

1
2
3 **British Thoracic Society Clinical Statement on the use of Biologic Therapies in Chronic**
4 **Obstructive Pulmonary Disease**

5
6
7
8 *Draft for consultation: 30 September 2026*
9

10
11 Authors: M Bafadhel*, CE Bolton, CE Brightling*, R Chan, E Davies, NJ Greening, S Holmes, JR
12 Hurst, AW Martinelli, HJC McAuley, D Singh, JS Watson, T Wilkinson, R Saggu*

13
14
15
16 **On behalf of the British Thoracic Society**
17

18
19 **Available for public consultation from**
20

21 30 September 2026 to 29 October 2026
22
23

24
25
26
27 * Co-chairs of Group
28
29
30
31
32
33
34
35
36

37

38

39 **1. Introduction**

40 Chronic obstructive pulmonary disease (COPD) affects millions of people worldwide and
41 remains a leading cause of avoidable morbidity, mortality and healthcare utilisation. COPD
42 disproportionately affects people living in areas of socioeconomic deprivation and is
43 associated with substantial health inequalities in diagnosis, access to care, disease burden
44 and outcomes. Reducing these inequalities remains a central objective of modern COPD care.

45 The management of COPD has hardly evolved over the last two decades. Smoking cessation,
46 pulmonary rehabilitation, vaccination, optimisation of inhaled pharmacotherapy, and
47 management of comorbid disease remain the fundamentals of care and should be available to
48 all people with COPD. Despite optimal use of these interventions, a proportion continue to
49 experience recurrent exacerbations, progressive impairment in quality of life and accelerated
50 decline in lung function.

51 Historically, COPD has been considered a predominantly neutrophilic inflammatory disease
52 with evidence of an altered airway ecology. However, increasing evidence demonstrates
53 substantial biological heterogeneity within COPD, with approximately one-third of patients
54 exhibiting evidence of type 2 inflammation characterised by eosinophilic airway and systemic
55 inflammation. Exacerbations of COPD can be a consequence of an amplification of this
56 background eosinophilic or neutrophilic inflammation, or an exaggerated response to new
57 infections most commonly viruses. The recognition of distinct inflammatory endotypes has
58 transformed understanding of COPD pathobiology and created opportunities for targeted
59 therapy.

60 The success of monoclonal antibody (biologic) therapies in severe asthma has provided proof
61 of concept that biomarker-directed treatment can improve outcomes in chronic airway
62 disease. Randomised controlled trials evaluating biologic therapies targeting type 2
63 inflammatory pathways have demonstrated clinically meaningful reductions in exacerbation
64 frequency in selected populations with COPD and evidence of eosinophilic inflammation.
65 These data have led to regulatory approvals and health technology assessments supporting
66 the use of biologics in carefully selected patients. At the time of drafting, dupilumab and
67 mepolizumab have received NICE approval for add-on maintenance treatment of uncontrolled
68 COPD with raised blood eosinophils. In parallel, monoclonal antibodies targeting IL-33
69 signalling, have reported encouraging phase III results in both those with eosinophilic or non-
70 eosinophilic inflammation and may further expand therapeutic options beyond type 2
71 inflammation for people living with COPD.

72 The rapid emergence of biologic therapies presents new opportunities but also new
73 challenges. Clinicians require practical guidance regarding patient identification, assessment
74 of eligibility, initiation of therapy, monitoring of treatment response, switching between
75 therapies, and decisions regarding discontinuation. Equally important is ensuring equitable
76 access to biologics across healthcare settings and avoiding the emergence of further
77 unwarranted variation in care.

78 This British Thoracic Society Clinical Statement provides a consensus-based overview of the
79 current evidence supporting biologic therapies in COPD and outlines principles of good clinical
80 practice for their use. It is intended to support clinicians involved in the care of adults with
81 COPD and should be considered alongside existing national and international COPD guidance.
82 The statement focuses specifically on biologic therapies and does not seek to provide
83 comprehensive guidance on the broader investigation or management of COPD.

84

85 **2. Methods**

86 This Clinical Statement was commissioned by the British Thoracic Society (BTS) Standards of
87 Care Committee in response to the rapidly evolving evidence base supporting biologic
88 therapies for COPD.

89 The writing group comprised respiratory physicians, researchers, specialist nurses,
90 pharmacists, general practitioners and early career members with expertise in COPD, severe
91 airways disease and biologic therapies. The group included representatives from primary,
92 secondary and tertiary care settings to ensure broad clinical representation and consideration
93 of service delivery across the United Kingdom.

94 The scope of the Clinical Statement was agreed and focused on the role of biologic therapies
95 in COPD. Key clinical questions were developed through consensus discussion within the
96 writing group and informed the literature review process.

97 A focused review of the published literature was undertaken. In keeping with BTS Clinical
98 Statement methodology, this review was intended to be pragmatic and targeted rather than a
99 formal systematic review. Evidence considered included randomised controlled trials,
100 observational studies, regulatory assessments, health technology appraisals, national
101 guidance documents and relevant conference presentations where peer-reviewed evidence
102 was not yet available.

103 Draft sections were prepared by members of the writing group and reviewed iteratively by the
104 wider committee. Areas where evidence was limited or absent were discussed using
105 structured consensus methods. Clinical Practice Points (CPPs) were developed through group
106 consensus and reflect the collective clinical experience and judgement of the committee.
107 CPPs should be regarded as statements of good clinical practice intended to support clinical
108 decision-making and service delivery. They do not constitute formal guideline
109 recommendations.

110 The completed draft underwent review by the BTS Standards of Care Committee prior to public
111 consultation. Following consultation, the document was revised in response to stakeholder
112 feedback before final approval by the BTS Standards of Care Committee.

113 All declarations of the expert panel were completed as per British Thoracic Society
114 requirement and publicly available.

115 3. Biological therapies and treatable endotypes of COPD

116 COPD has traditionally been regarded as a predominantly neutrophilic inflammatory disease¹
117 with evidence of an altered airway ecology (microbial dysbiosis)². However, evidence
118 demonstrates substantial biological heterogeneity³, with approximately one-third of patients
119 exhibiting evidence of type 2 inflammation characterised by eosinophilic airway and systemic
120 inflammation^{3,4}. Exacerbations of COPD can be a consequence of an amplification of this
121 background eosinophilic or neutrophilic inflammation³, or an exaggerated response to new
122 infections most commonly viruses⁵. The recognition of distinct inflammatory subgroups has
123 transformed understanding of COPD pathobiology and created opportunities for targeted
124 therapy. Recognition of this heterogeneity has led to the concept of COPD treatable traits⁶ and
125 endotypes⁷ (defined as a distinct biological or pathophysiological mechanism), creating
126 opportunities for targeted therapy.

127 The identification of type 2 inflammation in COPD has relied primarily on the peripheral blood
128 eosinophil count³. Currently the most widely available and clinically validated biomarker, the
129 blood eosinophil count has been associated with increased exacerbation risk⁸, greater
130 responsiveness to inhaled corticosteroids⁹ and, increasingly, response to biologic therapies¹⁰⁻
131 ¹³. Other biomarkers, including fractional exhaled nitric oxide (FeNO)¹⁴, may provide additional
132 information regarding inflammatory activity, although their role in routine COPD clinical
133 practice remains uncertain.

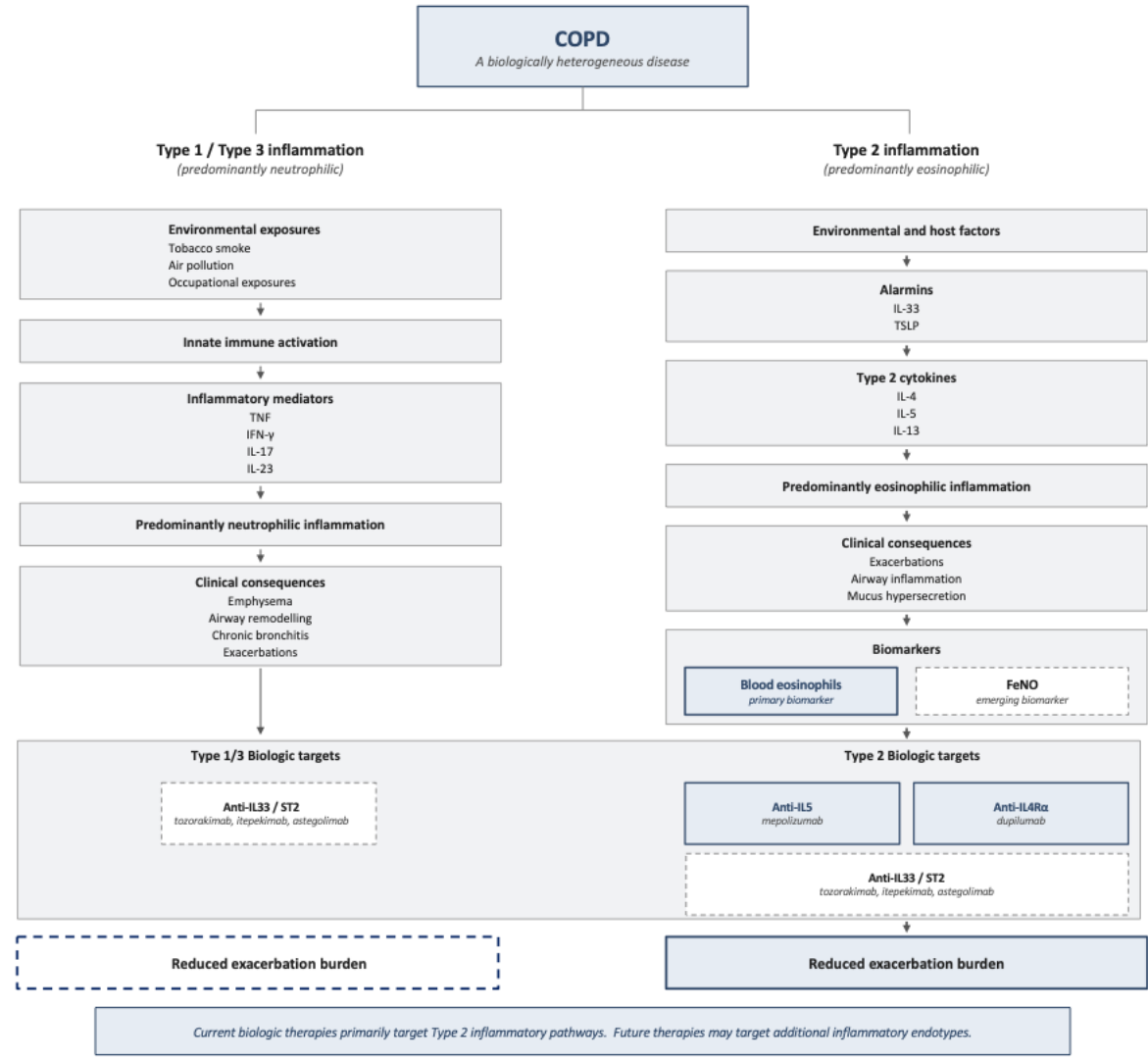
134 Inflammation can be mediated through interconnected cytokine pathways including IL-4, IL-5,
135 IL-13, IL-33 and thymic stromal lymphopoietin (TSLP)¹⁵. In the main, these pathways contribute
136 to type 2 inflammation with eosinophilic inflammation, mucus hypersecretion and
137 exacerbation susceptibility. IL-33 also affects other cells with emergent trials demonstrating
138 efficacy across eosinophilic and neutrophilic inflammation in COPD.

