Implantable & Wearable Medical Devices
for Chronic Obstructive Pulmonary Disease
Foreword

Chronic Obstructive Pulmonary Disease (COPD) is a condition with a significant burden not only to patients but also to the economy and society as a whole. On behalf of the NIHR Clinical Research Network, this report investigates how wearable and implantable medical devices can help alleviate the burden of COPD. It outlines some of the new technologies that have the potential to address unmet care needs and assist at different stages of the disease progression. The topics covered range from diagnosis, treatment, to rehabilitation, addressing key issues related to monitoring during exacerbations and patients with comorbidities.

This report reemphasises the importance of prevention for COPD, through appropriate educational interventions and smoking cessation programmes. Technological interventions via novel wearable devices can also address both psychological and physiological symptoms of addiction. Early screening and diagnosis represent a key priority as COPD develops slowly and asymptptomatically, and many patients are unaware of the condition until it manifests as a medical emergency. For patients already diagnosed with COPD, prevention and early detection of exacerbations continues to be an unmet clinical need and effective tools such as decision-making platforms capable of predicting exacerbations based on multi-parameter measurements of biological markers are highly desirable. The long-term nature of COPD care requires commitment for continuous disease management and behaviour changes. With the exception of a small number of people that require hospitalisation for treatment, COPD should be managed in a community setting, and medical devices should be tailored for home use, empowering patients to monitor their own conditions.

Effective management of COPD requires an interdisciplinary approach, bringing together specialists in respiratory medicine, rehabilitation, social and behavioural care. From disease prevention, early diagnosis, to long-term care, this report provides important translational considerations of new implantable and wearable medical devices for COPD, as well as emerging trends in personalised care pathways and stratified patient management.

I would like to thank all those involved in this report, particularly our expert panel for providing valuable advices and critical comments throughout the preparation of this report.

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Chronic Obstructive Pulmonary Disease (COPD) is the second most common cause of emergency admissions to hospital and one of the most costly inpatient conditions to be treated by the NHS.

Executive summary

Chronic Obstructive Pulmonary Disease (COPD) is the second most common cause of emergency admissions to hospital. It is also one of the most costly inpatient conditions that the NHS treats – the direct healthcare cost is estimated at over £800 million a year. There are about three million people in the UK with COPD, although approximately two million remain undiagnosed. More than 15% only receive a COPD diagnosis when going to hospital in an emergency. Most patients only present once they have persistent symptoms and hence later in the natural history of the disease.

Prevention is the most important strategy for managing COPD. So ‘stop smoking’ programmes are important. General therapies, such as good nutrition, vaccination and exercise should form the basis of all treatment. Pulmonary rehabilitation also has an important role and is usually offered to more symptomatic patients with increasing physical limitation. However, in many patients, COPD is just the pulmonary component of a complex multi-morbidity, characterised by concomitant chronic diseases and systemic effects. Comorbidities of COPD include cardiovascular diseases (e.g. pulmonary hypertension, ischemic heart disease, heart failure, and atrial fibrillation), lung cancer, osteoporosis, depression and anxiety, and metabolic syndrome and diabetes.

To date, COPD patients and healthcare providers alike have many unmet needs. This paper aims to outline major challenges and unmet clinical demands for COPD. From disease prevention and early diagnosis, to new wearable sensors, imaging technologies and smart implants, it highlights the importance of sensing, feedback and monitoring of COPD in community and workplaces, allowing self-management and reward for behavioural changes. The paper also outlines opportunities for developing new point-of-care devices, wearable micro-electronics, and smart implants for personalised care pathways and stratified patient management.
1. Chronic Obstructive Pulmonary Disease (COPD)

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung condition characterised by airway inflammation leading to a persistent airflow limitation that impeded normal breathing. The lung airflow limitation is not fully reversible and is associated with an abnormal inflammatory response of the lungs to airborne pollutants. The main symptoms are shortness of breath, wheezing (particularly when exhaling), and coughing with sputum production.

**Key features of COPD:**
- Airflow limitation is central to defining COPD and for its diagnosis and assessment; spirometry provides an objective way to measure airflow limitation.
- Non-fully reversible airflow limitation is characteristic of COPD. Patients with asthma generally have completely reversible airflow limitation.
- The inflammatory response is abnormal in COPD in terms of inflammatory cells and mediators, as well as abnormal healing and repair.
- Noxious particles and gases comprise various agents that can cause COPD, but the main recognised cause is cigarette smoke.

**COPD describes several phenotypes:**
- Chronic bronchitis: considered when a chronic, productive cough is present on most days for 3 months, over 2 consecutive years.
- Small-airway disease: obstructive bronchiolitis.
- Emphysema: entails an abnormal, permanent enlargement of the air spaces, which leads to the destruction of the lung tissue.

These features are present to varying degrees in individuals. Hence, the condition’s heterogeneous presentation.

**Epidemiology**
It’s thought COPD affects about three million people in the UK. That’s about 10% of the population aged over 40 years. However, the current prevalence rate for COPD in the UK is only about 900,000, suggesting a significant number of patients remain undiagnosed. Furthermore, respiratory disease accounts for about 700,00 hospital admissions each year (about 6 million bed days), with COPD admissions being a major contributor. Globally, COPD is now the third leading cause of death and in the UK accounts for over 22,000 deaths a year.

**Aetiology**
Cigarette smoke is considered to be the major aetiological factor for COPD and the risk of developing the condition increases with the total exposure to tobacco smoke. Approximately 10-20% of smokers develop a clinical form of the disease. While cigarette smoke is the main culprit for COPD, it is also worth noting that 10% of cases occur in patients who have never smoked. Occupational exposure to coal, silica and cadmium dust may also lead to COPD. Globally, another important risk factor is the exposure to smoke from biomass fuels. These include coal, straw, animal dung, and wood, used for heating and cooking in poorly ventilated homes.
1.1 Pathophysiology

Early manifestations
Most patients only present after persistent symptoms, so later in the natural history of the disease. Early diagnosis is important as the deterioration in lung function occurs slowly over time – usually over several decades. In the early stages, most patients don’t experience dyspnea, except with significant exertion. Identifying individuals at risk should be easy as the main risk factor is cigarette smoking.

Chronic bronchitis, mucus hypersecretion, and ciliary dysfunction
Cigarette smoke leads to chronic bronchitis in a similar way it leads to emphysema: smoke and damage caused by protease released by neutrophils leading to airway injury. Released proteases also stimulate mucus secretion and further cell inflammation. Hence, the inflammatory cycle is perpetuated. This chronic production of mucus is the key feature for chronic bronchitis, resulting in a chronic cough and expectoration of secretions. Plus, proteases can also cause airflow limitation due to mucus plugging of airways, and hence limitation in the recruitment of alveoli.

Airflow limitation
The inflammatory process in COPD can lead to airway damage and fibrosis. This in conjunction with airway secretions and smooth muscle constriction leads to peripheral airway narrowing. In obstructive bronchiolitis, this process appears to be particularly important in the small airways where airway-narrowing correlates well with decreased airflow. Furthermore, protease damage can lead to destruction of the alveoli and the surrounding attachments. A loss of these tethering elements leads to collapse of the distal airways during expiration, which is independent of effort. Hence, trying harder to breathe out in COPD does not improve airflow.

Alveolar destruction
In pulmonary emphysema, the alveolar structures of the lung are destroyed. This reduces the surface area for gas exchange. Pathologically, emphysema consists of a distinctive pattern of alveolar destruction, characterised as a permanent airspace enlargement, accompanied by the destruction of alveolar walls and a reduced capillary exchange area. Cigarette smoke is a major factor triggering alveolar destruction by the interaction of apoptosis, oxidative stress, and protease/antiprotease imbalance (Tuder et al., 2006). Alveolar destruction is associated with the destruction of lung elastin. The release of neutrophil elastase and metalloproteinases from inflammatory cells – such as neutrophils and macrophages – may overwhelm the lungs’ antiprotease defences and induce destruction (Chung and Adcock, 2008). Alveoli destruction due to emphysema can lead to a loss of the associated areas of the pulmonary capillary bed and pruning of the distal vasculature (Han et al., 2016).

Hyperinflation and air trapping
Peripheral airway obstruction traps air during expiration progressively. This results in lung hyperinflation and an increased resting lung volume (functional residual capacity). Air trapping reduces inspiratory capacity and deteriorates during exercise (dynamic hyperinflation), resulting in increased dyspnoea and reduced exercise tolerance (Barnes et al., 2015). Hyperinflation develops early during disease and has been identified as the main cause for exertional dyspnea in COPD patients (GOLD, 2016). Increasing airflow obstruction and expiratory airway collapse can lead to progressive air trapping. Hyperinflation (dynamic hyperinflation) is first observed only during exercise, but as the disease becomes more severe, it is also seen during tidal breathing at rest. A parallel compensatory effect of airflow limitation is an increase in the functional residual capacity (FRC). This is due to decreased elasticity of the lungs, premature airway closure, and the variable dynamic element of breathing patterns that have changed to cope with poor lung mechanics.

Gas exchange abnormalities
Regional inequalities of ventilation and perfusion cause gas exchange abnormalities. Commonly, these result in hypoxaemia, but in advanced disease can also contribute to hypercapnia and chronic respiratory acidosis (Talag and Wilcox, 2008). Gas transfer for oxygen and carbon dioxide generally deteriorates as the disease progresses. Reduced ventilation may be caused by decreased ventilator drive (GOLD, 2016). Pulmonary hypertension and impaired cardiac function are also contributing to gas exchange disturbances in advanced COPD (Talag and Wilcox, 2008).

Reduced exercise capacity
Exercise capacity is a major determinant of health status and is generally reduced in COPD in proportion to the disease’s severity. It is also a significant predictor of mortality and an important outcome measure when assessing patients with COPD. A lack of physical activity can lead to reduced exercise capacity and many COPD patients complain of exertional dyspnea and exercise intolerance. Decreased exercise capacity is attributed to combined effects of dynamic hyperinflation, decreased ventilatory reserve, and respiratory and peripheral muscle dysfunctions (Pynnaert et al., 2010). Management of deconditioning include pulmonary rehabilitation interventions specifically designed to mitigate exercise capacity.

Systemic effects
Patients with COPD have comorbidities that affect significantly the quality of life and survival rates. Airflow limitation and hyperinflation directly affect cardiac function and gas exchange. Inflammatory mediators in the circulation may lead to skeletal muscle wasting and cachexia. They may also initiate or contribute to deterioration of comorbidities such as ischemic heart disease, heart failure, osteoporosis, normocytic anaemia, diabetes, metabolic syndrome, and depression (GOLD, 2016).
1.2 Comorbidities

**Cardiovascular diseases**

In many patients, COPD is just the pulmonary component of a complex multi-morbidity characterised by concomitant chronic diseases and systemic effects. Cardiovascular disease is the most common, major comorbidity and possibly the most important contributor to the clinical severity of patients with COPD. As identified by the GOLD report (GOLD, 2016), these include separate entities such as ischemic heart disease, heart failure, atrial fibrillation and hypertension.

