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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 FEV<sub>1</sub> 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 FEV<sub>1</sub> 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, FEV<sub>1</sub> 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 FEV<sub>1</sub> value may result from abnormal  
297 lung development and/or early enhanced decline (**Figure 1**) (7) and, in the absence of historic  
298 data, these two trajectories are difficult to define (7). Second, absolute decline in FEV<sub>1</sub> is faster  
299 in patients with milder airflow limitation (32), who might be younger. If so, this may facilitate  
300 studying the impact of interventions on FEV<sub>1</sub> decline in younger patients. Absolute FEV<sub>1</sub> decline  
301 is also subject to bias from starting lung size which is influenced by factors such as height and  
302 gender. **Table 3** enumerates the change in FEV<sub>1</sub> among RCTs targeting mild to severe COPD  
303 patients with average ages 50-65. A systematic review of RCT suggests that a 5.0 ml/yr.  
304 reduction (95% CI 0.8-9.1 ml/yr.) has been suggested in the rate of FEV<sub>1</sub> decline in active  
305 treatment arms compared with placebo (84). Arguably, younger individuals show faster FEV<sub>1</sub>  
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 FEV<sub>1</sub> decline. However, a single FEV<sub>1</sub> measurement is not  
308 a good predictor of the future FEV<sub>1</sub> trajectory and rapid FEV<sub>1</sub> 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 FEV<sub>1</sub> 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 FEV<sub>1</sub> 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, FEV<sub>1</sub> 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<sup>fSAD</sup>**) 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 FEV<sub>1</sub> decline (114). Total airway  
382 count correlates with the number of terminal bronchioles on micro-CT (115) and is associated  
383 with FEV<sub>1</sub> 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 FEV<sub>1</sub> decline (117). Finally, the  
386 airway surface area to volume ratio reflects a combination of airway loss and airway narrowing,  
387 is associated with FEV<sub>1</sub> 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  $\alpha$ -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<sup>Emph</sup>**) is higher (132). This can allow a smaller sample  
397 size in RCTs (133). Finally, both PRM<sup>Emph</sup> and PRM<sup>fSAD</sup> 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 FEV<sub>1</sub> 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 FEV<sub>1</sub> 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 FEV<sub>1</sub>) 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 3<sup>rd</sup> 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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1194  
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1196 **Table 1. Nosology used in this review. For further explanations, see text.**  
 1197

<b>Term</b>	<b>Definition</b>
<b>Early COPD</b>	<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.
<b>Mild COPD</b>	<i>Functional</i> term that indicates that the disease is associated with mild airflow limitation (at any age)
<b>Young COPD</b>	<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)
<b>Pre-COPD</b>	<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
<b>Disease activity</b>	<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)
<b>Disease progression</b>	<i>Clinical</i> term that refers to a progressive deterioration in an objective marker of pathology or lung function
<b>Primary prevention</b>	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
<b>Secondary prevention</b>	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
<b>Tertiary prevention</b>	Aimed at <i>mitigating the impact</i> of an ongoing illness

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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 FEV<sub>1</sub> 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 FEV<sub>1</sub> Decline (mL/yr.) Study Results**

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

2 <sup>1</sup> Variable length follow-up

3 NS – not stated; UNK - unknown

4

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

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

4 <sup>1</sup> Variable length follow-up

5 NS – not stated; UNK – unknown

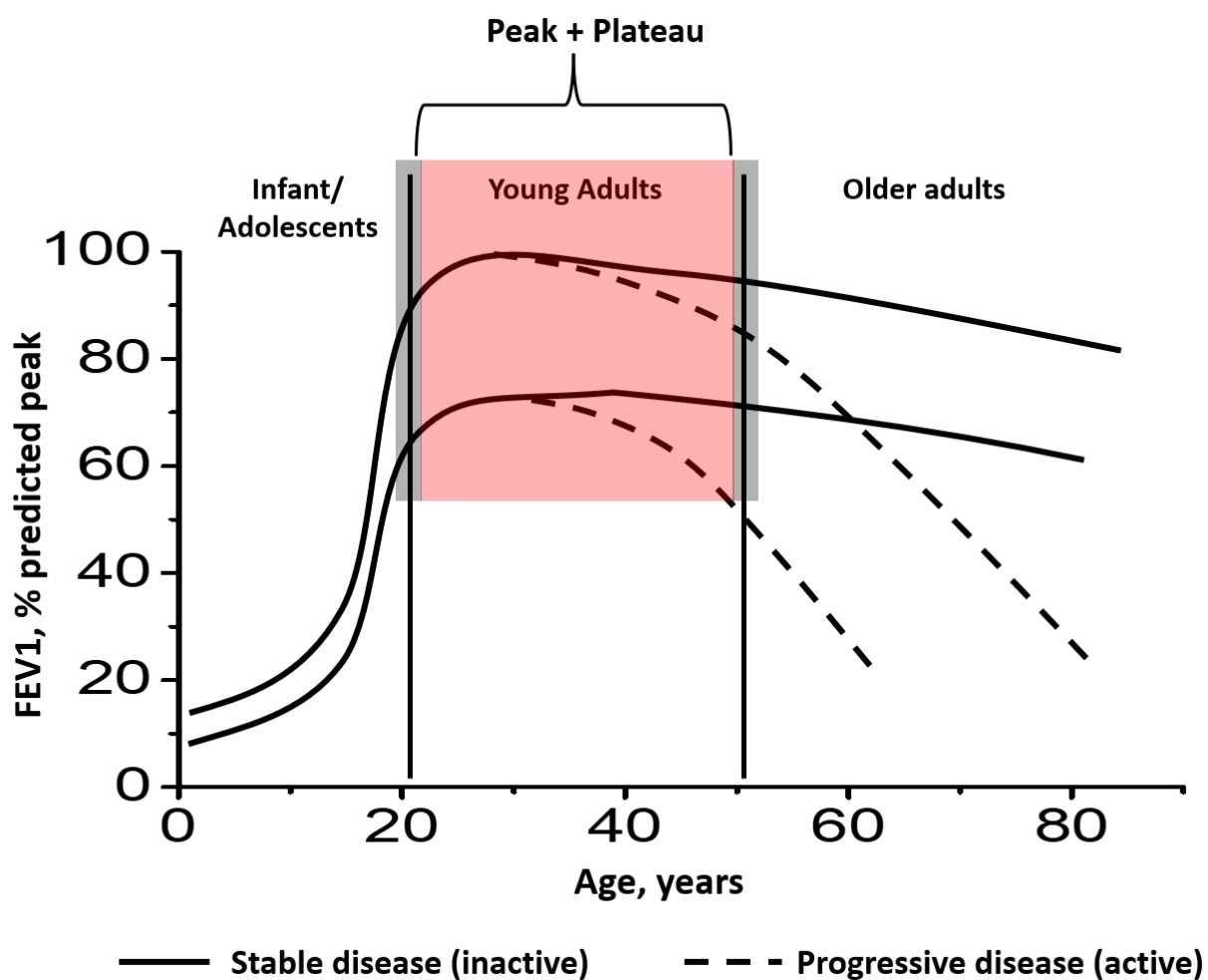
6 <sup>†</sup> Circulating eosinophils, microbial assessments (see text)

7 \*such as Clinically Important Deterioration (CID) examining time to FEV<sub>1</sub> decline, exacerbation or  
 8 symptom worsening.

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10

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).