139 Multiple monoclonal antibody (biologic) therapies targeting type 1, 2 and 3 inflammatory
140 pathways have been evaluated in phase II and phase III randomised clinical trials in COPD, with
141 some yet to conclude (table 1). While results have varied between studies and therapeutic
142 targets, the strongest evidence currently exists for type 2 inflammation targeted by dupilumab
143 and mepolizumab, both of which have demonstrated reductions in exacerbation frequency in
144 phase III clinical trials among patients with higher blood eosinophil counts. Other biologics
145 targeting the IL-33 signalling pathway including astegolimab (ALIENTO and ARNASA studies¹⁶),
146 itepekimab (AERIFY 1 and AERIFY 2 studies¹⁷) have reported promising results in selected
147 populations. Tozorakimab an anti-IL-33 monoclonal antibody inhibiting both the oxidised and
148 reduced form of IL-33, has shown efficacy in reducing exacerbations in the phase III OBERON
149 and TITANIA studies¹⁸, across eosinophil counts, with the greatest benefit seen in participants
150 with the highest eosinophil count.

151 Collectively, these studies support the concept that biologic therapies can reduce
152 exacerbation burden in carefully selected patients with COPD. While important questions
153 remain regarding patient selection, biomarker thresholds, treatment sequencing and long-
154 term outcomes, biologics now represent an important addition to the therapeutic options
155 available for COPD.

156

Figure 1. Inflammatory endotypes and therapeutic targets in COPD



Dashed border = emerging target / no established therapy Thicker arrows = stronger current therapeutic evidence. Only drugs with NICE TA approval, or with efficacy in peer-review or press-release have been highlighted.

Clinical practice points

1. COPD is a biologically heterogeneous disease and assessment of inflammatory endotypes using readily available biomarkers should form part of routine clinical practice.
2. Evidence of type 2 inflammation, particularly the blood eosinophil count, identifies a subgroup of patients with COPD who may benefit from currently approved biologic therapy.
3. The evidence base for biologic therapy in COPD is evolving rapidly, with multiple ongoing studies evaluating additional therapeutic targets and patient populations, with the greatest evidence for IL-33 targets.

168 **Table 1. Biologic therapies evaluated in COPD and current evidence base**

Target pathway	Biologic	Biomarker strategy	Key COPD studies	Population studied	Key primary outcome efficacy findings	Current UK status
IL-4Ra	Dupilumab	Blood eosinophils ^a	BOREAS ¹¹ , NOTUS ¹²	- Current or former smokers - 30% <FEV₁ ≤ 70% - Triple therapy - 2 moderate or 1 severe exacerbation in last year	Positive (300mg dose every 2 weeks) 30%¹¹ and 34%¹² reduction in exacerbation frequency	NICE approved
IL-5	Mepolizumab	Blood eosinophils ^a	METREX and METREO ¹⁰ , MATINEE ¹³	- Current or former smokers - 20% <FEV₁ ≤ 80% - Dual or triple therapy^b - 2 moderate or 1 severe exacerbation in last year - Dosing (100/300mg)^c	Positive^d (100mg dose every 4 weeks) 18%¹⁰ and 21%¹³ reduction in exacerbation frequency	NICE approved
IL-5Ra	Benralizumab	Blood eosinophils ^a	GALATHEA and TERRANOVA ¹⁹ , RESOLUTE ^e	- Current or former smokers - 20% <FEV₁ ≤ 65% - Dual or triple therapy^f - 2 moderate or 1 severe exacerbation in last year - Dosing (10/30/100mg)^g	Negative Across doses, 4% increase to 17% reduction in exacerbation frequency	No approval
TNF	Infliximab	Not biomarker restricted	NCT00056264 ²⁰	- Current or former smokers - 30% <FEV₁ ≤ 80% - CRQ total <120 units	Negative Safety signal showed increased cancer risk²¹	No approval

Target pathway	Biologic	Biomarker strategy	Key COPD studies	Population studied	Key primary outcome efficacy findings	Current UK status
IL-33	Tozorakimab	Not biomarker restricted	TITANIA and OBERON ¹⁸ , MIRANDA ^e	- Current or former smokers - $FEV_1 \geq 20\%$ - Triple therapy - 2 moderate or 1 severe exacerbation in last year - $CAAT \geq 10$ - Dosing (2 weeks^h vs. 4 weeks)	Positive ⁱ (300mg dose every 4 weeks) 29% and 34% reduction in exacerbation frequency	Submitted for regulatory approval
ST2 (IL-33 receptor)	Astegolimab	Not biomarker restricted	ARNASA and ALIENTO ¹⁶	- Current or former smokers - $20\% < FEV_1 \leq 80\%$ - Dual or triple therapy - 2 moderate or 1 severe exacerbation in last year - $MRC \geq 2$ - Dosing (2 weeks vs. 4 weeks)	Mixed 15% reduction in exacerbations for 2 weekly dosing and 7-18% reduction in exacerbations for 4 weekly dosing.	No approval
IL-33	Itepekimab	Not biomarker restricted	AERIFY-1 and AERIFY-2 ¹⁷	- Former smokers^j - Dual or triple therapy - 2 moderate or 1 severe exacerbation in last year	Mixed 2-27% reduction in exacerbations for 2 weekly dosing and 12 to 21% reduction in exacerbations for 4 weekly dosing	No approval
TSLP	Tezepelumab	Eosinophil enrichment ^k	JOURNEY EMBARK	- Current or former smokers - $20\% < FEV_1 \leq 70\%$ - Triple therapy	Ongoing evaluation	Investigational

Target pathway	Biologic	Biomarker strategy	Key COPD studies	Population studied	Key primary outcome efficacy findings	Current UK status
				- 2 moderate or 1 severe exacerbation in last year - CAAT ≥ 15		
IL5 (ultra long acting)	Depomokimab	Blood eosinophils ^a	ENDURA 1 ENDURA 2 VIGILANT	- Current or former smokers - 30% $<FEV_1 \leq 80\%$ - Triple therapy - 2 moderate or 1 severe exacerbation in last yearⁱ	Ongoing evaluation	Investigational
TSLP, IL13	Lunsekimig	Eosinophil enrichment ^k	PERSEPHONE THESEUS	- Current or former smokers - 20% $< FEV_1 \leq 70\%$ - Triple therapy - 2 moderate or 1 severe exacerbation in last year^e - CAAT ≥ 10	Ongoing evaluation	Investigational
IL4, IL13, TSLP	Tilrekimig	Eosinophil enrichment ^k	NCT07363694	- Current or former smokers - Dual or triple therapy - 2 moderate or 1 severe exacerbation in last year	Ongoing evaluation	Investigational
^a Blood eosinophil count ≥ 300 cells/ μ L at screening or randomisation visit; ^b MATINEE study only; ^c METREO study only; ^d MATINEE and METREX study only; ^e completed, awaiting peer-review publications; ^f triple only in RESOLUTE; ^g GALATHEA and TERRANOVA studies only; ^h dosing was every 2 weeks in MIRANDA only; ⁱ primary analysis in former smokers; ^j primary analysis in former smokers across both studies, but AERIFY-2 included cohort of current smokers; ^k Blood eosinophil count ≥ 150 cells/ μ L at screening or randomisation visit; ^l VIGILANT includes 1 moderate exacerbation in previous year. CRQ <i>Chronic respiratory questionnaire</i> ²² ; MRC <i>Medical Research Council dyspnoea score</i> ²³ ; CAAT <i>The Chronic Airways Assessment Test</i> ²⁴ ; FEV ₁ <i>forced expiratory volume in 1 second</i> ; FVC <i>forced vital capacity</i> . Positive and negative allocation aligned to primary outcome efficacy.						

