COPD-X Summary of Changes V2.49 March 2017

Implications for Clinical Practice

The following changes have been identified as being the most significant and likely to have an impact on clinical practice:

O5.1 Inhaler technique

Addition of a new paragraph discussing the problem of poly-pharmacy with the proliferation of new inhaler devices and the negative impact on outcomes in COPD patients (Bosnic-Anticevich 2017). A study of 16,450 COPD patients compared exacerbation frequency and SABA use of patients who were using similar style inhalers (e.g. all MDI) to those that were prescribed devices that required a different technique. Those in the similar device cohort experienced fewer exacerbations and used less SABA compared to the mixed device cohort. This supports the recommendation to minimise the number of different devices prescribed in COPD patients.

P7 Mucolytic therapy

Inclusion of evidence to support the use of high dose oral N-acetylcysteine in the reduction of COPD exacerbations and improvements in lung function. In a meta-analysis by Cazzola of 13 studies involving 4155 COPD patients, both low and high doses of N-acetylcysteine significantly reduced the frequency of exacerbations (Cazzola 2015). The effectiveness of N-acetylcysteine in reducing exacerbations was also confirmed by seven RCTs performed in patients who were enrolled based on ATS/ERS or GOLD guidelines, spirometry confirmed COPD.

All Changes

C. Confirm diagnosis and assess severity

No changes

O. Optimise Function

O1.2.2 Long-acting beta$_2$-agonists (LABA)

Addition of new wording discussing the cardiovscular safety of LABAs: A large meta-analysis of 24 clinical trials (Xia 2015) of inhaled LABAs (salmeterol, formoterol, indacaterol, vilanterol, olodaterol, aformoterol) for COPD of any severity with at least 3 months follow-up found that LABAs were associated with a **lower rate of fatal cardiovascular events compared with placebo**. This is contradictory to the findings of a meta-analysis of 33 trials lasting from 3 days to 1 year, in which beta$_2$-agonist treatment significantly increased the risk for a cardiovascular event compared to placebo (Salpeter 2004). Post hoc analysis of the 3-year TORCH dataset found that the probabilities of having a cardiovascular adverse event by 3 years were similar for placebo (24.2%), salmeterol (22.7%), fluticasone propionate (24.3%) and salmeterol-fluticasone propionate combination (20.8%) (Calverley 2010). Cardiac safety of LABAs is less evident when used inappropriately (e.g. overdosing) or in patients with COPD and substantial cardiovascular disease, prolonged QTc interval, or polypharmacy (Lahousse 2016).

O1.2.3 Long-acting bronchodilator combinations (LAMA/LABA)

Addition of a sentence from a network meta-analysis stating that benefits have been found for LAMA/LABA fixed dose combinations, compared with the monocomponents (Calzetta 2017).

O5.1 Inhaler technique

Addition of a new paragraph discussing the problem of poly-pharmacy with the proliferation of new inhaler devices and the negative impact on outcomes in COPD patients (Bosnic-Anticevich 2017). A study of 16,450 COPD patients compared exacerbation frequency and SABA use of patients who were using similar style inhalers (e.g. all MDI) to those that were prescribed devices that required a different technique. Those in the similar device cohort experienced fewer exacerbations and used less SABA compared to the mixed device cohort. This supports the recommendation to minimise the number of different devices prescribed in COPD patients.

O6.4 Neuromuscular Electrical Stimulation

Addition of new section based on evidence from a meta-analysis discussing the benefits of neuromuscular electrical stimulation (NMES) in patients with moderate to severe COPD (quadriceps strength and increased exercise capacity). However, there was no effect on quality of life. Ideally, pulmonary rehabilitation, which is known to improve both aspects, is preferable. It is unclear whether NMES added to pulmonary rehabilitation has an additive effect (Chen 2016).