- **Pulmonary hypertension** is a complication occurring late in the history of the COPD disease and can independently worsen its prognosis. Chronic hypoxia may lead to pulmonary vasconstriction. Endothelial dysfunction, remodelling of pulmonary arteries, and pulmonary capillary bed destruction (Talag and Wilcox, 2008) are among other factors for this comorbidity. A progressive pulmonary hypertension may lead to right ventricular hypertrophy and eventually failure (cor pulmonale), adding to the morbidity and mortality of COPD. Pulmonary hypertension can lead to heart failure and the condition typically affects patients in their 40s and 50s. Patients with pulmonary hypertension often have shortness of breath, fatigue, dizziness and fainting with everyday activities. These symptoms limit the patient’s activities and severely affect their quality of life.

- **Ischemic heart disease (IHD)** is characterised by a reduced blood supply to the heart and is a frequent comorbidity in COPD patients, due to the unfavourable IHD risk profile of this population. The evidence shows COPD increases morbidity and mortality among patients with IHD and myocardial injury is often overlooked and IDH is under-diagnosed in COPD (GOLD, 2016).

- **Heart failure (HF)** is another common comorbidity in COPD, highly interrelated with it – an estimated 30% of patients with stable COPD have some degree of HF and approximately 30% of patients in a HF clinic have COPD. Worsening of HF is a significant differential diagnosis indicator to a COPD worsening. Comorbid COPD is often the cause of admission for acute HF, and has significant implications on the prognosis, as FEV\(_1\) is a strong predictor for mortality in HF (GOLD, 2016).

- **Atrial fibrillation (AF)** has an increased incidence in COPD patients and is the most frequent cardiac arrhythmia. COPD with AF represents a challenge to clinicians because of the breathlessness disability resulting from their coexistence (GOLD, 2016).

- **Hypertension** is the most frequent occurring comorbidity in COPD and has implications for prognosis (GOLD, 2016).

**Lung cancer**

Lung cancer risk is increased in COPD but it is inversely related to the degree of airflow obstruction. In fact, COPD patients presenting airflow obstruction, evidenced by radiological emphysema or low diffusion capacity for carbon monoxide, are good candidates for lung cancer screening. Lung cancer is frequently seen in patients with COPD and is the most frequent cause of death in patients with mild COPD.

**Osteoporosis**

Osteoporosis is a condition that weakens bones, making them fragile and more likely to break. This major comorbidity is often overlooked and under-diagnosed in COPD, mainly because it is a clinically silent condition until it manifests as a fracture. A decreased body mass index and a low fat-free mass are often linked with osteoporosis, while the condition itself is associated with poor health status and prognosis. Osteoporosis may be more closely associated with emphysema than other subgroups of COPD.

**Depression and anxiety**

Along with cardiovascular disease and osteoporosis, depression and anxiety are also major comorbidities in COPD. Both are associated with poor health status and prognosis. Unrecognised and untreated, depression and anxiety symptoms have a negative impact on physical functioning and social interaction. The conditions are often associated with smoking female patients of younger age, with a lower FEV\(_1\), cough, and a history of cardiovascular disease (GOLD, 2016). There are many causes of depression and anxiety, including behavioural, social and biological factors. It is estimated that less than one-third of COPD patients with comorbid depression or anxiety symptoms are receiving appropriate treatment (Yohannes and Alexopoulos, 2014).

**Metabolic syndrome and diabetes**

Presence of metabolic syndrome and diabetes are more frequent in COPD. Diabetes is likely to affect a patient’s prognosis significantly. Thus far, diabetes should be treated according to the general guidelines in the presence of COPD.

A further systemic COPD comorbidity associated with worsened health status is gastroesophageal reflux – a recognised independent risk factor for exacerbations. The mechanisms responsible for increased risk of exacerbations are not fully understood and the best treatment for this condition in the context of COPD is yet to be found (GOLD, 2016).
Exacerbations

For COPD, frequent exacerbations are associated with worsened health status and a rapid lung function decline. Acute exacerbations are usually caused by infections (bacterial or viral), but can also be triggered by air pollution and cold temperatures. The basic mechanism of exacerbation is illustrated in Figure 1. Airway inflammation and increased mucus production can result in deteriorating airflow limitation. This leads to dynamic hyperinflation, causing an increased workload of breathing, which in turn precipitates respiratory failure.

The most common respiratory virus isolated is human rhinovirus, which can be detected up to a week after the start of the exacerbation episode. Most exacerbations recover after 7-10 days, though some may last as long as 12 weeks before returning to the baseline status. Around eight weeks after the onset of an exacerbation, approximately 20% of patients recover to their stable pre-exacerbation level. COPD exacerbations cause disease progression, with a higher likelihood when exacerbations do not recover (Wedzicha, 2015). Studies have found up to 25% of the lung function decline in COPD is attributable to exacerbations. Furthermore, severe exacerbations requiring hospital admission are often associated with cardiovascular events – especially myocardial infarction (Barnes et al., 2015).

There are two basic patterns of exacerbations – either a rapid onset and recovery, or a slower onset followed by recovery. The latter is most likely associated with viral triggers. Once patients experience an exacerbation, they will show increased susceptibility to subsequent exacerbation events. Early treatment may improve symptoms and also reduce the risk of hospitalisation or developing respiratory failure. Unfortunately, in patients with moderate to severe disease who have chronic symptoms, it is difficult to predict the onset of exacerbations until the flare is well established. The treatment in general comprises antibiotics and oral steroids. However, inappropriate use of these therapies can increase bacterial colonisation and resistance. Furthermore, COPD patients are vulnerable to steroid side effects such as muscle wasting and osteopenia. As such, accurate and early prediction of exacerbations is an important yet unmet need in managing COPD patients.

The long-term prognosis following an exacerbation requiring hospitalisation is poor, with a five-year mortality rate of 50%. Poor outcomes are associated with older age, lower body mass index, existing comorbidities (e.g. cardiovascular disease or lung cancer), a history of previous admissions for exacerbations, clinical severity, and the need for long-term oxygen therapy at discharge (GOLD, 2016).

Figure 1: Triggers of COPD exacerbations and associated pathophysiological changes leading to increased exacerbation symptoms (Adapted from Wedzicha and Seemungal 2007)
1.3 Healthcare Burden

COPD is the second most common cause of emergency admissions to hospitals. It is also one of the most costly inpatient conditions the NHS treats, with the total annual cost of direct healthcare estimated at more than £800 million (NICE, 2011). There are about three million people in the UK with COPD, although approximately two million of these remain undiagnosed. According to the UK Department of Health, only 15% are receiving a COPD diagnosis after attending the hospital as an emergency (DH, 2012).

- 80% of people with COPD have at least one other long-term comorbidity. In particular, COPD is linked to an increased risk of mortality from cardiovascular disease, and having depression and/or an anxiety disorder.
- Over 50% of people currently diagnosed with COPD are under 65 years of age. 24 million working days are lost each year to COPD, with £3.8 billion lost through reduced productivity (DH, 2012).
- COPD is generally higher in older age groups. The reported prevalence of diagnosed COPD in England is 1.6%. This figure has regional variations, ranging from 0.9% in London to 2.3% in the North East (NICE, 2011).
- Globally, COPD is a major health issue and ranked fifth for disease burden. It has a cumulated lifetime risk estimated at 25% (Barnes et al., 2015).
- In developing countries, COPD is a serious threat to the economy, because as well as its direct medical costs, the disease has a two-fold impact on human capital: health care systems in developing countries often can’t provide long-term supportive care for severely disabled patients. So for each COPD patient forced out of work, another family member has to provide care.
Implantable and Wearable Medical Devices for COPD

Worldwide, more than three million people died of COPD in 2012. This is equal to 6% of all deaths globally that year and more than 90% of these are in low and middle-income countries (WHO, 2014). East and South Asia contain the world’s largest proportion of population so present the most deaths from COPD. The regions also have the highest age-standardised mortality rates from COPD. These remain higher in men than in women, exponentially increasing with age for both genders (GOLD, 2016). The strongest association with mortality from COPD is poverty, and countries with low per capita gross national income have much higher recorded mortality rates (Barnes et al., 2015).

In the UK, there are about three million people with COPD and 80% of them have at least another long-term condition. This costs the NHS an estimated £1.2 billion a year. COPD is the fifth biggest killer disease in the UK. It is the second largest cause of emergency admission in the UK, accounting for more than one million ‘bed days’ each year in hospitals. In the UK 29,776 people died from COPD in 2012 (15,245 males and 14,531 females), equivalent to 5.3% of the total number of UK deaths and 26.1% of deaths from lung disease (BLF, 2016). In England alone, one person dies from COPD every 20 minutes – that’s around 23,000 deaths a year. Compared to the international context of the disease, COPD death rates in the UK are almost double the EU average. However, the prevalence of COPD in India is unclear (McKay et al., 2012). Although many population studies were conducted, the results were inconclusive due to the paucity of data, inconsistency in study setting, and population characteristics.

In Europe, estimates of COPD prevalence vary widely, from 0.2% to 18.3%. In part due to real differences in prevalence among countries and regions, and in part because of other factors (European COPD Coalition). The estimated prevalence for France is 3.5 million (6% of adult population and 16,000 death each year), for Germany, 2.7 million, Italy, 2.6 million, Spain, 1.5 million and Belgium, 0.4 million. It is estimated that the overall prevalence of COPD in Europe is between 4% and 10% in adults. COPD deaths are expected to rise from almost 270,000 in 2005 to 338,000 by 2030.

In the US, the prevalence of COPD rises with age for both men and women throughout most of the lifespan (i.e., across most age groups). COPD prevalence is highest among women aged 65–74 (10.4%) and 75–84 (9.7%) and among men aged 75–84 (11.2%).

India has one of the world’s highest COPD mortality rate (Bhome, 2012) – more than 64.7 estimated age standardised death rate per 100,000 amongst both sexes, translated into approximately 556,000 (>20%) out of a world total of 2,748,000 a year (Bhome, 2012). Apart from mortality, COPD can severely affect quality of life, and it is estimated 28 million Disability Adjusted Life Years (DALYs) were lost due to COPD in 2002 – out of which 9.5 million DALYs were from China and 6.74 million from India (Bhome, 2012). However, the prevalence of COPD in India is unclear (McKay et al., 2012). Although many population studies were conducted, the results were inconclusive due to the paucity of data, inconsistency in study setting, and population characteristics.