170 4.1 Identifying patients who may benefit from biologic therapy

171 Biologics should be considered as an additional component of comprehensive COPD
172 management, which includes five fundamentals as established interventions²⁵. Identification
173 of potentially eligible patients should be equitable, proactive and systematic, occurring across
174 primary, community and secondary care settings.

175 Evidence supports the use of biologic therapies in patients with recurrent exacerbations
176 despite optimal inhaled therapy. Thus, all patients with this clinical phenotype should be
177 considered for treatment with biologics. Identifying both clinical and inflammatory
178 components is important when considering referral for biologics assessment.

179

180 *Identifying the clinical phenotype*

181 The primary benefit from biologics in COPD is in reducing the incidence of exacerbations. The
182 clinical characteristic associated with biologic responsiveness should be recurrent
183 exacerbations. These patients have the greatest risk of further exacerbations²⁶, poor quality of
184 life²⁷, accelerated decline in lung function²⁸, and risk of mortality²⁹. Clinical trials evaluating
185 efficacy of biologics have recruited patients with a history of prior exacerbations, with study
186 entry requiring at least 2 moderate and/or 1 severe exacerbation in the prior 12 months.

187 Accurate identification of exacerbation burden can be a challenge. A prior exacerbation history
188 predicts risk of future exacerbations²⁶ and could be used to identify people at risk. Clinic
189 consultations often rely on patient recall determining exacerbation history and has shown poor
190 reliability³⁰. Self-reporting of exacerbations may underestimate or overestimate the burden³¹.
191 Use of oral corticosteroids (OCS) is associated with worse outcomes^{32,33}. Prescribing of
192 rescue packs may not routinely be recorded as an exacerbation on electronic health records
193 (EHR) when a repeat prescription is requested, thereby underestimating the number of
194 exacerbations leading to missing potential patients suitable for biologics. We suggest that
195 whenever possible, exacerbation frequency should be confirmed using additional resources,
196 such as searching within prescribing and dispensing records across healthcare settings and
197 the use of digital patient centred platforms.

198

199 *Identifying the inflammatory endotype*

200 The peripheral blood eosinophil count is a practical surrogate for identifying the different
201 inflammatory endotypes in patients with COPD, as a higher level can indicate type 2
202 inflammation and a lower level could suggest type 1 or 3 inflammation. Routinely, a full blood
203 count is completed as part of NICE guidance³⁴. As the measurement of a full blood count is
204 already part of routine care, recording the blood eosinophil count should now also be part of
205 this practice. Interpretation of blood eosinophil counts includes the consideration of timing.
206 Blood eosinophil counts are suppressed by systemic corticosteroids and during acute bacterial
207 infection³⁵. There is little interaction between blood eosinophil counts with inhaled
208 corticosteroids in COPD and these do not need to be withheld for sampling interpretation.
209 Blood eosinophil counts can be raised in patients with parasitic infection, but unless a patient
210 has a history of travel to a parasite endemic country, there is no requirement to routinely test
211 for parasitic infection. Within an individual COPD patient, the blood eosinophil count is
212 repeatable³⁵, whilst timing of sampling can affect the resulting inflammatory endotype
213 classification, usually underestimating type 2 inflammation during severe exacerbations of
214 COPD³⁶. Entry into the clinical trials of type 2 biologics required a blood eosinophil count of 300

215 cells/ μ L (or 0.3×10^6 cells/L) at least once in the screening or randomisation visit. Whilst there
216 are no current validated biomarkers for type 1 and type 3 inflammatory endotypes of COPD,
217 entry to clinical trials evaluating these pathways (such as anti-IL33) did not require an
218 eosinophil cut-off. The committee considers that review of serial blood eosinophil
219 measurements provides a more representative assessment of inflammatory endotype than a
220 single result alone, especially one that is <300 cells/ μ L.

221

222 *Asthma and smoking status*

223 The committee does not consider a current or historical diagnosis of asthma to be a barrier to
224 consideration of biologic therapy in patients with COPD. Type 2 inflammation occurs in
225 multiple diseases³⁷ and clinical overlap between asthma and COPD can commonly exist^{38,39}.
226 Treatment decisions should therefore be guided by the predominant clinical presentation.

227 Similarly, current smoking should not preclude consideration of biologic therapy. Active
228 smokers remain at high risk of exacerbations and adverse outcomes^{9,40}. Inflammation occurs
229 in both former and active smokers⁴¹⁻⁴³ but the response to inhaled corticosteroids is reduced
230 in active smokers leading to increased risk of exacerbations⁹. In many of the biologics clinical
231 trials, active smokers were included, with efficacy irrespective of smoking status^{11-13,16,18}.
232 Smoking cessation and tobacco dependency support should continue to be offered at every
233 opportunity.

234

235 *Opportunities for case finding*

236 Primary, integrated and secondary care services should develop pathways that enable
237 systematic identification of patients potentially eligible for biologics, reducing bias and
238 improving uptake for access. Attention should be paid to reducing healthcare inequalities and
239 ensuring equitable access for populations underserved by healthcare services, including those
240 living in areas of socioeconomic deprivation, communities with limited healthcare
241 engagement and groups traditionally underrepresented in specialist respiratory services⁴⁴.
242 Respiratory champions and public health clinicians should support the delivery of
243 identification approaches.

244 Primary care EHRs and electronic capture of data are highly successful and well-regarded in
245 the UK and globally. Opportunities to identify eligible patients should maximise the ability to
246 retrieve data from individual patients and practices. All healthcare professionals looking after
247 people living with COPD, should be trained and educated on biologics in COPD.

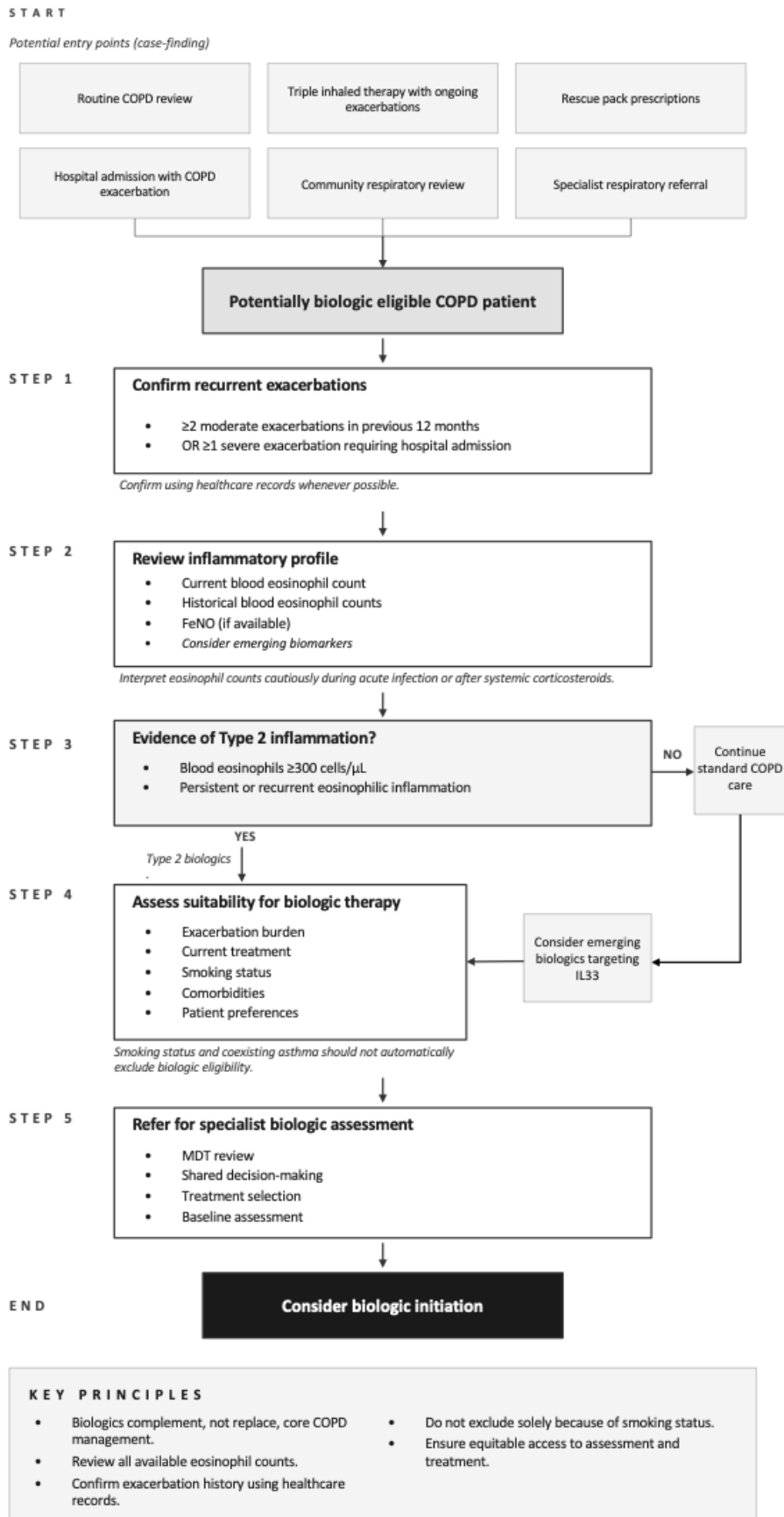
248 Potential eligible patients may be identified through several routes, by any member of the
249 COPD team, working in primary, integrated and secondary care:

- 250 • Routine COPD consultation
- 251 • Review of people living with COPD receiving triple inhaled therapy and still exacerbating
- 252 • Review of people living with COPD prescribed rescue packs
- 253 • Following hospital admission for an exacerbation of COPD
- 254 • Referral to specialist services including those in community settings

255

256

Figure 2. Five-step pathway for identification and referral of patients with COPD for biologic assessment



258

259 **Clinical practice points**

- 260 1. People living with COPD who experience recurrent exacerbations despite optimised inhaled
261 therapy should be assessed for potential eligibility for biologic therapy.
- 262 2. When considering suitability of biologics, exacerbation history should be confirmed using
263 available healthcare records wherever possible, rather than relying solely on patient recall.
- 264 3. All available blood eosinophil counts should be reviewed routinely as an assessment for
265 eligibility of biologics. If there are no blood counts available at stable state (outside an
266 exacerbation), then a full blood count should be performed.
- 267 4. Historical eosinophil measurements should be considered when assessing eligibility for
268 type 2 targeted biologic therapy, particularly if recent systemic corticosteroid treatment
269 may have influenced results.
- 270 5. If available, blood eosinophil counts at or around the time of an exacerbation should be
271 reviewed, to determine if eosinophilic exacerbations are a driving feature as this may also
272 indicate suitability for biologics targeting type 2 inflammation.
- 273 6. When considering suitability for biologics, a history of former, or current asthma should not
274 be an exclusion.
- 275 7. When considering suitability of biologics, active smokers should not be excluded based on
276 smoking status. Active smokers should be supported using evidence-based interventions.
- 277 8. In people living with COPD in whom a rescue pack has been prescribed, the eosinophil
278 blood count should be reviewed to support assessment of the underlying inflammatory
279 phenotype.
- 280 9. All healthcare practitioners managing COPD should be provided training and education on
281 biologics, for patient eligibility and management.

282

283

284

285 **4.2 Assessment and commencing a biologic**

286 People living with COPD identified as potential candidates for biologic therapy should undergo
287 a structured assessment to confirm eligibility and establish the likelihood of treatment
288 response, including decisions to review continuation or offering alternative treatment.
289 Assessment should support timely access to treatment while maintaining high-value care. The
290 purpose of assessment (table 2) is not to create additional barriers to treatment but to ensure
291 that biologic therapy is targeted towards individuals most likely to benefit.

292 Table 2. Suggested minimal assessment

Assessment		Value 1 (date)	Value 2 (date)
Clinical	Exacerbations in previous 12 months	#	#
	Severe (hospitalised) exacerbations	#	#
	Smoking status	Y/N	Y/N

Assessment		Value 1 (date)	Value 2 (date)
	Triple inhaled therapy	Y/N	Y/N
	Long-term prednisolone use	Y/N	Y/N
	Comorbidities	Y/N	Y/N
Biomarkers	Most recent blood eosinophil count	#	#
	FeNO (if available)	#	#
Patient-reported outcomes	MRC or CAAT score	#	#
Lung function:	FEV ₁ (L)	#	#
	FVC (L)	#	#
	FEV ₁ % predicted	#	#
	FEV ₁ /FVC	#	#

FeNO fractional exhaled nitric oxide; MRC Medical Research Council dyspnoea score²³; CAAT The Chronic Airways Assessment Test²⁴; FEV₁ forced expiratory volume in 1 second; FVC forced vital capacity. Highest recorded in the last 4 years

Confirmation of the clinical inflammatory phenotype

The primary evidence base for biologics therapy in COPD is derived from patients with recurrent exacerbations despite optimised inhaled therapy. Attention should be paid to:

- Number of moderate exacerbations requiring antibiotics or corticosteroids in the preceding 12 months
- Number of severe exacerbations requiring hospital admission
- For biologics targeting type 2 inflammation, evidence of an elevated eosinophil count, of 300 cells/ μ L.

Whilst the studies measured the peripheral blood eosinophil count close to randomisation as part of strict trial design, the committee does not recommend that suitability of a biologic relies on an eosinophil measurement within a short time frame of prescription. This recommendation is in line with both NICE^{45,46} and NHSE⁴⁷ and is supported to remove extra barriers and delays, reduce additional cost and inefficiency within services providing treatment. Evidence supporting the stability of an eosinophil count is established³⁵ and a single measurement of 300 cells/ μ L is associated with high likelihood of significant type 2 inflammation⁴⁸. Opportunities to review serial eosinophil counts should be taken.

Selecting a biologic therapy

At the time of publication, evidence supporting biologic therapy in COPD is strongest for agents targeting type 2 inflammation^{45,46}. Selection of an individual biologic should be guided by current regulatory approvals, national commissioning arrangements, biomarker profile (if relevant) and patient preference. Where multiple biologic options are available, treatment selection should be individualised and informed by the evolving evidence base. At present there is insufficient evidence to recommend one biologic preferentially over another in otherwise eligible patients. However, post market surveillance data may inform sequencing in future⁴⁹. An example initiation pathway is illustrated in Fig 3.

322

323 *Multidisciplinary review and shared decision-making*

324 Patients should be actively involved in treatment decisions. Discussions applying the benefits,
325 risks, alternative, do nothing (BRAN) model⁵⁰ should include anticipated benefits,
326 uncertainties regarding treatment response, any requirement for monitoring, potential adverse
327 effects and the likely timeframe over which benefits may become apparent. Decisions to
328 initiate a biologic should be undertaken by a multidisciplinary team (MDT)⁵¹ developed locally
329 (virtual, hybrid, or face-to-face), to include a minimum of two COPD focussed respiratory
330 physicians and one pharmacist. Additional members of the COPD multidisciplinary team such
331 as the respiratory nurse, respiratory physiotherapist, and primary care practitioner can be
332 invited. The role of the multidisciplinary team is to:

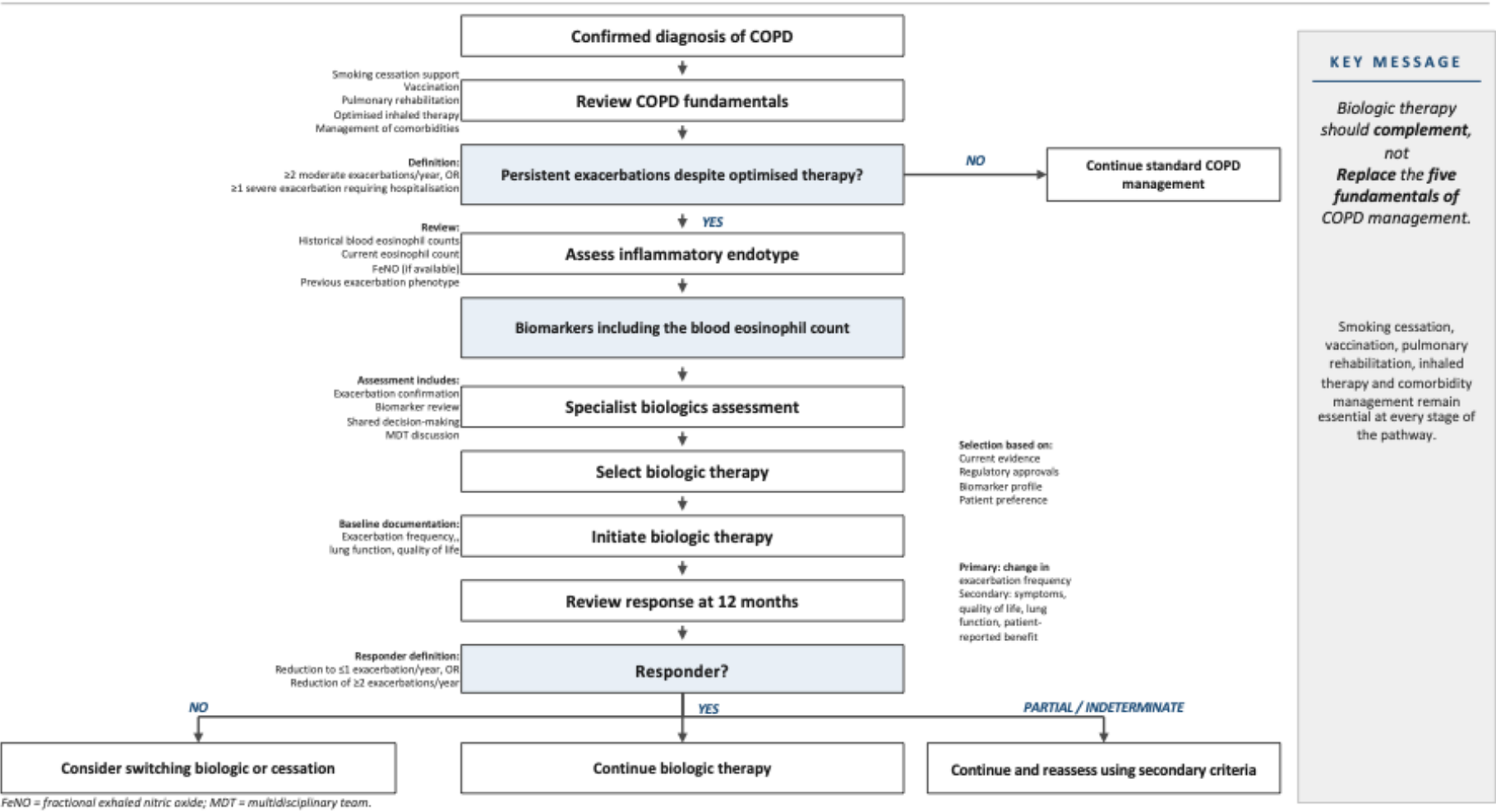
- 333 - Confirm eligibility
- 334 - Support treatment selection
- 335 - Facilitate equitable access to therapy