O6.10 Nutrition

Extensive revision of the whole section to include:

- Level I evidence showing nutritional support leads to improvements in inspiratory and expiratory muscle strength (Collins 2013);
- Discussion of the potential benefits of weight loss in obese patients – improvements in BMI, exercise tolerance and health status, while preserving fat free mass (McDonald 2016). However, there is currently a lack of RCTS in this area, which are needed to formulate clinical guidelines for managing obese COPD patients.
- Evidence from large observational cohort studies that a health dietary pattern protects against lung function decline and COPD onset, while an unhealthy diet has the opposite effect (Varraso 2015, Varraso 2007a, Varraso 2007b). In addition, high fruit and vegetable intake was associated with reduced risk of COPD (Kaluza 2017).
- Inclusion of a reference suggesting the benefit of long term vitamin E supplementation (Agler 2011).
- An additional large cohort study showing faster lung function decline and increased risk of COPD in patients with the lowest Vitamin D levels (Afzal 2014).
- Inclusion of a statement from an RCT using high dose vitamin D that there was a reduction in exacerbations in subjects with severe vitamin D deficiency at baseline (Lehouck 2012).
- Addition of level I evidence from a systematic review and meta-analysis that 8-26 weeks intervention with anabolic steroids led to improvements in body weight, FFM and SGRQ, while there was no improvement in lung function, handgrip strength or 6MWD (Pan 2014).

P: Prevent deterioration

Addition of new paragraph stating that avoidance of passive smoking is recommended to prevent deterioration. In a cohort study, exposure to second hand smoke (SHS) was found to be associated with worse clinical outcomes for people with COPD. Living with a smoker was associated with poorer health-related quality of life and increased risk of severe exacerbations, while SHS exposure in the last week was associated with worse SGRQ and more symptoms (Putcha 2016).

P4 Antibiotics

Inclusion of level II evidence on the effect of azithromycin (500mg, three times per week, over 12 months) - an almost halving of exacerbations in severe COPD patients, although 1 in 5 experienced diarrhoea (Uzun 2014).

Inclusion of level I evidence from a systematic review of prophylactic macrolide treatment in severe COPD, which showed that regular treatment of at least 6 months in duration results in a significant decrease in COPD exacerbations. Participants treated with macrolides were more likely to experience gastrointestinal reactions, ototoxicity, rash, and liver injury events compared to the placebo treated group (Yao 2013).

P7 Mucolytic therapy

Inclusion of a paragraph discussing the 2015 Cochrane review of mucolytics (Poole 2015) which found treatment with mucolytics was associated with an increased likelihood of being exacerbation free during the period of study. The authors calculated the number needed to treat with mucolytics for an additional beneficial outcome for an average of 10 months as eight. Mucolytic use resulted in a reduction in exacerbations compared with placebo. However, the results should be interpreted with care due to the very high heterogeneity and the smaller effect in more recent trials. The use of mucolytics may produce a small reduction in exacerbations and small improvements in quality of life.

Inclusion of evidence to support the use of high dose oral N-acetylcysteine in the reduction of COPD exacerbations and improvements in lung function. In a meta-analysis by Cazzola of 13 studies involving 4155 COPD patients, both low and high doses of N-acetylcysteine significantly reduced the frequency of exacerbations (Cazzola 2015). The effectiveness of N-acetylcysteine in reducing exacerbations was also confirmed by seven RCTs performed in patients who were enrolled based on ATS/ERS or GOLD guidelines, spirometry confirmed COPD.

P8. Humidification therapy

Inclusion of new evidence on the benefits of nasal high flow humidified air (NHF) from two 2016 studies. In a small trial involving 6 non-hypoxic COPD patients, Biselli *et al* found that nocturnal NHF significantly decreased the work of breathing and improved transcutaneous carbon dioxide levels, whereas oxygen produced only a minimal reduction in the work of breathing and increased carbon dioxide levels (Biselli 2017). Fraser *et al* compared the effects of 20 minutes of NHF (with oxygen) to standard supplemental nasal oxygen in 30 male oxygen dependent COPD patients, also finding that NHF reduced transcutaneous CO_2 and respiratory rate and increased tidal volume (Fraser 2016). Patients reported that the standard nasal oxygen interface provided more dyspnoea relief and was more comfortable.

The section concludes that prospective randomized control trials in the appropriate COPD patient population with meaningful clinical endpoints are required before long term domiciliary NHF can be recommended.

P11 Alpha-1 antitrypsin deficiency

Update of section to include the 2016 Cochrane Review by Gotzsche (updated from 2010) (Gøtzsche 2016) and a two year, open label extension trial of the previously cited RAPID study (Chapman 2015). 140 patients who had participated in the Chapman trial showed that the decrease in rate of lung density loss was maintained in patients who continued the same dose of active AAT augmentation therapy, and was achieved by patients who started therapy during the extension trial (McElvaney 2017).