The prevalence of COPD in China is 8.2% in people aged 40 or above, and the prevalence in rural areas (8.8%) is significantly higher than that of urban areas (7.8%) (Zhong et al., 2007). COPD is reported to be the fourth leading cause of death in rural areas (between 4.4% to 16.7%), while in urban areas it is considered the third leading cause of death (between 6.7% to 8.3%) (Gao and Prasad, 2013). The average annual direct medical cost may account for 40% of an average family income (He et al., 2009).

In Korea, studies have found that the prevalence of smokers was 29.9% in 2005, and the prevalence of COPD was 17.2% among subjects aged 45 or above (Kim et al., 2005). Predominately, the COPD among males was much higher (25.8%) than in females (9.6%). This was mainly due to a higher percentage of male smokers (60.6%) compared to female smokers (5.2%).

Figure 2: Global impact of COPD.

COPD – Global Impact

Worldwide, more than three million people died of COPD in 2012. This is equal to 6% of all deaths globally that year and more than 90% of these are in low and middle-income countries (WHO, 2014). East and South Asia contain the world’s largest proportion of population so present the most deaths from COPD. The regions also have the highest age-standardised mortality rates from COPD. These remain higher in men than in women, exponentially increasing with age for both genders (GOLD, 2016). The strongest association with mortality from COPD is poverty, and countries with low per capita gross national income have much higher recorded mortality rates (Barnes et al., 2015).

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Stop smoking reduces the rate of decline of lung function and increases life expectancy at any age. It is a major goal in treating smoking patients with COPD.

1.4 Diagnosis and treatment

Prevention is the most important strategy, so 'stop smoking' programmes are important. General therapies such as good nutrition, vaccination and exercise should form the basis of all treatment. Pulmonary rehabilitation also has an important role and is usually offered to more symptomatic patients with increasing physical limitation.

Diagnosis

COPD diagnosis is often suspected when the patient presents with an exacerbation. For example, they complain of a persistent cough, sputum production, dyspnoea or recurrent respiratory infections, or they have a history of a potentially causative exposure (cigarette smoke, environmental or occupational pollutants).

A physical examination in COPD looks for signs of quiet breath sounds, prolonged respiratory duration, hyperinflation of the lungs, cyanosis and weight loss. Detection of diminished breath sounds and hyperresonance has been identified as a moderately strong predictor of COPD (Celli et al., 2015). Respiratory rate, oxygen saturation (at rest and with exertion), weigh, height, body mass index, breathlessness and functional capacity (exercise test) are also routinely measured. Exercise tests in particular have shown to be good predictors of mortality in patients with COPD.

Thus far, the six-minute walk test is the predominant endpoint for licensing authorities for new drugs. The pharmaceutical treatments are expensive (ranging from £5k to £120k a year (Wilson and Chambers, 2012)), and can be cumbersome (in the form of continuous intravenous infusions), yet exercise intervention has shown to be just as effective to improve exercise capacity and quality of life.

Assessing lung function and confirming not fully reversible airflow limitation is done via a breathing test called spirometry. The spirometer measures the volume of air breathed out in one second (called the forced expiratory volume in one second or FEV1) and the total amount of air breathed out (called the forced vital capacity or FVC). Airflow limitation that is not fully reversible is defined by a low post-bronchodilator FEV1/FVC ratio (traditionally lower than the 0.7 threshold).

Additional tests like chest X-ray and blood tests are done to help exclude conditions with similar symptoms. Further tests may also confirm the diagnosis or indicate severity of COPD. These include peak flow test, electrocardiogram and echocardiogram, computerised tomography scan, blood oxygen level, and blood test for alpha-1-antitrypsin deficiency.

Treatment

Stopping smoking reduces the rate of decline of lung function and increases life expectancy at any age. It is a major goal in treating smoking patients with COPD. Pharmacological aids for stopping smoking can be categorised as controllers for long-term abstinence (nicotine patch, bupropion and varenicline), and relievers for rapid relief of acute cravings for tobacco or heightened withdrawal symptoms (nicotine gum). Evidence also shows combining pharmacotherapy with counselling helps smokers to stop.

Pharmacological therapies for improving lung function and/or reducing the frequency of acute exacerbation episodes consist of long-acting β-agonists (LABAs), inhaled corticosteroids (ICS), combined LABA/ICS, and long-acting antimuscarinic antagonists (LAMAs).

Various short and long acting bronchodilators exist for reducing intrinsic bronchial narrowing. Short acting anti-cholinergic drugs and beta-2-agonists are usually used in the early phase where patients may have intermittent symptoms on significant activity. Where there are more persistent symptoms of breathlessness long acting anti-choline raid drugs, long acting beta-2-agonists, or a combination of these two drugs are used. Patients with more frequent exacerbations or who have evidence of overlap with asthma may be treated with a combination of inhaled steroids, with long acting beta-2-agonists.
Rehabilitation and changes in life-style

- Smoking is a major contributor to COPD and patients are required to stop smoking to alleviate symptoms and avoid secondary smoke. They should also stay away from places with dust, fumes, and other pollutants, and avoid exposure to smoke from biomass fuels.
- Combined with medication and therapy, life-style changes have a positive effect on COPD management. These include healthy diet, regular exercise and maintaining physical activity to increase muscle strength.
- Pulmonary rehabilitation is routinely used in managing COPD patients. This involves mentored exercise, along with nutritional and psychological counselling.

Medications and therapy

- Various medications are available for managing or alleviating the symptoms of COPD. These include medications for bronchodilators, corticosteroids to reduce irritation and swelling of the airways, as well as antibiotics for respiratory infection and anxiolytics for alleviating anxiety. Opioids are also used for late and terminal stages of COPD.
- Bronchodilators work either by binding directly to beta receptors on smooth muscle cells (β-agonists) to mediate their bronchodilatory effect, or as anticholinergic to block the neurotransmitter (acetylcholine) causing the airways to constrict.
- Stopping smoking medication comes in different forms, including controllers for long-term abstinence (nicotine patch, bupropion and varenicline), and rapid relievers for acute tobacco cravings or heightened withdrawal symptoms (nicotine gum).

Surgeries

- Surgery is used only in severe cases of COPD, but with advances in implants and minimally invasive endobronchial intervention, new treatment options may expand significantly in futures years.
- Common surgical procedures include bullectomy (removing large dilated air spaces (bulla) in the lung parenchyma, typically larger than 1cm in diameter), and lung volume reduction (removing wedges of damaged lung tissue). In very severe cases, lung transplant is carried out when no other viable options are available.
- Several new bronchoscopic based interventions have been developed in the last 10 years to improve patients’ pulmonary function, exercise capacity and quality of life. These include endobronchial valves, endobronchial coils, and endobronchial cryospray and vapour therapy.
- Further miniaturisation of implants and simpler deployment mechanisms (for example robotic assisted techniques combined with in situ, in vivo microscopic imaging) would see a surge of activities in such interventional procedures.
COPD is largely considered a preventable disease and early diagnosis is essential. Surgery is used only in severe cases of COPD, but with advances in implants and minimally invasive endobronchial intervention, new treatment options may expand significantly in future years.

### 1.5 Unmet clinical needs

There are many unmet needs for patients with COPD – both from patient and healthcare provider perspectives. Various solutions are available for some of these, but many remain inadequate and more genuine innovation is needed.

- **Disease Prevention:** stopping smoking programmes & public education
- **Early diagnosis**
- **Improved symptom control**
- **Prevention of exacerbations**
- **Early detection of exacerbations**
- **Ameliorate disease progression**
- **Reducing hospital admissions**
- **Reducing disease-related mortality**
- **Identifying and reducing systemic disease secondary to COPD**
- **Managing high co-existent chronic disease (co-morbidities)**

COPD is largely considered a preventable disease and more emphasis should be put on stopping smoking strategies and educating and/or using media aimed at younger generations.

Early diagnosis is essential as millions of people currently still remain undiagnosed – the ‘missing millions’ as estimates range between 1.8 – 2.0 million in the UK alone. Special screening should focus on people with a history of smoking, and in this context should target 40-50 year-olds and the so-called ‘smart phone’ generation.

**Diagnosis and Monitoring**

- **Tools to distinguish COPD subtypes**
- **Access to difficult to reach patients**
- **Role of GPs and tools they need**
- **Variable conditions, different life histories**
- **Early monitoring of exacerbations**
- **Reporting of exacerbations episodes**
- **Self-management**
- **Hyperinflation monitoring**
- **Sensing for accurate and full range of breathing monitoring**
- **Severity of disease and patient stratification**
- **Multimorbidity and frailty**
- **Understanding a diverse patient population (poverty, low literacy association – social aspect of COPD)**
- **Home monitors for acute exacerbation of COPD (AECOPD) to:**
  - evaluate severity of exacerbation
  - identify events to receive further biomarkers tests
- **CO2 monitoring**

### Rehabilitation and changes in life-style

- **Stopping smoking**
- **What to measure for life-style index**
- **Sensing, feedback, and monitoring in community and workplaces**
- **Self-management**
- **Rewards and behaviour change:**
  - reward to ensure compliance
  - reward and real-time feedback
  - reward and concordance
- **Simpler devices for home care**
- **Support for physical activity and home-based rehabilitation**
- **Symptoms management and education – scope for monitoring cough, sputum, dyspnea, and psychological state**
- **Wearable sensing technologies with intelligent on-node processing**
- **Improved embodiment and flexible electronics to ensure compliance and comfort**
- **Data processing and fusion of data streams to flag adverse events**

### Medications and therapy

- **Better therapeutic approaches**
- **Inhaler use – reinforce correct use**
- **Secondary prevention**
- **Exacerbations management**
- **More reliable home biomarkers**

### Surgeries

- **Improved minimally-invasive surgical interventions**
- **Endobronchial intervention and potential integration of microscopic imaging and robotic guidance**
- **New materials and designs for bronchial implants**
- **Smart implants both for functional restoration and real-time sensing and monitoring**
Psychological impact of COPD

In addition to its pulmonary manifestations, COPD is associated with significant extrapulmonary effects. These may further affect the severity of the disease and physiological well-being of patients and their quality of life. Despite being major COPD comorbidities, depression and anxiety still remain under-recognised and poorly treated. They contribute to a substantial burden of COPD through their impact on physical functioning and social interaction. Furthermore, they often contribute to a reduced adherence to treatment (Yohannes and Alexopoulos, 2014). Depression and anxiety are difficult to identify because their symptoms often overlap with those of COPD, and there are many underlying causes. These are multifactorial in nature and include behavioural, social and biological factors.

The prevalence of depression and anxiety in patients with COPD is higher than in the general population. For stable COPD patients, depression ranges from 10% to 57%, while for anxiety, this varies from 7% to 50%. Patients requiring long-term oxygen have a depression rate of around 57%, while about 18% have a severe form of depression (Pumar et al., 2014). Risk factors for COPD related depression include living alone, increased severity of respiratory symptoms (especially dyspnoea), having exacerbation or needing hospitalisation, impaired physical functioning, and gender (with females having a higher rate of both anxiety and depression).