336

337

338

Figure 3. Optimised COPD treatment pathway for biologic therapy initiation



343 *Equity and minimising unwarranted variation*

344 Services should be organised to reduce health inequalities by avoiding de-facto exclusion of
 345 people facing barriers to engagement (e.g., transport, carer duties, language, digital access,
 346 adverse social determinants) and taking an equity approach. Where a person does not
 347 complete elements of the fundamentals of care, such as pulmonary rehabilitation or continues
 348 to smoke, this should not deny eligibility for biologic therapy when clinical criteria are
 349 otherwise met. Instead, clinicians should identify and address barriers while continuing with
 350 the biologic care plan, in line with the statement's principle that fundamentals should be
 351 delivered but not used as a gatekeeping step. Common pitfalls when assessing patients with
 352 COPD for biologic therapy are listed in table 3. Learnings from other chronic disease
 353 management shows that delays from MDT decision to first dose are associated with increased
 354 harm and worsened outcomes^{52,53}. The committee recommends that once the MDT confirms
 355 suitability, the first dose initiation should occur within 30 days of the MDT decision.

356 Table 3. Common pitfalls in assessment for biologics therapy

Assessment domain	Potential pitfall	Clinical implication	Suggested approach
Exacerbation history	Reliance on patient recall alone	Under- or over-estimation of exacerbation burden	Confirm using primary care records, rescue pack prescriptions, hospital admissions and electronic healthcare records
Rescue pack use	Rescue packs prescribed or collected without exacerbation coding	Eligible patients may not be identified	Review repeat prescriptions and pharmacy records when assessing exacerbation frequency
Blood eosinophil count	Measurement taken during or shortly after oral corticosteroid treatment	Falsely low eosinophil count	Review historical results and repeat measurement when clinically stable if required
Blood eosinophil count	Measurement during acute infection	Suppression of eosinophil count	Interpret cautiously and review previous results
Blood eosinophil count	Reliance on a single eosinophil measurement	Misclassification of inflammatory endotype	Review serial eosinophil counts where available
Symptom deterioration	Day-to-day symptom variability interpreted as exacerbations	Inappropriate biologic assessment	Confirm that 'events' meet accepted exacerbation definitions
Smoking status	Assuming active smoking excludes biologic eligibility	Potential inequity in access	Continue smoking cessation support but do not exclude solely on smoking status
Asthma history	Excluding patients with co-existing asthma and COPD	Missed treatment opportunities	Consider the predominant clinical phenotype and relevant licensing arrangements

Assessment domain	Potential pitfall	Clinical implication	Suggested approach
Healthcare access	Failure to identify patients from underserved populations	Widening health inequalities	Use systematic case-finding approaches across primary, community and secondary care settings

357

358 Clinical Practice Points

- 359 1. Optimisation of standard COPD care should occur alongside biologic assessment and
360 should not be used as a barrier to accessing treatment.
- 361 2. Biologic therapy should be initiated within a structured service with appropriate COPD
362 expertise, supported by multidisciplinary review and shared decision-making.
- 363 3. Shared decision making should form part of all biologic treatment initiation discussions
- 364 4. Patients should receive education regarding biologic treatment administration, monitoring
365 and expected outcomes.
- 366 5. Selection of biologic agent should be guided by current evidence, regulatory approvals,
367 commissioning arrangements and patient preference.
- 368 6. Baseline assessment should include documentation of exacerbation burden and other
369 measures that will support future assessment of biologic treatment response

370 4.3 Ongoing treatment with biologic therapy

371 Initiation of biologics can occur where clinically appropriate and supported through agreed
372 commissioning arrangements, community-based services, virtual review pathways and
373 homecare delivery models. Following initiation, biologic therapy may be administered through
374 a range of service models, including secondary care, integrated care and home care provision.
375 The optimal model will vary according to national funding arrangements, local resources,
376 infrastructure and workforce availability. Regardless of the delivery model, patients should
377 have access to a multidisciplinary team with appropriate expertise and clinical governance
378 oversight. In keeping with NHS priorities, delivering more care in the community, closer to
379 home and avoiding inappropriate hospital attendances where possible should be a goal.

380 Service delivery models could include:

- 381 1. Secondary care led: Delivery within secondary care, including use of virtual or telephone
382 clinics for stable patients
- 383 2. Integrated care: Delivery by community respiratory teams or primary care with access to
384 specialist COPD input as needed
- 385 3. Hub-and-spoke: For complex cases (e.g., with coexistent hyperinflation assessment, or
386 ventilatory failure) delivery in tertiary centres with maintenance managed locally

387

388 *Monitoring treatment response*

389 Monitoring of biologic therapy is essential to ensure effective use of healthcare resources and
390 to identify individuals delivering meaningful clinical benefits. Assessment should include:

- 391 - Exacerbation frequency

- Hospital admission and unscheduled healthcare utilisation
- Adverse effects
- Health-related quality of life
- Lung function where available
- Reduction in oral corticosteroid cumulative dosing

Clinical trials have primarily assessed efficacy through reduction in moderate and severe exacerbations over a 12-month period, with continuation of inhaled therapy throughout^{11-13,16}. There is no role in measuring blood eosinophil counts as a marker of response and no role in stopping inhalers during treatment with biologics. The committee therefore considers annual exacerbation frequency to be the principal measure of biologic therapy effectiveness in routine clinical practice. Patients with COPD should not necessarily expect rapid or dramatic improvements in symptoms following initiation of a biologic. The greatest treatment benefit may therefore be observed through reduction in future exacerbation risk rather than immediate symptomatic improvement. There were no new emerging safety signals for biologics in COPD.^{11-13,16,17}

Assessment of response to biologic therapy

Exacerbations are associated with substantial morbidity⁵⁴, healthcare utilisation⁵⁵, mortality⁵⁶ and cost⁵⁷, so even modest reductions in exacerbation burden may be clinically meaningful for individual patients⁵⁸. A rigid threshold for continuation or cessation risks disadvantaging frequent exacerbaters, in whom a substantial absolute reduction in exacerbation frequency will be important despite leaving a residual exacerbation burden. As there is no clear validated definition of biologic response in COPD, or what contributes as “good response”, the committee have developed a consensus framework to support clinical decision with primary and secondary response criteria. For this reason, response assessment at one and two years after initiation should focus on primary responses and secondary responses.

For the primary response criteria (table 4), the number of exacerbations in the year after biologic initiation should be compared to the number of exacerbations in the year before biologic therapy (exacerbation change). The treatment goal should be the prevention of exacerbations. Individuals whose exacerbation frequency falls to zero or one exacerbation per year, or who experience a reduction of two or more exacerbations annually, should generally be regarded as responders and continue treatment. This response is measured in moderate and severe exacerbations.

Table 4. Primary criteria for assessing biologic therapy response

Exacerbation change	Exacerbation total after 12m	Category	Management
Reduction to ≤ 1	0 or 1	Responder	Continue biologic
Reduction by ≥ 2	Any	Responder	Continue biologic
Reduction by 1	≥ 1	Partial ^{*L} responder	Continue biologic

			Evaluate at 2 years after initiation with primary and secondary criteria
No change or increase by 1	≥2	Indeterminate response*	Evaluate secondary criteria for additional assessment of response Consider continuation, alternative, or cessation of biologic
Increase by ≥2	Any	Non-responder*	Consider biologics alternative or cessation

These response criteria represent expert consensus and have not yet been prospectively validated. *For primary partial, indeterminate and non-responders, re-evaluate five fundamentals and whether additional therapy is required including macrolides, oxygen therapy, non-invasive ventilation, lung volume reduction surgery, or transplant. [†]If there is partial response at 1 year after initiation, continue biologics for a further 1 year and evaluate both primary and secondary criteria before continuation, alternative or discontinuation of biologics.

Where the impact on exacerbation burden is less clear (e.g., in primary partial responders or those with primary indeterminate response), secondary response criteria including quality of life, symptom burden, lung function and patient reported improvement should be considered (table 5). No single secondary outcome should determine treatment success in isolation.