Despite the inclusion of further evidence, it is noted that the optimal dosing regimen has not yet been determined, and the cost-effectiveness of AAT therapy is not known. On the balance of the

evidence to date and methodological considerations, AAT augmentation therapy with this current treatment approach is not yet recommended, and results from additional RCTs underway and other analyses are awaited.

D: Develop a plan of care

D3. Self-management

Inclusion of an additional paragraph on the effect of self management from a systematic review and meta–analysis by Cannon *et al* (Cannon 2016) which aimed to evaluate the impact on health-related quality of life, exercise capacity, anxiety and depression, self efficacy and hospitalisations. Twenty five RCTs involving 4,083 participants were included. The results of this review were both concordant and discordant with previous ones. Self-management programs lead to statistically significant improvements in health status measured by the SGRQ, however unlike Zwerink (Zwerink 2014), this did not meet the Minimum Clinically Important Difference (MCID) of 4 units. Exercise capacity measured by the 6MWD also improved, as did the negative effect, physical exertion and behavioural risk factor domains of the COPD self efficacy scale. There were no significant differences in anxiety, depression or hospital admissions.

D5. Treat anxiety and depression

Inclusion of a paragraph discussing a nurse-delivered minimalist version of Cognitive Behaviour Therapy (CBT) facilitated by the use of laminated cards and delivered in 1-2 home visits of 20-60 minute duration. There were clinically and statistically significant improvements in HADS anxiety scale and the CRQ Mastery scale, in the intervention arm (n=22) compared to the control arm (n=22), when followed up at 3 months (Bove 2016).

X: Manage eXacerbations

Inclusion of a paragraph discussing a systematic review of seven trials with a total of 880 patients who were hospitalised with an exacerbation of COPD and underwent a CT pulmonary angiogram which found that 16% had a pulmonary embolism (Aleva 2016). There was a large variation in the prevalence of pulmonary embolism between studies; 3% to 29%. Only one third of patients had small isolated subsegmental pulmonary embolism. Based on the high prevalence of pulmonary embolism, this diagnosis should be considered in patients presenting with an exacerbation of COPD when signs of an infection are absent and chest pain and cardiac failure are present.

Inclusion of a paragraph stating that exacerbations of COPD are associated with accelerated loss of lung function, particularly in patients with mild disease. Each severe exacerbation was associated with an additional FEV_1 loss of 87mls/year (Dransfield 2017).

X4 Uptake and impact of guidelines for exacerbations

Addition of a new section discussing the proliferation of COPD guidelines around the world, but that there has been little evaluation of their uptake into clinical practice, or their impact on clinical

outcomes. A study of the compliance to COPD-X (Gerber 2016) recommendations in 381 COPD patients attending the EDs of two hospitals within one local Australian health service, has demonstrated moderately satisfactory results, with compliance to individual recommendations of the order of 74-90%, and to the whole list of recommendations of 49%, indicating some room for further improvement. Highest levels of compliance were seen in the most severe COPD cases. This study did not show a reduction in length of stay with greater compliance; however this analysis did not adjust for severity.

References

AFZAL, S., LANGE, P., BOJESEN, S. E., FREIBERG, J. J. & NORDESTGAARD, B. G. 2014. Plasma 25-hydroxyvitamin D, lung function and risk of chronic obstructive pulmonary disease. *Thorax,* 69**,** 24-31.

AGLER, A. H., KURTH, T., GAZIANO, J. M., BURING, J. E. & CASSANO 2011. Randomised vitamin E supplementation and risk of chronic lung disease in the Women's Health Study. *Thorax,* 66**,** 320-5.

ALEVA, F. E., VOETS, L. W., SIMONS, S. O., DE MAST, Q., VAN DER VEN, A. J. & HEIJDRA, Y. F. 2016. Prevalence and Localization of Pulmonary Embolism in Unexplained Acute Exacerbations of COPD: A systematic review and meta-analysis. *Chest*.

BISELLI, P. J., KIRKNESS, J. P., GROTE, L., FRICKE, K., SCHWARTZ, A. R., SMITH, P. & SCHNEIDER, H. 2017. Nasal high-flow therapy reduces work of breathing compared with oxygen during sleep in COPD and smoking controls: a prospective observational study. *J Appl Physiol (1985),* 122**,** 82-88.

BOSNIC-ANTICEVICH, S., CHRYSTYN, H., COSTELLO, R. W., DOLOVICH, M. B., FLETCHER, M. J., LAVORINI, F., RODRIGUEZ-ROISIN, R., RYAN, D., WAN YAU MING, S. & PRICE, D. B. 2017. The use of multiple respiratory inhalers requiring different inhalation techniques has an adverse effect on COPD outcomes. *Int J Chron Obstruct Pulmon Dis,* 12**,** 59-71.