The mechanism of linking COPD with depression and anxiety is bi-directional in nature. Among the causes for increased mortality with anxiety and depression are failure in smoking cessation and poor treatment compliance. In other words, patients with anxiety and depression are more likely not to complete rehabilitation programmes and they are often non-adherent to their prescribed medications. Depression can also have direct effects on the immune system and consequently predisposing to infections that may further lead to increased exacerbations frequency. Worsened perception of dyspnoea may prompt patients to seek medical attention unnecessarily, thus increasing hospital admissions. Patients with anxiety and depression tend to have worse dyspnoea scores during admission, despite having less severe physiological parameters (e.g., pH, partial pressure of oxygen and carbon dioxide). Anxiety could also be used as a clinical marker of disease severity and risk of death (Pumar et al., 2014).

The experience of COPD sees patients coming to terms with a loss of a range of taken-for-granted body functions. The limiting aspects of COPD have been captured by Gullick in a recent review of the disease’s psychosocial dimensions (Gullick, 2012). It illustrates the nature of the changes experienced by people living with COPD and their families.

The impact on natural breathing is at the forefront of the COPD manifestations, with distressing breathlessness being brought about even by simple activities (e.g. walking and climbing stairs), strong emotions, or environmental triggers (e.g., extreme temperature change, smoke, or even perfumes). During acute breathlessness episodes, patients can feel helpless with little control of their bodies. They can panic and develop a fear of suffocation or dying. However, patients can bring respiratory distress under control through breathing techniques such as slow breathing, diaphragmatic breathing and pursed-lipped breathing. All these are effective ways to manage breathlessness attacks.

The COPD experience is also marked by other issues such as a loss of control and changed body behaviors (e.g., coughing and wheezing or spum production), thus drawing unwanted attention to the patient. The ‘visibility of the illness’ often means patients detracting from enjoyable participation in family and community activities, thus diminishing their sense of personal worth and social status (Gullick, 2012).

Many of the COPD patients also suffer from anorexia and weight loss that are correlated with worsening breathlessness. Meals are often challenging during exacerbations, as coughing before or during meals can be tiring, making eating difficult. Furthermore, people feel embarrassed by food left on their plate, and they tend to have a sense of failure, anger or sadness when they are not able to eat properly (Gullick, 2012). COPD is also characterised by a loss of the body’s spontaneity, and activities such as talking while walking can be difficult. Breathlessness requires more planning, allowing for more time, pacing the body, and spacing out of activities.

Physical effectiveness, defined as ‘being able’, is a core component of personal worth. If contribution is diminished or lost due to ineffectiveness and dependence, people can feel ashamed, self-blame and perceive the blame of others (Barnett, 2005, Lindqvist and Hallberg, 2010). If a loss of independence is a threat to a patient’s sense of hope, then the feeling of ‘becoming a burden’ closely follows. The loss of independence and corroborated with the loss of family and community roles may lead to frustration, irritability, depression and a sense of meaningless of life. People often communicate hopelessness, worthlessness and resignation. Furthermore, hypoxia may result in cognitive and personality changes including manifested as hallucinations, confusion, memory loss, or unreasonable and unsociable behaviours (Boyle, 2009, Gullick and Stainton, 2008).

The confining nature of COPD has also been defined as living within a shrinking world (Gullick and Stainton, 2008). The physical boundaries of the patient’s life diminish as they avoid taxing outings. This means they become increasingly socially isolated and their consciousness of their failing body and loss of control makes them reluctant to engage in new social activities. Consequently, patients lose shared experiences with family and friends, leading to feelings of loneliness, sadness and abandonment.
Psychological treatments used in COPD are based on guidelines already used for depression and anxiety in the wider population. Treatments can be divided into psychological and pharmacological interventions. Pulmonary rehabilitation, a specific treatment for COPD, also has beneficial effects on anxiety and depression.

Cognitive behavioural therapy (CBT) is a type of psychotherapy based on an ‘information-processing model, in which emotional symptoms are thought to be driven by negatively biased evaluations of the world, the future, or the self’ (Pumar et al., 2014). CBT is often performed as a collaboration between the therapist and the patient and uses strategies to correct for these biased evaluations.

The effectiveness of pharmacotherapy for anxiety and depression is surrounded by controversies, though several studies have shown the benefit of medication in the treatment of anxiety and depression (Pumar et al., 2014). Antidepressants are the mainstream treatment for depression and anxiety, but benzodiazepines, antipsychotics, anticonvulsants and azapirones are also used. Finally, Behaviour Change Interventions (BCIs) offer advice, support, and relevant information. Traditionally, they have been used to improve both physical and mental well-being.

More recently, the Internet has been explored as a medium for mass BCI delivery through the development of Digital Behaviour Change Interventions (DBCIs). DBCIs can provide continuous, multi-modal access to information and surveys, and tools like LifeGuide, EmotionSense and SociableSense have been developed to allow for DCBIs to be designed, built, and deployed seamlessly on the web (Lathia et al., 2013).
Evolution of Wearable Technologies

1976
Mini-Holter Recorder (NMAH, 2011)

2001
Artifact-resistant power-efficient design of finger-ring plethysmographic sensors (Rhee et al., 2001)

2003
Reconfigurable point-of-care systems designed with interoperability standards (Warren et al., 2004)

2005

2006
HealthGear: a real-time wearable system for monitoring and analysing physiological signals (Oliver and Flores-Mangas, 2006)

2008
A wireless sensor network compatible wearable u-healthcare monitoring system using integrated ECG, accelerometer and SpO2 (Chung et al., 2008)

2012
An Electronic Patch for Wearable Health Monitoring by Reflectance Pulse Oximetry (Haahr et al., 2012)

2014
Development of a luminous textile for reflective pulse oximetry measurements (Krehel et al., 2014)

All-organic optoelectronic sensor for pulse oximetry (Lochner et al., 2014)
Spirometry
The chronic airflow limitation characteristic of COPD is best evaluated by spirometry. Spirometry is the most widely available way of assessing lung function by measuring the volume of air a patient can expel from the lungs after a maximal inspiration. It is a reliable way to differentiate between obstructive airways disorders (e.g., COPD, asthma) and other restrictive diseases (where lung size is reduced, e.g., fibrotic lung disease). If performed correctly, spirometry is considered the most reproducible and objective measurement of airflow limitation and the most effective way of determining the severity of COPD. Approximately 70–80% of UK practices are equipped with spirometers and their use is increasing. Practice nurses predominantly perform the tests but many lack confidence to carry out the procedure or interpret the results. Hence many clinicians are concerned about the accuracy of spirometry performed by untrained people.

Spirometry measures the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC) and the volume of air exhaled during the first second of this manoeuvre (forced expiratory volume in one second, FEV₁). The ratio of these two measurements (FEV₁/FVC) should be calculated. The ratio between FEV₁ and slow vital capacity (VC), FEV₁/VC, is sometimes measured instead of the FEV₁/FVC ratio. This often leads to lower values of the ratio, especially in pronounced airflow limitation. However, the cut-off point of 0.7 should still be applied. Spirometry measurements are evaluated by comparison them with reference values based on age, height, sex, and race (GOLD, 2016).

2.1 Devices for COPD

Oximetry and arterial blood gas measurement
Pulse oximetry can be used to evaluate a patient’s oxygen saturation and need for supplemental oxygen therapy. Pulse oximetry should be used to assess all stable patients with FEV₁ < 35% predicted or with clinical signs suggestive of respiratory failure or right heart failure. If peripheral saturation is < 92% arterial blood gases should be assessed (GOLD, 2016).

Inhalers
Inhalers are small, handheld devices that deliver a puff of liquid, dry powder or soft mist medicine to the airways. Metered-dose inhalers contain the liquid medicine in a small, pressurised reservoir and deliver a predetermined dose as an aerosol spray. Dry powder inhalers are similar, but release a puff of dry powder, while the soft mist inhalers provide a pre-measured amount of medicine in a slow moving mist that helps the inhalation of the medicine.

Nebulizers
Nebulisers convert liquid medicine into a mist that’s inhaled into the lungs. Nebulisers can be small in size and portable. Traditionally mains powered, they’re mainly designed for use in clinic or at home. Medicine is measured and poured into a cup attached by tubing to the machine. The air-flow creates a mist that is inhaled through a mask or mouthpiece. Depending on the amount of medication, it can take 20-25 minutes to inhale the medicine.

Oxygen therapy device
Oxygen therapy is a key part of treating patients with chronic respiratory failure. Long-term administering of oxygen (more than 15 hours a day) has been shown to increase survival rates of patients with severe resting hypoxemia. Oxygen therapy is also a key hospital intervention in treating exacerbations, where supplemental oxygen is titrated to improve patient’s hypoxemia to a target oxygen saturation of 88–92%. Oxygen is delivered via nasal cannula (prongs) or venturi masks. High-flow oxygen therapy devices, such as nasal prongs offer a more accurate and controlled delivery of oxygen, but fewer patients accept them.

Ventilatory support
Ventilatory support can be non-invasive ventilation (NIV) or invasive mechanical ventilation (by orotracheal tube or tracheostomy).

NIV allows ventilator support without using an invasive artificial airway, as it’s delivered through the nose or facemasks. The use of NIV has markedly increased over time among patients hospitalised with acute exacerbations, and those with stable but severe COPD. NIV’s success rate is 80–85% and has been shown to improve acute respiratory acidosis, decrease respiratory rate, work of breathing, severity of breathlessness, complications and length of hospitalisation (GOLD, 2016). Moreover, NIV reduces mortality and intubation rates and has become an integral tool in the management of acute and chronic respiratory failure, both in hospital critical care units and domestic settings.

Invasive mechanical ventilation is a way to assist or replace spontaneous breathing via the use of an orotracheal tube or tracheostomy. It’s designed as a lifesaving intervention for patients with respiratory failure, but its indication during an exacerbation includes failure of an initial NIV trial. Weaning from mechanical ventilation can be particularly difficult and hazardous among patients with COPD (GOLD, 2016).
A spirometer measures the volume of air inspired and expired. There are different techniques for air measurements, ranging from pneumotachometer, body plethysmograph, incentive spirometer, peak flow meter to and windmill type spirometer. Different parameters can be measured or deduced. The most used one are FEV₁, FVC, TLC and VT.