Table 5. Secondary criteria for assessing biologic success in COPD

Outcome	Positive Response	Undetermined Response	No Response or disease worsening
Quality of Life e.g., CAAT ²⁴ SGRQ ^{59,60} MRC ²³	CAAT reduced by 2 points or more, and/or SGRQ reduced by 4 points or more, and/or MRC reduced by 1 point or more.	CAAT reduced by 1 point or increased by 1 point and/or SGRQ reduced or increased by up to 3 points, and/or No change in MRC	CAAT increased by 2 points or more, and/or SGRQ increased by 4 points or more, and/or MRC increased by 1 point or more.
Visual analogue scale score⁶¹ e.g., domains of Cough	All domains improve by 1	Some domains improve by 1	No domains improve

Dyspnoea Sputum production			
Lung function (FEV₁)	An absolute increase in FEV ₁ of 50mL or more ⁶² An FEV ₁ decline that is better than age-related lung function loss (i.e., below 25mL per year) ⁶³	An absolute increase in FEV ₁ of less than 50mL, or an absolute reduction of FEV ₁ of up to 100mL	An absolute reduction in FEV ₁ of 100mL or more ⁶²
Clinical Response	"I feel better"	'I do not feel any different'	"I feel worse"

441

442 *Continuation, switching and cessation*

443 Patients classified as responders should continue biologic therapy. For individuals with a
444 partial or indeterminate response, reassessment using both primary and secondary response
445 criteria is recommended. These patients may continue treatment while additional data are
446 gathered regarding long term benefit. Patients demonstrating worsening exacerbation burden
447 despite biologic treatment should undergo specialist review for additional therapeutic review.
448 Potential explanations for deterioration include disease progression, comorbidity or lack of
449 biological effectiveness. Cessation should be considered where there is no evidence of
450 response according to the primary and secondary response criteria outlined in Tables 4 and 5,
451 or where the burden of treatment outweighs any observed clinical benefit. If adverse effects
452 attributable to biologic therapy are judged to outweigh clinical benefit, the patient and treating
453 team may make a shared decision to discontinue treatment. Treatment-emergent adverse
454 events have been broadly comparable between biologics and placebo in clinical trials^{11-13,16};
455 however, individual tolerability, treatment burden and patient preference remain important
456 considerations.

457 Where cessation is indicated, biologic therapy can be stopped without dose tapering. Stopping
458 biologic therapy should not prevent future reassessment, particularly if emergent biologic
459 options become available or if there is a marked deterioration following treatment withdrawal.
460 As additional biologic therapies become available, switching between agents may become an
461 important component of COPD management. Although evidence remains limited, the
462 committee considers it reasonable to adopt principles of switching due to partial or inadequate
463 response, adverse effects or evolving eligibility for alternative therapies.

464

465 *Registry participation and real-world data*

466 The introduction of biologic therapies provides an important opportunity to improve
467 understanding of treatment effectiveness in routine clinical practice. Participation in a national
468 biologic registry should be regarded as a core component of biologic service delivery. Services
469 should contribute to national audits, research programmes and quality improvement
470 programmes. Standardised collection of clinical outcomes, treatment persistence, adverse
471 events and equity of access will be essential for understanding long-term effectiveness and

informing future service development. Automated data capture and linkage to existing healthcare datasets should be encouraged wherever feasible.

Clinical practice points

1. Ongoing biologic therapy should be supported by a multiprofessional respiratory team, regardless of the service model used.
2. Annual exacerbation frequency should be regarded as the primary measure of biologic effectiveness in COPD.
3. Response assessment should incorporate both exacerbation burden and wider measures of disease impact, including quality of life and patient-reported outcomes.
4. Patients who demonstrate a clinically meaningful reduction in exacerbation frequency should continue biologic therapy.
5. Patients with uncertain response should undergo reassessment using both primary and secondary response criteria before decisions regarding continuation or cessation of biologic therapy is made.
6. There should be no discontinuation of inhaled therapy whilst on biologic therapy
7. Services prescribing and managing biologic therapies should contribute to national registry and audit programmes to support surveillance and generation of real-world evidence.

5. Biologic therapies and acute exacerbations of COPD

Severe exacerbations which lead to emergency department attendance or hospitalisation identifies a population at particularly high risk of future exacerbations, readmission and death⁶⁴. Individuals with severe exacerbations therefore represent an important group in whom consideration of future biologic therapy may be appropriate.

Although biologic therapies have primarily been studied as exacerbation prevention strategies in clinically stable COPD^{10-13,16,19}, there is increasing interest in biologics as treatment for the acute exacerbation⁶⁵, or initiation of biologics following hospital discharge⁶⁶. This approach is based on the observation that a proportion of exacerbations are characterised by eosinophilic inflammation and may therefore represent an acute manifestation of type 2 inflammation amenable to acute targeted therapy. The phase 2 ABRA study⁶⁵ evaluated benralizumab as treatment for acute eosinophilic exacerbations of asthma and COPD in individuals with blood eosinophil counts ≥ 300 cells/ μ L. Compared with prednisolone alone, benralizumab-containing treatment strategies reduced treatment failure and prolonged time to subsequent exacerbation, supporting the concept that eosinophilic exacerbations represent a biologically distinct and treatable event³. Whilst the study included both asthma and COPD populations and was not designed specifically to evaluate COPD outcomes, it provides important proof-of-concept that biologic therapies have a role beyond long-term exacerbation prevention. The COPD-HELP study⁶⁶ was a phase 2 study evaluating mepolizumab, initiated following hospitalisation for a severe exacerbation of eosinophilic COPD, in people with a blood eosinophil count ≥ 300 cells/ μ L in the preceding 12 months. Compared with placebo, monthly mepolizumab did not significantly reduce the risk of readmission or death but did show numerical reduction in moderate or severe exacerbations over a 12-month period. These studies raise important questions about identifying patients with highest risk and opportunities to intervene, either for acute therapy or maintenance therapy. Further clinical trials comparing standard of care versus initiating biologics in hospitalised COPD exacerbations are awaited with rademikibart [NCT06940154], dupilumab [NCT07587658] and in a sub-set of patients with

516 tozorakimab [NCT05624450]. These studies reflect a broader shift towards precision medicine
517 approaches in acute exacerbations of COPD. Rather than viewing all exacerbations as a single
518 clinical entity, the evidence suggests that inflammatory endotyping may allow targeted
519 treatment strategies to be deployed during acute events. However, current evidence remains
520 insufficient to recommend initiation of biologic therapy during acute exacerbations outside of
521 clinical trials. Further studies are required to establish efficacy, safety, patient selection
522 criteria and cost-effectiveness before implementation can occur in routine practice.

523 Hospitalisation provides an important opportunity to identify patients who may benefit from
524 future assessment. Individuals admitted with an exacerbation despite optimised inhaled
525 therapy should have their eligibility for biologic assessment considered as part of discharge
526 planning and post-exacerbation review. Services should develop pathways that facilitate
527 identification of potentially eligible patients following hospitalisation. This may include review
528 of exacerbation history, assessment of blood eosinophil counts, referral to specialist COPD
529 services and incorporation of biologic assessment into existing post-discharge care pathways.
530 Such approaches may help reduce delays in treatment assessment and improve access to
531 specialist review. Referral to a biologics MDT is recommended within 3 months of hospital
532 discharge.

533

534 **Clinical Practice Points**

- 535 1. Hospital admission for an exacerbation of COPD should be recognised as a marker of high
536 future exacerbation risk and an opportunity to identify patients who may benefit from
537 biologic assessment.
- 538 2. There is currently insufficient evidence to recommend initiation of biologic therapy during
539 an acute exacerbation of COPD.
- 540 3. Discharge and post-exacerbation review pathways should incorporate assessment for
541 future biologic eligibility where appropriate.
- 542 4. Emerging evidence suggests that eosinophilic exacerbations may represent a biologically
543 distinct and potentially treatable inflammatory endotype; however, the role of biologic
544 therapies as acute exacerbation treatments remains investigational.

545

546

547

548

549

550

551

552

553 6. Future considerations and research priorities

554 The introduction of biologic therapies represents one of the most significant advances in COPD
555 management in recent decades. For the first time, treatments targeting specific inflammatory
556 pathways have demonstrated clinically meaningful reductions in exacerbation burden in
557 selected patient populations. These developments signal the beginning of a precision
558 medicine era in COPD, in which treatment selection may increasingly be guided by biological
559 characteristics rather than clinical phenotype alone.

560 Despite this progress, substantial uncertainties remain regarding the optimal implementation
561 of biologic therapies in routine practice. The populations enrolled in clinical trials represent
562 only a proportion of the wider COPD population encountered in clinical services. Further
563 evidence is therefore required to understand treatment effectiveness in older adults,
564 individuals with multiple comorbidities and populations experiencing socioeconomic
565 disadvantage who have historically been underrepresented in clinical research.

566 Current evidence is strongest for biologic therapies targeting type 2 inflammatory pathways.
567 However, COPD is a biologically heterogeneous condition, and many patients demonstrate
568 evidence of type 1 and/or 3 inflammation⁴³. The development of therapies targeting alternative
569 inflammatory mechanisms⁶⁷ and other upstream inflammatory pathways⁶⁸, may further
570 expand treatment options and improve outcomes for individuals.

571 A key priority is the identification and validation of biomarkers that can more accurately predict
572 treatment response. Blood eosinophil count is currently the most widely used biomarker in
573 COPD biologic studies and clinical practice³⁵. The role of fractional exhaled nitric oxide (FeNO)
574 in identifying patients with COPD who may benefit from biologic therapy remains uncertain.
575 Subgroup analyses of the BOREAS and NOTUS trials suggested greater reductions in
576 exacerbation frequency with dupilumab among patients with both higher blood eosinophil
577 counts and FeNO levels ≥ 20 ppb^{11,12}. However, these findings should be interpreted cautiously
578 as FeNO measurements are influenced by multiple factors, including smoking status and
579 corticosteroid exposure⁶⁹, which were not fully accounted for in these analyses. At present,
580 FeNO may provide supportive evidence of type 2 inflammation but should not be used in
581 isolation to determine eligibility for biologic therapy. Further prospective studies are required
582 to establish its role as a predictive biomarker and to determine whether combining FeNO with
583 blood eosinophil counts improves identification of patients most likely to benefit from biologic
584 treatment targeting type 2 inflammation. Future research should explore multimodal
585 approaches incorporating clinical characteristics, physiological measurements, imaging and
586 molecular biomarkers to better define biologically distinct COPD endotypes.

