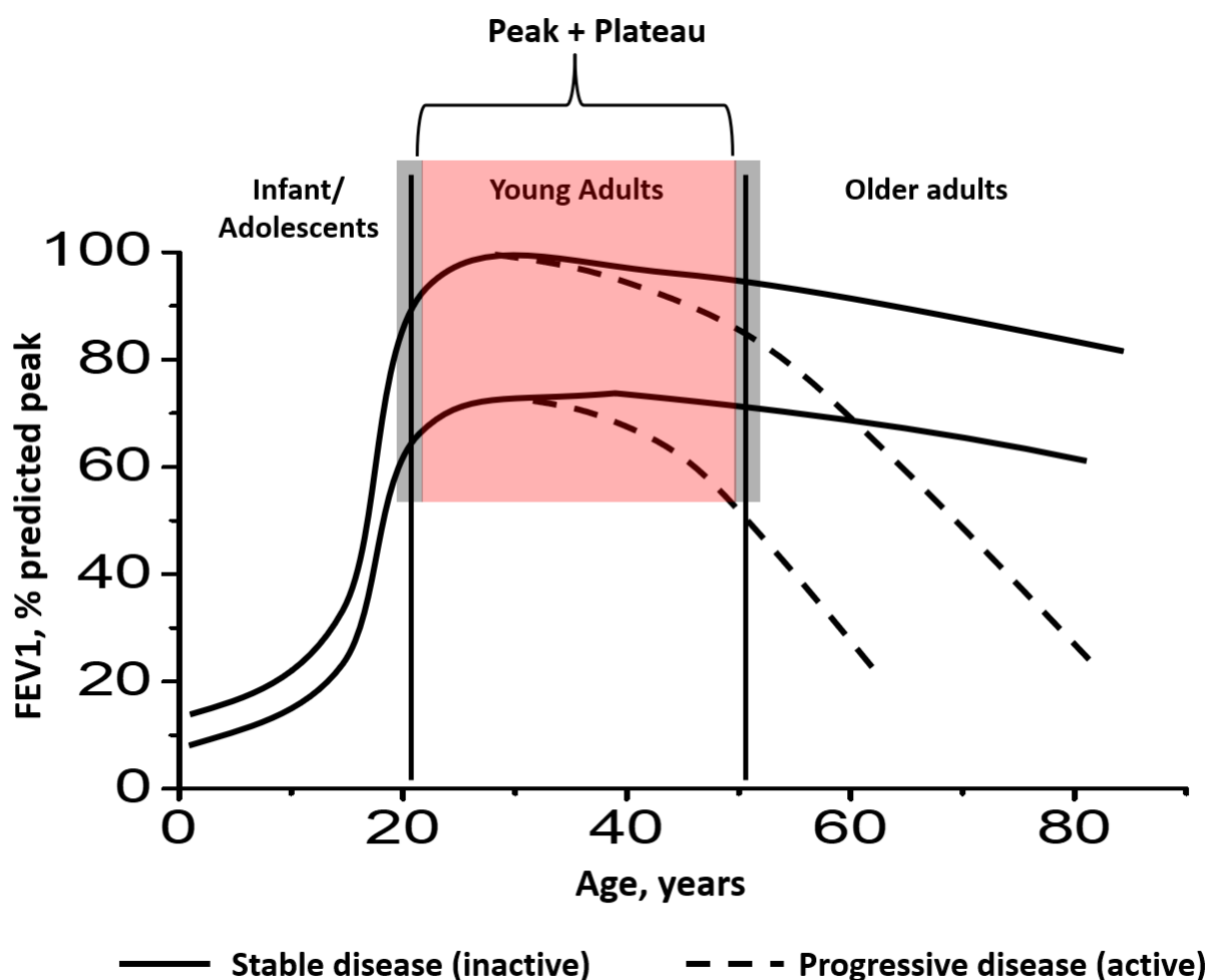
6 [†] Circulating eosinophils, microbial assessments (see text)

7 *such as Clinically Important Deterioration (CID) examining time to FEV₁ decline, exacerbation or
 8 symptom worsening.