BOVE, D. G., LOMBORG, K., JENSEN, A. K., OVERGAARD, D., LINDHARDT, B. O. & MIDTGAARD, J. 2016. Efficacy of a minimal home-based psychoeducative intervention in patients with advanced COPD: A randomised controlled trial. *Respir Med,* 121**,** 109-116.

CALVERLEY, P. M., ANDERSON, J. A., CELLI, B., FERGUSON, G. T., JENKINS, C., JONES, P. W., CRIM, C., WILLITS, L. R., YATES, J. C. & VESTBO, J. 2010. Cardiovascular events in patients with COPD: TORCH study results. *Thorax,* 65**,** 719-25.

CALZETTA, L., ROGLIANI, P., ORA, J., PUXEDDU, E., CAZZOLA, M. & MATERA, M. G. 2017. LABA/LAMA combination in COPD: a meta-analysis on the duration of treatment. *Eur Respir Rev,* 26.

CANNON, D., BUYS, N., SRIRAM, K. B., SHARMA, S., MORRIS, N. & SUN, J. 2016. The effects of chronic obstructive pulmonary disease self-management interventions on improvement of quality of life in COPD patients: A meta-analysis. *Respir Med,* 121**,** 81-90.

CAZZOLA, M., CALZETTA, L., PAGE, C., JARDIM, J., CHUCHALIN, A. G., ROGLIANI, P. & MATERA, M. G. 2015. Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis. *Eur Respir Rev,* 24**,** 451-61.

CHAPMAN, K. R., BURDON, J. G., PIITULAINEN, E., SANDHAUS, R. A., SEERSHOLM, N., STOCKS, J. M., STOEL, B. C., HUANG, L., YAO, Z., EDELMAN, J. M., MCELVANEY, N. G. & GROUP, R. T. S. 2015. Intravenous augmentation treatment and lung density in severe alpha1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. *Lancet,* 386**,** 360-8.

CHEN, R. C., LI, X. Y., GUAN, L. L., GUO, B. P., WU, W. L., ZHOU, Z. Q., HUO, Y. T., CHEN, X. & ZHOU, L. Q. 2016. Effectiveness of neuromuscular electrical stimulation for the rehabilitation of moderate-to-severe COPD: a meta-analysis. *Int J Chron Obstruct Pulmon Dis,* 11**,** 2965-2975.

COLLINS, P. F., ELIA, M. & STRATTON, R. J. 2013. Nutritional support and functional capacity in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Respirology,* 18**,** 616-29.

DRANSFIELD, M. T., KUNISAKI, K. M., STRAND, M. J., ANZUETO, A., BHATT, S. P., BOWLER, R. P., CRINER, G. J., CURTIS, J. L., HANANIA, N. A., NATH, H., PUTCHA, N., ROARK, S. E., WAN, E. S., WASHKO, G. R., WELLS, J. M., WENDT, C. H. & MAKE, B. J. 2017. Acute Exacerbations and Lung Function Loss in Smokers with and without Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med,* 195**,** 324-330.

FRASER, J. F., SPOONER, A. J., DUNSTER, K. R., ANSTEY, C. M. & CORLEY, A. 2016. Nasal high flow oxygen therapy in patients with COPD reduces respiratory rate and tissue carbon dioxide while increasing tidal and end-expiratory lung volumes: a randomised crossover trial. *Thorax,* 71**,** 759-61.

GERBER, A., MOYNIHAN, C., KLIM, S., RITCHIE, P. & KELLY, A. M. 2016. Compliance with a COPD bundle of care in an Australian emergency department: A cohort study. *Clin Respir J*.

GØTZSCHE, P. C. & JOHANSEN, H. K. 2016. Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. *Cochrane Database of Systematic Reviews*.

KALUZA, J., LARSSON, S. C., ORSINI, N., LINDEN, A. & WOLK, A. 2017. Fruit and vegetable consumption and risk of COPD: a prospective cohort study of men. *Thorax*.

LAHOUSSE, L., VERHAMME, K. M., STRICKER, B. H. & BRUSSELLE, G. G. 2016. Cardiac effects of current treatments of chronic obstructive pulmonary disease. *Lancet Respir Med,* 4**,** 149-64.