587 The optimal timing of biologic therapy within the COPD treatment pathway remains uncertain.
588 Future studies should evaluate whether earlier intervention can alter disease trajectory,
589 reduce healthcare utilisation and improve long-term outcomes. Further research is required to
590 determine the role of biologics following severe exacerbations and whether treatment initiation
591 during, or shortly after, hospitalisation can reduce the risk of future admissions.

592 Important evidence gaps also remain regarding switching between biologic therapies,
593 sequencing of treatments and criteria for discontinuation. As additional therapies become
594 available, understanding how best to select and transition between agents will become

595 increasingly important. Long-term follow-up studies will be required to establish durability of
596 response, long-term safety and the consequences of treatment withdrawal.

597 The committee considers collection of high-quality real-world data to be a research and
598 service priority. National registries and audit programmes will be essential to understand
599 treatment uptake, effectiveness, safety and equity of access. Attention should be paid to
600 ensuring that biologic therapies do not widen existing health inequalities in COPD care.
601 Monitoring access across geographical regions, socioeconomic groups and traditionally
602 underserved populations should form part of ongoing service evaluation.

603 Future research should also consider outcomes beyond exacerbation reduction alone. While
604 prevention of exacerbations remains a key treatment objective, patients consistently identify
605 symptoms, physical function, independence and quality of life as outcomes of equal
606 importance. Studies evaluating the impact of biologic therapies on these domains, as well as
607 their potential effects on disease progression, lung function decline and survival, are therefore
608 needed.

609 Important questions remain regarding the safety, efficacy and optimal timing of treatment
610 initiation during hospitalised exacerbations of COPD. As evidence evolves, future studies
611 should evaluate whether biologic therapy initiated during, or shortly after, an exacerbation can
612 reduce the risk of recurrent exacerbations, readmission and disease progression. These
613 questions represent important priorities for future research.

614 As the evidence base evolves, biologic therapies are likely to become increasingly integrated
615 within comprehensive COPD care pathways. Continued collaboration between clinicians,
616 researchers, patients, professional societies, healthcare providers and industry partners will
617 be essential to ensure that advances in precision medicine translate into meaningful
618 improvements in outcomes for people living with COPD.

619

620 **Research priorities**

621 Table 6. **Key research priorities for biologic therapies in COPD**

Research area	Priority research questions
Biomarkers and patient selection	How can blood eosinophils, FeNO, imaging and molecular biomarkers be combined to improve identification of patients most likely to benefit from biologic therapy?
Acute exacerbations	Can biologic therapies be initiated during, or shortly after, an acute exacerbation improve recovery, reduce treatment failure, prevent readmission and reduce future exacerbation risk?
Response assessment and treatment optimisation	What constitutes a clinically meaningful response to biologic therapy in COPD, and what are the optimal strategies for treatment monitoring, switching and discontinuation?
Non-type 2 inflammatory COPD	How can biologic and other targeted therapies be developed for patients with COPD who do not demonstrate evidence of type 2 inflammation?
Long-term outcomes	What impact do biologic therapies have on lung function decline, disease progression, healthcare utilisation, survival and patient-reported outcomes and experiences?
Combination and adjunct therapies	How do other therapies (macrolides, PDE4, PDE3/4 inhibitors) influence efficacy with biologics?
Real-world implementation	How can biologic therapies be delivered safely, effectively and equitably in routine practice, including through national registries and integrated care pathways?

622
623 **Summary**

624 Biologic therapies represent a major advancement in the management of COPD and are the
625 first targeted treatments to demonstrate clinically meaningful reductions in exacerbation
626 burden in selected patient populations. The emergence of therapies directed against type 2
627 inflammatory pathways marks an important step towards precision medicine in COPD and
628 challenges the traditional view of COPD as a single inflammatory disease.

629 Successful implementation of biologic therapies will require systematic case-finding,
630 equitable access to specialist assessment, multidisciplinary decision-making and robust
631 monitoring of treatment response. Biologics should complement, rather than replace,
632 established components of COPD care including smoking cessation support, pulmonary
633 rehabilitation, vaccination, optimisation of inhaled therapy and management of comorbidities.

634 Important uncertainties remain regarding optimal patient selection, assessment of treatment
635 response, biologic sequencing, duration of therapy and the role of biologics during acute
636 exacerbations. Continued collection of real-world data through national registries and audit
637 programmes will be essential to inform future practice and ensure equitable delivery of these
638 therapies.

639 This Clinical Statement provides a framework for the identification, assessment and ongoing
640 management of patients with COPD receiving biologic therapy. As the evidence base continues
641 to evolve, these recommendations should be interpreted alongside emerging clinical trial data,
642 regulatory guidance and future national guidance.

643 BOX 1. Key Messages for Clinical Practice

I	Biologic therapies are an important new treatment option for selected people with COPD and recurrent exacerbations despite optimised inhaled therapy
II	Biologics should complement, not replace, the fundamentals of COPD care including smoking cessation support, vaccination, pulmonary rehabilitation, optimisation of inhaled therapy, and management of comorbidities.
III	COPD is a biologically heterogeneous disease; and identification of inflammatory endotype identifies subgroups of people most likely to benefit from currently available biologic therapies.
IV	Blood eosinophil count is currently the most clinically useful biomarker for identifying patients who may be suitable for biologic therapy.
V	Assessment for biologic therapy should include confirmation of exacerbation burden using healthcare records wherever possible and review of all available historical eosinophil measurements.
VI	A history of asthma or current smoking status should not automatically exclude consideration of biologic therapy in patients with COPD.
VII	Annual exacerbation frequency should be regarded as the primary measure of biologic treatment response in routine clinical practice.
VIII	Decisions regarding continuation, switching or cessation of biologic therapy should consider both exacerbation reduction and broader measures of clinical benefit.
IX	Hospital admission for an acute exacerbation should be recognised as an opportunity to identify patients who may benefit from future biologic assessment.
X	Participation in national registries and audit programmes should be encouraged to support evaluation of long-term effectiveness, safety and equitable access.

644

645

646

References

1. Stockley RA. Neutrophils and the pathogenesis of COPD. *Chest* 2002;121:151S-5S.
2. Wang Z, Bafadhel M, Haldar K, et al. Lung microbiome dynamics in COPD exacerbations. *Eur Respir J* 2016;47:1082-92.
3. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011;184:662-71.
4. Saha S, Brightling CE. Eosinophilic airway inflammation in COPD. *Int J Chron Obstruct Pulmon Dis* 2006;1:39-47.
5. Papi A, Belletato CM, Braccioni F, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006;173.
6. Agustí A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016;47:410-9.
7. Agustí A, Celli B, Faner R. What does endotyping mean for treatment in chronic obstructive pulmonary disease? *The Lancet* 2017;390:980-7.
8. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood eosinophils and exacerbations in chronic obstructive pulmonary disease. The Copenhagen General Population Study. *American journal of respiratory and critical care medicine* 2016;193:965-74.
9. Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med* 2018;6:117-26.
10. Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2017.
11. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. *N Engl J Med* 2023;389:205-14.
12. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation. *N Engl J Med* 2024;390:2274-83.
13. Sciurba FC, Criner GJ, Christenson SA, et al. Mepolizumab to Prevent Exacerbations of COPD with an Eosinophilic Phenotype. *N Engl J Med* 2025;392:1710-20.
14. Antus B, Barta I, Horvath I, Csiszer E. Relationship between exhaled nitric oxide and treatment response in COPD patients with exacerbations. *Respirology* 2010;15:472-7.
15. Polverino F, Sin DD. Type 2 airway inflammation in COPD. *European Respiratory Journal* 2024;63:2400150.
16. Papi A, Greening NJ, Bhatt SP, et al. Safety and efficacy of astegolimab for COPD with frequent exacerbations regardless of baseline blood eosinophil counts (ALIENTO and ARNASA): randomised, double-blind, placebo-controlled, phase 2b and 3 trials. *The Lancet* 2026;407:2027-39.
17. Rabe K, Martinez F, Bhatt SP, et al. e. Efficacy and safety of itepekimab in former smokers with COPD: AERIFY-1 and AERIFY-2 Trials [abstract]. *Am J Respir Crit Care Med* 2026;211.
18. Sciurba FC, Watz H, Bourdin A, et al. Tozorakimab to Prevent COPD Exacerbations. *N Engl J Med* 2026.
19. Criner GJ, Celli BR, Brightling CE, et al. Benralizumab for the Prevention of COPD Exacerbations. *N Engl J Med* 2019;381:1023-34.
20. Rennard SI, Fogarty C, Kelsen S, et al. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175:926-34.
21. Rennard SI, Flavin SK, Agarwal PK, Lo KH, Barnathan ES. Long-term safety study of infliximab in moderate-to-severe chronic obstructive pulmonary disease. *Respir Med* 2013;107:424-32.
22. Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;42:773-8.