Spirometry has been used as the gold standard of early stage COPD detection. Yet, test quality and reproducibility are crucial to monitor the evolution of the patient’s COPD condition. For example, using the tiotropium anticholinergic bronchodilator, 5,993 COPD patients took part in a randomised, double-blind, placebo controlled study using the tiotropium anticholinergic bronchodilator to evaluate spirometry quality and reproducibility tests (Janssens et al., 2013). With at least three tests performed during 93% of the visits, FEV₁ was measured for within-test variability of pre and post- bronchodilator and compared across visits. Results showed a decrease in the within-test for both pre and post- bronchodilator (SD=0.092 and 0.098 L). Between-test variability was also assessed and showed similar results: \( \text{pre-FEV}_1 (\text{visit 3-5} = 0.141 \pm 0.138 \text{ L}; \text{visit 9-11} = 0.129 \pm 0.121 \text{ L}; \text{visit 17-19} = 0.121 \pm 0.122 \text{ L}) \) and post-\( \text{FEV}_1 (0.139 \pm 0.140, 0.126 \pm 0.123, 0.121 \pm 0.122 \text{ L}, \text{respectively}). \) Further analysis suggested that those results depended on age, sex, smoking status and disease stage, but were independent on the bronchodilator. In addition, the factor from which the FEV₁ depends on hardens the definition of strong personalised thresholds.

To ensure quick diagnoses and intervention, it is crucial to make spirometers easily available. Most devices are used in laboratories, but patients usually first complain and expose their symptoms to a GP. A study involving 388 patients to investigate the validity of spirometric tests in 61 GP clinics, compared with laboratory tests. FEV₁ and FEV were measured in each site (Schermer et al., 2003). Mean of the difference FEV₁ between GP and laboratory tests is 0.069 l (95% CI 0.054 to 0.084), while, the difference FVC between GP and laboratory test is 0.081 l (95% CI 0.053 to 1.09). Further research was performed on the necessity of spirometry measurement for early detection of COPD in GP clinics (Buffels et al., 2004). A prospective survey involving 3,408 patients was conducted; excluding patients with already diagnosed with COPD (n=250). It was demonstrated that although the questionnaire provided 58% sensitivity, 78 % specificity and 2.6 likelihood ratio, 216 cases of obstructive lung disease (OLD) were detected and 42% would not have been diagnosed without spirometry.

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>FEV₁</td>
<td>Force expiratory volume in 1 second</td>
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<tr>
<td>ERV</td>
<td>expiratory reserve volume</td>
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<tr>
<td>IRV</td>
<td>inspiratory capacity volume</td>
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<tr>
<td>IC</td>
<td>inspiratory capacity</td>
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<tr>
<td>IVC</td>
<td>inspiratory vital capacity</td>
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<tr>
<td>VC</td>
<td>vital capacity</td>
</tr>
<tr>
<td>FVC</td>
<td>forced vital capacity</td>
</tr>
<tr>
<td>FIF</td>
<td>forced inspiratory flow</td>
</tr>
<tr>
<td>PEF</td>
<td>peak expiratory flow</td>
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<tr>
<td>MVV</td>
<td>maximum voluntary ventilation</td>
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<tr>
<td>FRC</td>
<td>functional residual capacity</td>
</tr>
<tr>
<td>RV</td>
<td>residual volume</td>
</tr>
<tr>
<td>TLC</td>
<td>total lung capacity</td>
</tr>
<tr>
<td>VT</td>
<td>tidal volume</td>
</tr>
<tr>
<td>EVC</td>
<td>expired vital capacity</td>
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With increasing miniaturisation of sensing technologies, mobile spirometers are becoming increasingly available. Whilst their accuracy and regulatory considerations are being addressed, they offer significant opportunities in patient self-management combined with remote rehabilitation. Figure 3 outlines the evolution of spirometer and how it moves from specialist laboratory equipment to everyday use.
<table>
<thead>
<tr>
<th>Technics</th>
<th>Description</th>
<th>Advantages</th>
<th>Limitations</th>
<th>References</th>
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<tbody>
<tr>
<td>Pneumotachometer</td>
<td>Converts the flow of gas into a proportional signal of pressure difference.</td>
<td>• Portable</td>
<td>• Only investigates exhaled flow</td>
<td>(Turney and Blumenfeld, 1973, Yeh et al., 1982)</td>
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<td></td>
<td></td>
<td>• Cheap</td>
<td>• Requires strong calibration</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Disposable</td>
<td></td>
<td></td>
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<tr>
<td>Body plethysmograph</td>
<td>Using a volume constant box, volume variation can be measured based on pressure changes. Main parameters deduced include: FRC, RV, ERV, EVC, IC, VT and TLC.</td>
<td>• A range of parameters can be measured and deduced including alveolar pressure and intrathoracic gas volume.</td>
<td>• Laboratory use • Price</td>
<td>(Criée et al., 2011)</td>
</tr>
<tr>
<td>Incentive spirometer</td>
<td>Based on the gauge results, the patients can monitor their own progress.</td>
<td>• Prevents pulmonary complications • Provides direct visual feedback • Improves oxygenation and lung function</td>
<td></td>
<td>(Bellet et al., 1995, Basoglu et al., 2005)</td>
</tr>
<tr>
<td>Peak flow meter</td>
<td>Measures the maximum speed of expiration. It provides qualitative results on the degree of obstruction in the airways.</td>
<td>• Cheap • Hand held</td>
<td>• Requires careful calibration • Results are qualitative</td>
<td>(Wright, 1978)</td>
</tr>
<tr>
<td>Windmill type spirometer</td>
<td>Similar to incentive spirometer.</td>
<td></td>
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<tr>
<td>Compact devices</td>
<td>Hand held devices with direct visualisation of the results.</td>
<td>• Can be used by both clinicians and patients • Includes a built in monitor</td>
<td>• Bulky system • Price</td>
<td>Contec company (Contec, 2016) • Nspire health (nSpire Health, 2016)</td>
</tr>
<tr>
<td>Smartphone based spirometry</td>
<td>Using a hand held device for blowing, the device is linked to a mobile application for data recording and display.</td>
<td>• Price • Can be used by both clinicians and patients • Flexible platform</td>
<td>• Requires a hand held device in addition to a smart phone</td>
<td>MySpiroo (HealthUp, 2016) • SmartSpirometry (Pond Healthcare Innovation, 2016) • Respi (Respi, n.d.) • Cohero (CoheroHealth, 2016) • SmartOne (MiR, 2016) • SandPiper (Indiegogo, 2016) • Wing</td>
</tr>
<tr>
<td>Mobile application</td>
<td>Different parameters are measured by using the smartphone’s microphone. It can also be used for training to improve lung capacity with simple games.</td>
<td>• No additional device is required • Can reach a large number of people for early detection of COPD and prevention of AECOD • Display and evolution of the data is directly accessible to the patient and potentially to the clinical team with an online server</td>
<td>• Calibration and measurements can be difficult because of different smartphone hardware settings. During use, it needs to properly place the smart phone at a certain distance</td>
<td>SpiroSmart (Larson et al., 2012) • iSpirometer(iSpirometer, 2015, Barnes et al., 2015) • iBlow Ping-Pong Ball (iBlow, 2015) • iLung (iLung, 2015) • iPranayama (iPranayama, 2015) • Leaf Blower (Leaf Blower, 2015) • Blow Champ (Blow Champ, 2015, Chouvarda et al., 2014a)</td>
</tr>
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</table>

*Figure 3: Evolution of spirometer towards everyday use.*
Pulse oximetry – design and miniaturisation

Pulse oximetry is a non-invasive optical method based on spectroscopy that allows in vivo measurement of different haemoglobin concentrations. Spectroscopy is the study of interaction of light with materials: it takes into account the distinct physical interactions with the light source wavelength and the material. This interaction mostly depends on the type of covalent liaisons between atoms forming the molecules of the material. Each type of covalent liaison with specific atoms reacts (vibrates) to a specific light source wavelength. From this reaction, at the molecular level, light absorption or scattering is induced. The remaining light (scattered) can be measured using a photo detector to deduce the amount of specific material the incident light encountered. Indeed, the light diffuses in the environment before reaching the detector; according to the amount of light reaching the detector, the concentration of the parameter is deduced. In practice, the light can reach the photo detector using transmission or reflectance technics (Tamura et al., 2014). Either way, the environment needs to be reasonably transparent or thin for the photo detector measurements to be considered (Wukitsch et al., 1988).

Discovered in the early 1940’s, pulse oximetry and other spectroscopy technics, such as near infrared spectroscopy (NIRS), typically use red (680nm) and infrared (940nm) light sources in order to respectively measure oxygenated and deoxygenated haemoglobin levels. It is based on the fact that red light is extinct by deoxygenated haemoglobin, while, infrared light is extinct by oxygenated haemoglobin. It is widely used clinically for blood flow, velocity and oxygen level monitoring and neurovascular monitoring.

Specifically, pulse oximetry for blood pulse and arterial oxygenation saturation (SpO2) is based on the systolic and diastolic phases of the heart and provides a photoplethysmograph (PPG). They are usually placed on finger, ears, nose, forehead, and cheeks – where the blood vessels are close to the surface of the skin. Indeed, the light needs to go through all the skin layers in order to reach the blood vessels before being scattered towards the surface where measurement can be performed. Penetration depth needs to be deep enough to provide consistent results. It is generally proportional to the distance between the photo detector and the light source, with the scattering coefficient of the environment for the specific light wavelength and the light intensity. In cases where systolic and diastolic phases of the heart can not be detected, it is possible to measure the general oxygen level in the tissue (StO2). This also gives an approximation of the general oxygen level in the blood vessels.

Recent technological advances have made it possible to manufacture small and powerful light emitting diodes (LEDs) of different wavelengths, as well as miniaturised photo detectors. With the evolution of pervasive wearable sensors and computational devices, lightweight, comfortable, wireless pulse oximeters with real-time data analysis are emerging (Figure 4). Such devices can be used for COPD patients, who require continuous monitoring to detect AECOPD at an early stage and to request hospitalisation if necessary.

A study showed that pulse oximetry is widely used by GP (11 centres interviewed) for acute (14) and non-acute (11) situations. It is especially useful for close monitoring of patients with a severe stage of COPD or worsening symptoms, such as dyspnoea (Schermer et al., 2009). It is also used for SpO2 monitoring during physical exercise in stable and dyspnoea COPD patients. Although pulse oximetry is widely used for different situations, it is important to ensure that pulse oximetry can detect hypoxaemia. Although pulse oximetry is widely used with a high rate of true positive hypoxaemia detection, it is crucial to provide reliable thresholds to clinicians to help diagnosing the severity of the patient. In particular, a cross-sectional study monitoring 2,181 AECOPD episodes in 16 Spanish hospitals aimed at detecting and validating thresholds for hypoxemia has been performed (Garcia-Gutierrez et al., 2015). SpO2, arterial blood gasometry values, socio-demographic information, background medical history and clinical variables are measured at arrival. Results showed high correlation (0.89) between SpO2 and arterial blood gasometry, with the area under the ROC curve for hypoxemia model at 0.97 and the SpO2 threshold being 90%. For hypercapnic respiratory failure, the area under the ROC curve is 0.90 and the SpO2 threshold is at 88%.