LEHOUCK, A., MATHIEU, C., CARREMANS, C., BAEKE, F., VERHAEGEN, J., VAN ELDERE, J., DECALLONNE, B., BOUILLON, R., DECRAMER, M. & JANSSENS, W. 2012. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med,* 156**,** 105-14.

MCDONALD, V. M., GIBSON, P. G., SCOTT, H. A., BAINES, P. J., HENSLEY, M. J., PRETTO, J. J. & WOOD, L. G. 2016. Should we treat obesity in COPD? The effects of diet and resistance exercise training. *Respirology,* 21**,** 875-82.

MCELVANEY, N. G., BURDON, J., HOLMES, M., GLANVILLE, A., WARK, P. A., THOMPSON, P. J., HERNANDEZ, P., CHLUMSKY, J., TESCHLER, H., FICKER, J. H., SEERSHOLM, N., ALTRAJA, A., MAKITARO, R., CHOROSTOWSKA-WYNIMKO, J., SANAK, M., STOICESCU, P. I., PIITULAINEN, E., VIT, O., WENCKER, M., TORTORICI, M. A., FRIES, M., EDELMAN, J. M. & CHAPMAN, K. R. 2017. Long-term efficacy and safety of alpha1 proteinase inhibitor treatment for emphysema caused by severe alpha1 antitrypsin deficiency: an open-label extension trial (RAPID-OLE). *Lancet Respir Med,* 5**,** 51-60.

PAN, L., WANG, M., XIE, X., DU, C. & GUO, Y. 2014. Effects of anabolic steroids on chronic obstructive pulmonary disease: a meta-analysis of randomised controlled trials. *PLoS One,* 9**,** e84855.

POOLE, P., CHONG, J. & CATES, C. J. 2015. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*.

PUTCHA, N., BARR, R. G., HAN, M. K., WOODRUFF, P. G., BLEECKER, E. R., KANNER, R. E., MARTINEZ, F. J., SMITH, B. M., TASHKIN, D. P., BOWLER, R. P., EISNER, M. D., RENNARD, S. I., WISE, R. A. & HANSEL, N. N. 2016. Understanding the impact of second-hand smoke exposure on clinical outcomes in participants with COPD in the SPIROMICS cohort. *Thorax*.

SALPETER, S. R., ORMISTON, T. M. & SALPETER, E. E. 2004. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. *Chest,* 125**,** 2309-21.

UZUN, S., DJAMIN, R. S., KLUYTMANS, J. A., MULDER, P. G., VAN'T VEER, N. E., ERMENS, A. A., PELLE, A. J., HOOGSTEDEN, H. C., AERTS, J. G. & VAN DER EERDEN, M. M. 2014. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med,* 2**,** 361-8.

VARRASO, R., CHIUVE, S. E., FUNG, T. T., BARR, R. G., HU, F. B., WILLETT, W. C. & CAMARGO, C. A. 2015. Alternate Healthy Eating Index 2010 and risk of chronic obstructive pulmonary disease among US women and men: prospective study. *BMJ,* 350**,** h286.

VARRASO, R., FUNG, T. T., BARR, R. G., HU, F. B., WILLETT, W. & CAMARGO, C. A. J. 2007a. Prospective study of dietary patterns and chronic obstructive pulmonary disease among US women. *Am J Clin Nutr,* 86**,** 488–495.

VARRASO, R., FUNG, T. T., HU, F. B., WILLETT, W. & CAMARGO, C. A. 2007b. Prospective study of dietary patterns and chronic obstructive pulmonary disease among US men. *Thorax,* 62**,** 786-91.

XIA, N., WANG, H. & NIE, X. 2015. Inhaled Long-Acting beta2-Agonists Do Not Increase Fatal Cardiovascular Adverse Events in COPD: A Meta-Analysis. *PLoS One,* 10**,** e0137904.

YAO, G. Y., MA, Y. L., ZHANG, M. Q. & GAO, Z. C. 2013. Macrolide therapy decreases chronic obstructive pulmonary disease exacerbation: a meta-analysis. *Respiration,* 86**,** 254-60.

ZWERINK, M., BRUSSE-KEIZER, M., VAN DER VALK, P. D., ZIELHUIS, G. A., MONNINKHOF, E. M., VAN DER PALEN, J., FRITH, P. A. & EFFING, T. 2014. Self management for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev,* 3**,** CD002990.