- 698 23. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the
699 Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic
700 obstructive pulmonary disease. *Thorax* 1999;54:581-6.
- 701 24. Tal-Singer R, Chalmers JD, Jones PW, et al. The Chronic Airways Assessment Test
702 (CAAT™): Evolution From the COPD Assessment Test (CAT™). *Chronic Obstr Pulm Dis*
703 2025;12:203-6.
- 704 25. Hopkinson NS, Molyneux A, Pink J, Harrisingh MC. Chronic obstructive pulmonary disease:
705 diagnosis and management: summary of updated NICE guidance. *Bmj* 2019;366.
- 706 26. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive
707 pulmonary disease. *N Engl J Med* 2010;363:1128-38.
- 708 27. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of
709 exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *American*
710 *journal of respiratory and critical care medicine* 1998;157:1418-22.
- 711 28. Donaldson G, Seemungal TA, Bhowmik A, Wedzicha J. Relationship between exacerbation
712 frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;57:847-
713 52.
- 714 29. Whittaker H, Rubino A, Müllerová H, et al. Frequency and severity of exacerbations of COPD
715 associated with future risk of exacerbations and mortality: a UK routine health care data study.
716 *International journal of chronic obstructive pulmonary disease* 2022;427-37.
- 717 30. Frei A, Siebeling L, Wolters C, et al. The inaccuracy of patient recall for COPD exacerbation
718 rate estimation and its implications: results from central adjudication. *Chest* 2016;150:860-8.
- 719 31. Kessler R, Ståhl E, Vogelmeier C, et al. Patient understanding, detection, and experience of
720 COPD exacerbations: an observational, interview-based study. *Chest* 2006;130:133-42.
- 721 32. Tse G, Ariti C, Bafadhel M, et al. Oral Corticosteroid-Related Healthcare Resource Utilization
722 and Associated Costs in Patients with COPD. *Advances in Therapy* 2025;42:375-94.
- 723 33. Majeed A. Steroid Safety in Respiratory Primary Care: When “Short Courses” Cause Long-
724 term Harm. *Journal of Patient Safety* 2026.
- 725 34. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary
726 disease in adults in primary and secondary care. National Clinical Guideline Centre 2004 Royal
727 College of Physicians of London. <http://www.nice.org.uk/nicemedia/live/13029/49425/49425.pdf>.
- 728 35. Bafadhel M, Pavord ID, Russell REK. Eosinophils in COPD: just another biomarker? *Lancet*
729 *Respir Med* 2017;5:747-59.
- 730 36. Martínez-Gestoso S, García-Sanz M-T, Calvo-Álvarez U, et al. Variability of blood eosinophil
731 count and prognosis of COPD exacerbations. *Annals of Medicine* 2021;53:1153-9.
- 732 37. Rosenberg HF, Dyer KD, Foster PS. Eosinophils: changing perspectives in health and disease.
733 *Nature Reviews Immunology* 2013;13:9-22.
- 734 38. Abramson MJ, Perret JL, Dharmage SC, McDonald VM, McDonald CF. Distinguishing adult-
735 onset asthma from COPD: a review and a new approach. *International journal of chronic obstructive*
736 *pulmonary disease* 2014;945-62.
- 737 39. Stolz D, Mkorombindo T, Schumann DM, et al. Towards the elimination of chronic
738 obstructive pulmonary disease: a Lancet Commission. *The Lancet* 2022;400:921-72.
- 739 40. Li X, Wu Z, Xue M, Du W. Smoking status affects clinical characteristics and disease course
740 of acute exacerbation of chronic obstructive pulmonary disease: a prospectively observational study.
741 *Chronic respiratory disease* 2020;17:1479973120916184.
- 742 41. Rabe KF, Rennard S, Martinez FJ, et al. Targeting type 2 inflammation and epithelial alarmins
743 in chronic obstructive pulmonary disease: a biologics outlook. *American journal of respiratory and*
744 *critical care medicine* 2023;208:395-405.
- 745 42. Pauwels NS, Bracke KR, Dupont LL, et al. Role of IL-1 α and the Nlrp3/caspase-1/IL-1 β axis
746 in cigarette smoke-induced pulmonary inflammation and COPD. *European Respiratory Journal*
747 2011;38:1019-28.
- 748 43. Barnes PJ. Inflammatory endotypes in COPD. *Allergy* 2019;74:1249-56.

44. Pleasants RA, Riley IL, Mannino DM. Defining and targeting health disparities in chronic obstructive pulmonary disease. *International journal of chronic obstructive pulmonary disease* 2016;24:75-96.
45. National Institute for Health and Care Excellence. Mepolizumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils [TA1166]. Available at: <https://www.nice.org.uk/guidance/ta1166>. Date accessed 20 June 2026. London 2026.
46. National Institute for Health and Care Excellence. Dupilumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils. London: NICE; 2026. Report No.: TA1142. <https://www.nice.org.uk/guidance/ta1142>. Date accessed 20 June 2026.
47. Business case guidance: COPD biologics. NHS England, 2020. (Accessed 18 September 2026, at <https://www.england.nhs.uk/long-read/business-case-guidance-copd-biologics/>.)
48. Bafadhel M, Martinez FJ, Criner GJ, et al. Using Historical Blood Eosinophil Counts to Guide Treatment Decisions in Patients With COPD. *CHEST* 2026.
49. Woo EJ. Postmarketing safety of biologics and biological devices. *The Spine Journal* 2014;14:560-5.
50. Academy of Medical Royal Colleges (2020). Right Choice Using BRAN. <https://www.aomrc.org.uk/projects-and-programmes/choosing-wisely/>. Date accessed 20 June 2026. London.
51. Raine R, Wallace I, Bhaird C, et al. Improving the effectiveness of multidisciplinary team meetings for patients with chronic diseases: a prospective observational study. *Health Serv Deliv Res* 2014;2.
52. Wong C, Bassett P, Kamperidis N, et al. Prolonged time to treatment of biologics in inflammatory bowel disease: disparities from a retrospective study in a tertiary referral centre in the UK. *BMC Gastroenterology* 2025;25:352.
53. Martini M, Cecchi L, Aliani M, et al. Biologic Therapy Timing and Severe Asthma Progression: Insights from the Italian Registry on Severe Asthma. *Respiration* 2026:1-7.
54. Anzueto A. Impact of exacerbations on COPD. *European Respiratory Review* 2010;19:113-8.
55. May SM, Li JT. Burden of chronic obstructive pulmonary disease: healthcare costs and beyond. *Allergy and asthma proceedings*; 2015. p. 4.
56. Seemungal TA, Hurst JR, Wedzicha JA. Exacerbation rate, health status and mortality in COPD—a review of potential interventions. *International journal of chronic obstructive pulmonary disease* 2009;20:23-23.
57. Blasi F, Cesana G, Conti S, et al. The clinical and economic impact of exacerbations of chronic obstructive pulmonary disease: a cohort of hospitalized patients. *PloS one* 2014;9:e101228.
58. Alqahtani JS, Aquilina J, Bafadhel M, et al. Research priorities for exacerbations of COPD. *Lancet Respir Med* 2021;9:824-6.
59. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. *Respir Med* 1991;85 Suppl B:25-31; discussion 3-7.
60. Meguro M, Barley EA, Spencer S, Jones PW. Development and Validation of an Improved, COPD-Specific Version of the St. George Respiratory Questionnaire. *Chest* 2007;132:456-63.
61. Nishiyama O, Taniguchi H, Kondoh Y, et al. The effectiveness of the visual analogue scale 8 in measuring health-related quality of life for COPD patients. *Respiratory medicine* 2000;94:1192-9.
62. Donohue JF. Minimal Clinically Important Differences in COPD Lung Function. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2005;2:111-24.
63. Scanlon PD, Connett JE, Waller LA, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease: the Lung Health Study. *American journal of respiratory and critical care medicine* 2000;161:381-90.
64. Alqahtani JS, Aldabayan YS, Aldahahir AM, Al Rajeh AM, Mandal S, Hurst JR. Predictors of 30- and 90-Day COPD Exacerbation Readmission: A Prospective Cohort Study. *Int J Chron Obstruct Pulmon Dis* 2021;16:2769-81.

- 800 65. Ramakrishnan S, Russell REK, Mahmood HR, et al. Treating eosinophilic exacerbations of
801 asthma and COPD with benralizumab (ABRA): a double-blind, double-dummy, active placebo-
802 controlled randomised trial. *Lancet Respir Med* 2025;13:59-68.
- 803 66. Flynn CA, McAuley HJC, Elneima O, et al. Mepolizumab for COPD with Eosinophilic
804 Phenotype following Hospitalization. *NEJM Evid* 2025;4:EVIDoa2500012.
- 805 67. Hughes R, Brailsford W, Ferreira J, et al. Phase 2a, Randomized Trial of Mitiperstat Versus
806 Placebo in Patients with COPD at High Risk of Exacerbation (CRESCENDO). *International Journal*
807 *of Chronic Obstructive Pulmonary Disease* 2025;20:3305-15.
- 808 68. Singh D, Brightling CE, Rabe KF, et al. Efficacy and safety of tezepelumab versus placebo in
809 adults with moderate to very severe chronic obstructive pulmonary disease (COURSE): a randomised,
810 placebo-controlled, phase 2a trial. *The Lancet Respiratory Medicine* 2025;13:47-58.
- 811 69. Al Badri FM, Jeebhay MF. Factors associated with serial longitudinal changes in exhaled
812 nitric oxide (FeNO)—a review of the literature. *Current Allergy & Clinical Immunology* 2017;30:98-
813 109.

814