Figure 4: Road to miniaturisation, smaller, smarter pulse oximetry with motion resilience and multi-wavelength detections.

Pulse oximetry – design and miniaturisation

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Discovered in the early 1940’s, pulse oximetry and other spectroscopy technics, such as near infrared spectroscopy (NIRS), typically use red (680nm) and infrared (940nm) light sources in order to respectively measure oxygenated and deoxygenated haemoglobin levels. It is based on the fact that red light is extinct by deoxygenated haemoglobin, while, infrared light is extinct by oxygenated haemoglobin. It is widely used clinically for blood flow, velocity and oxygen level monitoring and neurovascular monitoring.

Specifically, pulse oximetry for blood pulse and arterial oxygenation saturation (SpO2) is based on the systolic and diastolic phases of the heart and provides a photoplethysmograph (PPG). They are usually placed on finger, ears, nose, forehead, and cheeks – where the blood vessels are close to the surface of the skin. Indeed, the light needs to go through all the skin layers in order to reach the blood vessels before being scattered towards the surface where measurement can be performed. Penetration depth needs to be deep enough to provide consistent results. It is generally proportional to the distance between the photo detector and the light source, with the scattering coefficient of the environment for the specific light wavelength and the light intensity. In cases where systolic and diastolic phases of the heart can not be detected, it is possible to measure the general oxygen level in the tissue (StO2). This also gives an approximation of the general oxygen level in the blood vessels.

Recent technological advances have made it possible to manufacture small and powerful light emitting diodes (LEDs) of different wavelengths, as well as miniaturised photo detectors. With the evolution of pervasive wearable sensors and computational devices, lightweight, comfortable, wireless pulse oximeters with real-time data analysis are emerging (Figure 4). Such devices can be used for COPD patients, who require continuous monitoring to detect AECOPD at an early stage and to request hospitalisation if necessary.

A study showed that pulse oximetry is widely used by GP (11 centres interviewed) for acute (14) and non-acute (11) situations. It is especially useful for close monitoring of patients with a severe stage of COPD or worsening symptoms, such as dyspnoea (Schermer et al., 2009). It is also used for SpO2 monitoring during physical exercise in stable and dyspnoea COPD patients. Although pulse oximetry is widely used for different situations, it is important to ensure that pulse oximetry can detect hypoxaemia. Although pulse oximetry is widely used with a high rate of true positive hypoxaemia detection, it is crucial to provide reliable thresholds to clinicians to help diagnosing the severity of the patient. In particular, a cross-sectional study monitoring 2,181 AECOPD episodes in 16 Spanish hospitals aimed at detecting and validating thresholds for hypoxemia has been performed (Garcia-Gutierrez et al., 2015). SpO2, arterial blood gasometry values, socio-demographic information, background medical history and clinical variables are measured at arrival. Results showed high correlation (0.89) between SpO2 and arterial blood gasometry, with the area under the ROC curve for hypoxemia model at 0.97 and the SpO2 threshold being 90%. For hypercapnic respiratory failure, the area under the ROC curve is 0.90 and the SpO2 threshold is at 88%.
2.2 Biomarkers for COPD

COPD is associated with reactions at different levels according to the pathology and its severity. At the macroscopic level, direct consequences of COPD are for example exacerbations, weight loss, reduced quality of life and other comorbidities (Jones and Agusti, 2006). These symptoms generate measurable physiological changes, using for example, imaging technics (e.g. CT scan, MRI) or other parameters (e.g. FEV1, 6MWD, bronchial hyperactivity, lung hyperinflation or inspiration capacity scores). At a lower level, physiological changes are associated with biological processes involving protein reactions from either genic (depending on a patient’s genes) or drug treatment (depending on reactions to drugs taken) processes. Consequently, physiological and biological changes involve markers. These are defined as ‘a measurement known to be associated with a clinical outcome’ (Jones and Agusti, 2006). A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological process, pathogenic process or pharmacological response to therapeutic interventions’ (Jones and Agusti, 2006).

Mostly considered as a biochemical substance, they are particularly measured and considered using concentration, rate, and presence or absence. Generally, the severity of the dyspnoea and other symptoms are not correlated with lung function measurement (Nishimura et al., 2002). Similarly, COPD has numerous extra pulmonary effects that can’t be recognised with one marker alone (Agusti et al., 2003). Comorbidities and life environment also impact markers’ measurements (Agusti et al., 2012) and may bias results and diagnosis. One symptom can therefore be characterised by many markers (Jones and Agusti, 2006). In addition, not all markers provide the same indication on the pathology and its severity. Some markers (physiological and biological), for example, only provide a binary answer about pathology in terms of its presence or absence, or beyond a certain threshold.

Using different levels (e.g. mild, moderate and severe), the pathology can be defined with other categories of markers called disease severity markers. Disease progression can be measured in terms of the occurrence or disappearance of functionalised markers at some specific stage of the disease. These are called disease progression markers. Treatment effect markers are similar to disease progression markers as they usually inversely or oppositely evolve (Jones and Agusti, 2006).

With different classes of markers, COPD pathologies and comorbidities, as well as heterogeneousness responses among patients, it’s crucial to discover new markers that can potentially be combined to widen the current understanding of COPD – while providing better and personalised treatment. Discovery and acceptance of new markers is challenging; high correlation with macroscopic symptoms and the value or rate of the marker at all disease stages and all interventions usually takes years to demonstrate (Jones and Agusti, 2006).

Different extraction sites exist for biomarkers (e.g. blood, sputum, exhaled breath – volatile organic compounds (VOC) and exhaled breath condensate (EBC) – or urine sample). Each can provide different information about COPD condition and reaction to drug treatment. The number of biomarkers mainly depends on biochemical reactions or physical interactions (e.g. light), which provide reliable results after strong calibration.

However, sample requirements from patients imply possible GP or hospital visits with discrete results and monitoring. Despite the fact that in the particular case of expired gas samples, technical issues for collection and further condensation of the sample are raised, the exhaled gases contain direct information about the lung status and potential inflammation state. The choice of sample type relies on observed symptoms and knowledge of correspondent biomarkers and its likelihood presence; urine biomarkers are also found in blood and plasma at different concentration levels.

Specifically, possible biomarker analysis in a free-living environment is listed as eosinophil, α2-Val, C - reactive protein, HSP27, autoantibody antigen array, α-1-antitrypsin, α-2-macroglobulin, ceruloplasmin, hemopexin, sRAGE, MPO, hydrogen sulphide and peroxide, hyaluronic acid, NGAL, cysteinyll leukotriene, heparan sulphate and MMP9. Other biomarkers such as micro particles in plasma can be analysed clinically with FTIRS method, for example. However, most sample assessment is done in laboratories.
Although a promising number of biomarkers have been found for AECOPD prevention and COPD monitoring and comorbidities, more research and trials are needed to better understand the correlation between COPD pathology and status, and biomarkers concentration and occurrence. Similarly, specific combinations of biomarkers at different concentrations can provide further understanding of COPD conditions. Because each participant involved in treatment (patient and clinical team in particular) has different needs and expectations, the potential impact and full benefit of biomarker analysis remain to be determined. In the case of VOC, electronic nose gas chromatographs have been developed for possible GP use, as they showed high reproducibility and can distinguish between different pulmonary disease and asthma (Shaw et al., 2014).

### Common Abbreviations Used for COPD Biomarker Analysis

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>6MWD</td>
<td>6minutes walk distance</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>HSP27</td>
<td>Heat shock protein 27</td>
</tr>
<tr>
<td>sRAGE</td>
<td>Soluble receptor for advanced glycation end products</td>
</tr>
<tr>
<td>MPO</td>
<td>Sputum myeloperoxidase</td>
</tr>
<tr>
<td>NGAL</td>
<td>Neureophil gelatinase-associated lipocalin</td>
</tr>
<tr>
<td>FTIRS</td>
<td>Fourier transform infrared spectroscopy</td>
</tr>
<tr>
<td>MMP9</td>
<td>Matrix metalloproteinase-9</td>
</tr>
<tr>
<td>VOC</td>
<td>Volatile organic compounds</td>
</tr>
<tr>
<td>EBC</td>
<td>Exhaled breath condensate</td>
</tr>
<tr>
<td>HRQL</td>
<td>Health related quality of life</td>
</tr>
<tr>
<td>α1-antitrypsin</td>
<td>A1AT</td>
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Table 1: Categories of markers
Imaging Technologies for COPD

Chest radiography (X-ray) is integral to the first evaluation of a patient with suspected COPD as it offers a differential diagnostic tool. Although not a definite diagnosis modality for COPD, it helps exclude other diseases with similar symptoms such as congestive heart failure, interstitial lung disease, pleural effusions and pulmonary infections (Barnes et al., 2015). In early COPD, X-rays frequently appear normal, but as the disease progresses, radiographic changes become apparent. These changes include lung hyperinflation and hyperlucent areas in the lungs, with peripheral trimming of vascular markings (Celli et al., 2015).

Computer tomography (CT) has contributed substantially to the understanding COPD over the past decade. Although not routinely recommended, CT remains the most effective modality to characterise and quantify COPD, particularly if a diagnosis is in doubt. CT scans can estimate the degree of emphysema and its distribution, and identify bronchial wall thickening and gas trapping. These estimates correlate with lung-function abnormalities, but there are considerable variations among interpretations of these studies. Additional advantages of CT scanning include:

- helping differentiate between structural abnormalities causing airflow limitation (e.g. emphysema, bronchiolitis, and bronchiectasis)
- identifying abnormalities associated with clinically significant features (i.e. phenotypes)
- detecting pulmonary comorbidities (e.g. lung cancer, interstitial lung disease, pulmonary hypertension) and non-pulmonary comorbidities (e.g. coronary artery calcifications, heart failure, diseases of the mediastinum) (Celli et al., 2015).

Magnetic resonance imaging (MRI) of the lung is challenging using conventional techniques. However, advances in MRI imaging have shown that visualising low-proton areas of emphysema is possible with standard (proton) MRI (Lynch, 2014). Furthermore, administering contrast agents via inhalation can enhance the image details. Non-radioactive noble gas isotopes such as hyperpolarised 3-He and 129-Xe are used for imaging emphysema. Following inhalation of 3-He, MRI’s diffusivity can be used to estimate the size of lung microstructures, including alveolar ducts and alveoli. In cigarette smokers with absent or mild spirometric abnormality, this technique showed a significant decrease in alveolar depth and enlargement of alveolar ducts (Lynch, 2014). However, using hyperpolarised helium for research or clinical applications is limited by this isotope’s scarcity and high cost. Hence, 129-Xe gas is receiving more attention, as it’s more abundant and less expensive. Other potential agents include oxygen, carbon-13 and perfluoropropane (Lynch, 2014). Despite the progress in magnetic resonance imaging, it is still only used as a research tool to evaluate COPD.