9

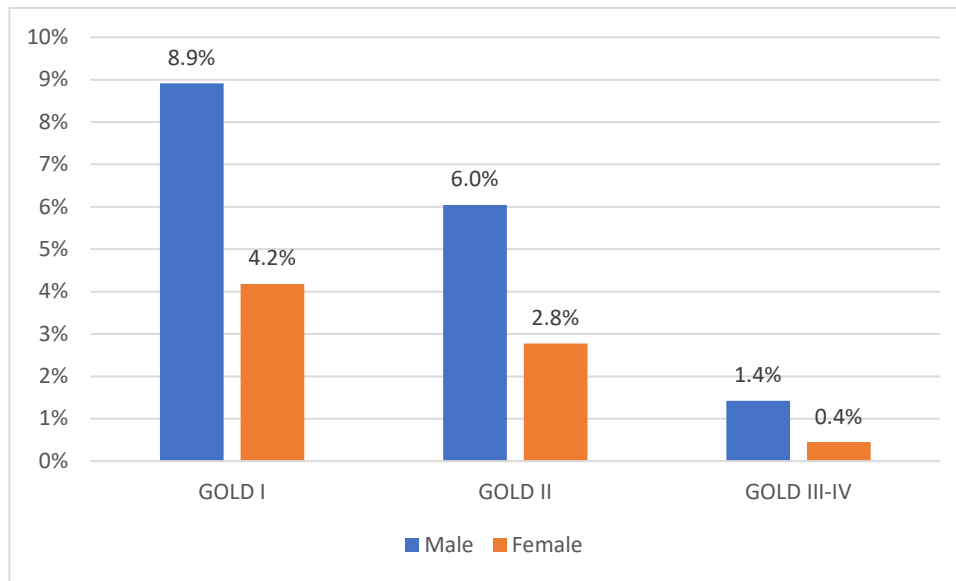
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1 **Figure 1.** Examples of lung-Function Trajectories from birth to death. The red shaded area
 2 highlights the population of young adults with COPD to be included in treatment trials. Grey
 3 shaded areas indicate that these age-limits are somewhat arbitrary (based on normal peak +
 4 plateau lung function), and that therefore some age variability may be acceptable. Note also that
 5 this age range includes trajectories with normal peak lung function (100% ref) as well as those
 6 with reduced peak lung function (<80% ref.) and that both can have a normal (stable) or an
 7 enhanced decline with time (progressive disease) For further explanations, see text.
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1 **Figure 2.** Prevalence of COPD in young individuals (20-49 years) in the general population in
2 China. Data from (44).
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Supplemental Table 1: Imaging metrics associated with FEV₁ Decline

Metric	FEV ₁ Decline in ml/year	GOLD Grades Stratification	Variables adjusted for in the model
Airway			
Pi10, per mm increase (108)	34.0 (12.0 to 56.0)	*0, 1-3	Age, pack-years of smoking, smoking status, and FEV ₁ z-score
Total Airway Count, Per count decrease (116)	6.6 (1.7 to 13.3)	0, 1-2	Age, sex, race, BMI, , smoking status, FEV ₁ and CT emphysema
PRM ^{ISAD} , per 5% increase (113)	2.2 (0.1 to 4.2)	*0, 1-2, 3-4	Age, race, sex, height, smoking status, pack-years of smoking, baseline FEV ₁ , baseline FVC, bronchodilator reversibility, and scanner type
ND-E/I, per unit increase (114)	3.0 (1.5 to 4.5)	*0, 1-4	Age, race, sex, BMI, smoking status, pack-years of smoking, CT scanner type, CT emphysema, and Wall Area% of segmental airways
Airway fractal dimension, per unit decrease (117)	31.5 (10.4 to 52.7)	*0, 1-4	Age, race, sex, BMI, smoking status, pack-years of smoking, % CT emphysema, FEV ₁ at baseline, and CT scanner type
Airway SA/V, per 100cm ² /ml decrease (119, 173)	21.8 (6.6 to 36.9)	0, 1-4	Age, race, gender, BMI, smoking status, pack-years of smoking, CT emphysema, airway wall thickness, TAC, number of exacerbations in the prior year, total lung capacity, baseline FEV ₁ , and CT scanner type
Parenchyma			
Emphysema (Perc15), per 1 HU decrease (120)	4.5 (3.3 to 6.1)	*0, 1-3	Age, height, BMI, smoking status, pack-years of smoking, and center
Emphysema (Perc15), per 10 HU decrease (108)	10.0 (5.0 to 15.0)	*0, 1-3	Age, pack-years of smoking, smoking status, and FEV ₁ z-score
Lung mass, per 100 g increase (121)	4.7 (1.4 to 8.0)	0, 1-4	Age, sex, height, weight, smoking status, CT emphysema, exacerbation in the prior year, baseline FEV ₁ and CT scanner type
MAL ₂ , per 1 unit change in Jacobian determinant decrease (135)	22.2 (0.2 to 44.3)	0, 1-2, 3-4	Age, race, sex, BMI, smoking status, pack-years of smoking, baseline FEV ₁ , CT emphysema, CT gas trapping, Wall Area% of segmental airways, and CT scanner type

*Specifically evaluated and found associations with FEV₁ decline in individuals without airflow obstruction.

FEV₁ = Forced expiratory volume in 1 second. GOLD = Global Initiative for Chronic Obstructive Lung Disease. Perc 15 = HU at the lowest 15th percentile of a cumulative frequency distribution for all HU values. HU = Hounsfield Units. MAL₂ = Mechanically affected lung within 2 mm of emphysematous areas. Pi10 = Square root of the wall area of a theoretical airway with 10 mm internal

perimeter. TAC = Total airway count. PRM^{fSAD} = Parametric response mapping derived functional small airways disease. FVC = Forced vital capacity. ND-E/I = Ratio of expiratory density to inspiratory density in lung regions termed normal using density thresholds. SA/V = Surface Area-to-Volume ratio

Supplemental Figure 1. COPD360Net is a network of COPD Foundation accredited care centers. It also includes patient advocates, a health economist assessing patient preferences and valuation of possible therapeutic pipeline, a psychosocial expert studying cognitive impairment in chronic disease, and primary care physicians. COPD360Net’s mission is to support the development and adoption of novel digital health tools, medical devices and therapeutics that treat COPD, bronchiectasis, and nontuberculous mycobacterial lung disease. COPD360Net is designed to facilitate, review of treatment approaches, implementation of clinical trials and support of adoption in the clinic – facilitating discovery to delivery.