Endobronchial ultrasound (EBUS) was initially developed for diagnosing and staging of non–small cell lung cancer. EBUS is increasingly used in nononcologic pulmonary diseases. It has emerged as a promising technique to assess airway remodelling of patients with asthma. EBUS combines bronchoscopy with ultrasound to enhance the definition of mediastinal structures and aid in visualising parabronchial anatomy (Jalil et al., 2015). Other advantages of EBUS include rapid on-site results and fewer biopsy sampling errors.

Optical coherence tomography (OCT) is a high spatial resolution imaging technique. It uses low-coherence near-infrared light to image cellular and extracellular structures by detecting reflected light from tissue structures and building cross-sectional images through optical interferometry. OCT – performed during bronchoscopic examination – is safe for patients (no associated risks from weak near-infrared light) and can be used for in vivo imaging of small airways with near microscopic resolution (Chung et al., 2011). When applied to COPD patients, OCT measures of airway dimensions correlated well with CT measures and lung function.

Confocal florescence endomicroscopy is a real-time, microscopic technique using excitation laser light (488nm or 660 nm), along with thin flexible miniprobes in the working channel of a bronchoscope for in vivo imaging of the pulmonary tissue. The technique has a small field of view (600 µm) and a lateral resolution of 3 µm, but has potential applications in qualitative and quantitative assessment of the basement membrane, terminal airways, and alveoli in obstructive lung disease (Chung et al., 2011).
While COPD is recognised as a heterogeneous lung disease, the underlying mechanisms leading to the disorder are still not fully understood. There is also a lack of precise, biologically based and clinically applicable definitions of emphysema and COPD. In particular, certain subtypes of emphysema have been found to correlate with different risk factors and are therefore likely to represent different diseases. Computed tomography (CT) imaging provides rich in-vivo information of the lung parenchymal structures, airways and vasculature.

On going research work in this field (Hame et al., 2015a, Hame et al., 2015b, Hame et al., 2014) aims to exploit CT lung imaging as a new ‘microscope’ for lung structure examination and categorisation into quantitative emphysematous lung texture patterns (LTPs). Two large cohorts of COPD subjects are used: the large Multi-Ethnic Study of Atherosclerosis (MESA, 2016) counting 319 full-lung CT scans and the SubPopulations and InteRmediate Outcome Measures In COPD study (Spiromics, 2016).

The computational system uses a novel and robust segmentation tool, based on a hidden Markov measure field (HMMF) model to for the segmentation of emphysema on CT scans. The results are shown in figure below.

Further developments aim for unsupervised discovery of emphysematous LTPs using radiological features. This is to demonstrate the clinical relevance of the LTPs by correlating with respiratory symptoms, patient’s outcomes (respiratory hospitalisation and death), and genetics. Longitudinal progression of LTPs in the general and disease populations over 10 years will confirm the sensitivity of patients’ follow-up with CT scans. The final goal is to validate LTPs as a reliable method to phenotype emphysema into sub-types that have major prognostic significance, contribute to symptoms, and have a genetic underpinning. The proposed LTPs, being derived from automated processing tools, will be efficient, low-cost, reproducible, comprehensive, and highly translatable into clinical practice.
Figure 3: Pipeline for the unsupervised learning of emphysematous lung texture patterns (LTPs) on CT images. Several image features (Textons, DoG and LBP) are tested to characterize the texture. Output enables the labeling of lung regions into K=100 distinct LTPs. We showed that LTPs can predict the three standard emphysema subtypes (CLE, PLE and PSE) currently used by radiologists.

- **Unsupervised Learning of LTPs.**
- **Represents lung volumes with LTP histograms.**
- **“validation”:** Predict the extent of standard emphysema subtypes from LTP histograms.
3 Emerging technologies of COPD

3.1 Wearable devices

Advances in sensing technologies allow the development and commercialisation of high-quality miniaturised wearable platforms at relatively low cost. Numerous pervasive sensing platforms have been proposed for health monitoring, from detecting arrhythmias and abnormal gait, to behavioural and stress analysis. Being able to continuously stream physiological and activity data and seamlessly integrate it with the Internet of Things, means wearable devices could provide key information for big data analytics and knowledge discovery for disease diagnosis, patient management, and epidemiological analysis.

Due to a growing interest from consumers, numerous wearable devices are commercially available, although the majority are designed for fitness and wellbeing applications. Many devices have also been introduced for monitoring patients with COPD and the associated comorbidities (see table 1). Most are based on movement recognition (e.g. pneumogram, physical activity, body positioning), blood flow and pulse analysis, and use different detection methods, such as spectroscopy (the interaction of light with a material), accelerometry, temperature and audio sensing. Although they allow home and continuous monitoring wirelessly and online data management, the technologies lack demonstrable evidence of the clinical benefits. They’re bulky, have limited battery life, and often aren’t used widely as they require user input. In addition to dedicated devices, recent studies have looked at the use of new low-cost consumable activity monitors to assess the energy expenditure and state of patients (Caufield et al., 2014).

Further research and clinical trials are required to show evidence of the clinical benefit of wearable devices and patient acceptance. Specifically, the parameters measured by the wearable devices would have to be combined with other biomarker measurements to enable definitive diagnosis and a clear overall evolution of pathologies.

Highly specialised equipment such as mass spectroscopy is often used to analyse biomarkers. New equipment is smaller and significantly more cost-effective and may become widely available. Studies show volatile organic compound (VOC) profiles can be used to diagnose COPD using mass spectrometry, which can identify individual compounds and the compositions from breath very accurately. However, the size and high cost of the machine has prohibited the general use of mass spectroscopy in clinical diagnosis. Recent research has proposed a portable spectrometer to enable detailed chemical analysis (Hendricks et al., 2014). Although the instrument – designed for environmental and forensic monitoring – is still far too cumbersome for widespread use, the advances could lead to further miniaturisation and development of low-cost diagnosis instruments. On the other hand, the concept of e-Nose has been developed rapidly following advances in biochemical sensing. From the breath, new e-Nose sensors can detect multiple clinically relevant parameters for diagnosing COPD (De Vries et al., 2015, Sibila et al., 2014).

Recent advances in material science have led to the development of novel sensing technologies, such as flexible electronics, organic optoelectronics (Lochner et al., 2014), photonic textiles (Krehel et al., 2014), tattoo sensing etc. The new generation of wearable technologies may no longer be wristbands or glasses, and instead be fabrics, patches, tattoo papers or stamps.
Evolution of wearable technologies

Wearable technologies have been widely used in medical and healthcare applications for many decades. The Holter monitor, was first introduced in 1970s, and it is still being used as a main medical device to assess condition of cardiac patients. Early wearable healthcare devices were mainly designed with dedicated functions and tend to be bulky.

Recent advances in the semiconductor and wireless technologies have allowed the miniaturisation of devices, and introduced a range of new wearable technologies for sports, well-being and healthcare applications. Following Moore’s low, computer and associated technologies have advanced in an exponential rate. Apart from increasing the density of transistors on the silicon and speed of the processors, the size and energy consumption of the computers have been reduced rapidly. Advances in computer technologies together with the recent developments in low-power wireless communication and biosensors have led to the rapid development of wearable technologies. This has motivated the development of body sensor networks (Yang, 2007, 2014).

Current designs of wearable healthcare devices are mainly targeted for capturing physiological parameters, such as chest strap ECG sensors, PPG ring sensors, the ear-worn activity recognition sensor, wrist worn activity monitors, waist worn gait analysis systems. The introduction of new materials has also led to the development of smart fabric sensors and e-textiles. Recent research has also been focused on stretchable electronics, tattoo and contact lens sensing for physiological monitoring. The size of the devices has reduced significantly over the years, evolving from backpack-sized devices to one that is as small as a finger nail.

In the last few years, many wearable devices aimed at consumers have been launched, from glasses, wristbands, to foot insoles and rings. Many believe that wearable technologies will be the next wave of technology after smartphones that will transform our society and daily life. Most of the available wearable technologies available today on the market are designed for fitness and human computer interface applications, but it is anticipated that wearable products will be widely adopted by the healthcare services soon.

Figure 6: Evolution of wearable technologies and uptake in recent years.
Recent research has explored the use of wearable devices for continuous monitoring of COPD and its comorbidities. In addition to their deployment in hospitals, wearable devices can be used in everyday life, providing real-time data and ensuring prompt intervention in case of AECOPD.

Different parameters can be monitored such as physical activity, heart rate, respiratory rate, tissue hydration, oxygen saturation, body weight, blood pressure, and blood glucose to provide crucial information about a patient’s general health. Different parameters can be measured using accelerometers (based on movements or vibrations), microphones (based on sounds), bio-impedance devices (based on skin resistance to electric current), and optical devices (based on the amplitude and frequency of the systolic and diastolic phases of the heart in blood vessels, or the amount of oxygenated haemoglobin in the skin or blood vessels).

Encouraging physical activities and exercises among COPD patients is essential for managing the progression of COPD and its comorbidities. An internet-mediated pedometer-based exercise intervention was performed with 239 COPD patients randomised in a 2:1 ratio (Moy et al., 2015). Assessing the health-related quality of life (HRQL) with the St George’s respiratory questionnaire total score (SGROQ-TS) and symptom, activities and impact domain scores at four months, the Omron HJ-720 ITC pedometer and an internet mediated program were used. Results show that the pedometer group walked 779 more steps a day than the control group with an improved HRQL. The study showed pedometer-based exercise intervention can indeed improve quality of life and physical activity levels.

Patel et al. (Patel et al., 2009) introduced an accelerometer-based device for motion monitoring – in particular, heart rate and respiration rate were investigated. With 15 COPD patients asked to perform activities of daily living (ADLs), results showed that using three sensors placed on the right side of the body with appropriate algorithmic training for activity recognition, different types of ADLs can be recognised. Similarly, results from (Chen et al., 2011) show that placing sensors on the forearm, thigh, and sternum can provide real-time classification of COPD patient activities.

Vests and t-shirts with integrated sensors have been developed to minimise a patient’s need to place sensors. Wearable Sensing and Smart Cloud Computing for Integrated Care to COPD Patients with Comorbidities (WELCOME) (Chouvarda et al., 2014b) and CHRONIOUS (Bellos et al., 2014) are cloud-connected platforms for remote control and monitoring of COPD using a vest with multiple sensors (based on accelerometers). Specifically, CHRONIOUS combines the vest sensors with external devices, such as blood pressure and glucose monitoring and a questionnaire in order to record the overall patient’s health condition. 30 COPD patients at stage III-IV according to the GOLD guidelines were involved in the CHRONIOUS study. After randomising the records to split patients into training and testing groups for disease classification into five levels, results show it is possible to categorise, with 94% accuracy, the severity of a patient’s status. Similarly, (Cuba-Gyllensten et al., 2014) developed a wearable vest evaluating tissue hydration to track clinical evolution by investigating signs and symptoms of congestion due to heart failure.

Although in principle more sensors can be deployed to each patient due to their increasingly small size and rapidly declining price, a large amount of data needs to be processed in order to produce meaningful clinical information. To this end, processing algorithms need to be made smarter to provide real-time outcomes. (Behara et al., 2013) developed a clinical support system for re-admission risk profiling for discharged patients. In addition to structured data (such as blood pressure, heart rate, oxygen level), the algorithm also takes into account unstructured data (such as notes, lab reports, drug treatment). Using a clinical natural language processing system, unstructured data is converted into a structured view to extract evidence that supports the likelihood of hospital re-admission or imminent AECOPD.

Current studies indicate that the use of wearable devices for monitoring COPD could reduce hospital admissions for home manageable AECOPD episodes. Continuous monitoring can provide an overview of disease evolution as well as the efficacy of drug treatment. However, larger studies are needed to ensure real positive healthcare impacts can be achieved for both COPD patients and clinicians.
3.2 Emerging sensing technologies

A range of sensing technologies can be used for COPD. These include lactate, volatile organic components, and tissue bio-impedance. These can be traditional sensing electronics or newly emerging smart textiles or flexible electronics.

**Volatile organic components (VOCs)** – (VOCs) – represents a wide class of organic molecules that are volatile at room temperature, which include various pathophysiological processes in the liver, kidneys and pancreas, or compounds formed by bacteria (Cazzola et al., 2015). A recent study found that there are 872 different types of VOCs detectable in the breath, and 359 VOCs in saliva (Costello et al., 2014). In particular, some VOCs from exhaled air have been identified as biomarkers for COPD, asthma, cystic fibrosis, and respiratory tract infections. Studies have shown VOC profiles could accurately identify patients with COPD (Basanta et al., 2010, Hauschild et al., 2012, Phillips et al., 2012). However, other studies have found that VOC profiles cannot differentiate COPD patients from (former) smokers (Fens et al., 2009, Cristescu et al., 2011). Although promising, standardisation and extensive clinical validation are required before the use of VOC can be adopted in clinical practice (Kant et al., 2012).

To analyse the content in breath, gas chromatography combined with mass spectrometry (GC-MS) are often used, as the process can reveal detailed concentrations of VOC compositions (Buszewski et al., 2007). However, the GC-MS process is time consuming and can’t be done in situ. New approaches, such as selected ion flow tube mass spectrometry (SIFT-MS) have been developed to analyse human breath. SIFT-MS measures complex mixtures in real-time without the time-consuming sample preparation. Studies show it can measure acetone, acetaldehyde, ammonia, ethanol and water vapour in a single-breath exhalation in real time (Spinhrine et al., 2003).

Although mass spectrometry can measure the chemical content in the breath very accurately, high equipment cost has prevented its widespread use for clinical diagnosis. Following advances in odour sensing, the concept of e-Nose has been investigated for clinical diagnosis, and some technologies have been adopted in medical diagnosis for tuberculosis (TB), and urinary tract infection (UTI) (Turner and Magan, 2004). Recent studies have shown that e-Nose can identify patients with COPD and analyse airway infection during COPD exacerbations (De Vries et al., 2015, Sibila et al., 2014). With new sensing technologies, such as the weight-dealtable quartz microbalance and silicon-based microcantilever sensor, e-Nose is getting smaller and more accurate (Yamagiwa et al., 2014).

Other methods for analysing VOCs for pulmonary diseases have also been proposed. These include proton transfer reaction mass spectrometry (PTR-MS), ion mobility spectrometry (IMS), laser spectroscopy, colorimetric sensor array and gold nano particles sensors (GNPs) (Kant et al., 2012).

**Lactate** - Exercise induces lactic acidosis in the body. With bronchioles clogged with mucus or air sacs walls destroyed, patients with COPD may not breathe in sufficient oxygen to remove the lactic acid produced during normal activities or exercise. Patients suffering from COPD often have a relatively high blood lactate level during normal activities compared to a healthy subject (Engelen et al., 1995). Lactate acid has therefore been proposed as the biomarker for assessing the severity of COPD pathology (Maekura et al., 2013). With advances in flexible electronics, novel approaches have also been proposed for sensing lactate in tears (Thomas et al., 2012), saliva (Kim et al., 2014) and sweat (Bergeron, 2003). Their practical use for COPD patients would need further investigation.

**Tissue bio-impedance** – Tissue bio-impedance can be used for non-invasive, continuous, low-cost, miniaturised, portable (and so point-of-care) and real-time imaging of the lungs and the heart (electrical impedance tomography, EIT) by using an array of electrodes (e.g. 16 or 32) (Leonhardt and Lachmann, 2012). Recently, several commercially available systems have emerged, all focusing on respiration monitoring to optimise mechanically assisted lung ventilation therapy (Timpel, 2012). Such imaging systems have been used clinically in COPD patients. In (Vogt et al., 2012) 14 young healthy adults with no history of lung disease, 12 elderly healthy subjects with no history of lung disease, and 33 patients with COPD were examined. According to the study’s results, EIT identified pathologic and age-related spatial and temporal heterogeneity of regional lung function. It’s important to highlight that the above indices cannot be identified by spirometry. A similar study was also presented in (Becher et al., 2016). As an imaging technique EIT is also used for cancer diagnostics, epileptic seizure detection and neurophysiological
Implantable and Wearable Medical Devices for COPD monitoring (Aristovich et al., 2016). Rather than a wearable imaging technology, bioimpedance can also be used as a wearable or implantable spectroscopic technique for interrogating tissues. It is used for detecting tissue ischemia and implantable probes have been used for monitoring the heart, liver, kidneys and intestines in the form of flexible electrode probes (Tijero et al., 2009), patches (Kassanos et al., 2015) or catheters (González et al., 2003), assessing extravascularly on large arteries cardiovascular parameters (Theodor et al., 2014). It is also applied to monitoring tissue hydration levels and detecting cancers (Prakash et al., 2015). In the micro and nano-scales, it is used to detect proteins, ss-DNA and clinically important markers (e.g. cancer biomarkers (Wu and Qu, 2015)) or bacteria (Jiang et al., 2015a).

Contactless sensing – Respiratory and heart rate monitoring can be performed in a contactless fashion using ultra wide band (UWB) radio methods (Chen and Rapajic, 2008, Nijsure et al., 2013, Zito et al., 2011). UWB radar allows unobstructive contactless monitoring of patients using impulses with pulse duration in the sub-nanosecond to nanosecond region (a 7.5 GHz bandwidth has been allocated between 3.1 and 10.6 GHz). The high resolution of such techniques allows the detection of the respiration and heartbeat. The disadvantage of these techniques is that the subject must not move. So current proposals for applying this technology are limited to monitoring subjects who are driving vehicles, sleeping, or in a hospital bed. Custom ASICs for such application have been proposed as well as novel antenna designs based on e.g. sinuous antenna geometries.

Smart textiles – Driven by the design industries, electronic textiles (e-textiles) are now more robust and reliable and being integrated into commercial products. By weaving circuits and sensors into fabrics, e-textiles have allowed comfortable, fashionable and biocompatible embodiment for healthcare, sports and wellbeing applications. These are important factors for long-term monitoring, particularly for ensuring COPD patient compliance. Recent studies have proposed using textile sensing to estimate the respiratory volume for patients with COPD (Enokibori et al., 2013).

Flexible electronics – After printable electronics using ink-jet printing, new materials, nanoscale resolution 3D printing, and advanced processing, approaches have led to developing new flexible and stretchable sensors. For example, tattoo-based sensors can enable continuous monitoring of glucose (Bandodkar et al., 2015). For example, MC10 has recently launched the BioStamp Research Connect (RC), a stretchable sensor patch for capturing cardiac and muscle activities (MC10, n.d.).

Figure 10: Factors allowing the emergence of 4P medicine

32 Implantable and Wearable Medical Devices for COPD
Flexible electronics

Wearable and, in particular, implantable medical devices, must address many additional design requirements – when compared to traditional portable electronics and sensing applications. The human body is intrinsically flexible and stretchable and not flat. Wearable and implantable devices must be integrated seamlessly so they don’t cause discomfort, bias or harm. They should conform to the geometry of the body, which is not possible using traditional rigid electronics. Together with advances in thin-film and other materials, micro- and nano-fabrication and nanotechnology, new advances have been made in the development of flexible and stretchable electronics using polymeric substrates.

Traditional clean room fabrication techniques, e.g., lithography using masks and photoresists, can be used to fabricate passive (resistors, inductors, antennas, capacitors and electrodes) and semiconductor devices (diodes and transistors), sensors and complete systems on flexible substrates. The development of nanoparticle-based inks has allowed screen and inkjet printing techniques among others to be used also for the development of such devices (Khan et al., 2015, Vyys et al., 2011). The advantage of these is lower fabrication costs and in the case of inkjet printing, maskless fabrication and thus reduced ink consumption, simplifying further the fabrication process and the associated costs.

Typical substrates used in flexible electronics applications include plastic polymer substrates such as polyimide (PI), polyethylene terephthalate (PET), polyethylene naphthalate (PEN) and polydimethylsiloxane (PDMS) silicone and other rubbers such as Solaris (Smooth-On, Inc., PA, USA) (Kim et al., 2011, Nathan et al., 2012, Xu et al., 2014, Yeo et al., 2013) and even with paper (Tobjörk et al., 2012) and silk (Tao et al., 2014) substrates for transient resorbable electronic devices. Flexibility and stretchability require special geometrical designs for the various devices and interconnects of the patterned features on the flexible substrates to allow durability and unhindered device performance under mechanical stresses.

Materials such as low-temperature polycrystalline silicon (LTPS), semiconducting metal oxides based on rare earth elements, hydrogen terminated amorphous silicon (α-Si:H) and organic semiconductors have all been investigated as candidate and promising materials for flexible electronics applications. These however do not simultaneously satisfy requirements such as low-temperature processing, high carrier mobility, stability, current capacity and thermal conductivity, low cost and large area availability (Sun et al., 2013). High aspect ratio 1D and 2D carbon-based materials, such as carbon nanotubes and graphene (Nathan et al., 2012, Sun et al., 2013) are an important family of materials with unique properties, which address all these issues and thus they play an important role in the development of flexible electronics for wearable, implantable, human computer interfaces and robotics applications (Nathan et al., 2012).

Electrodes fabricated on flexible and stretchable substrates with any of the above mentioned techniques can be functionalized for the realisation of electrochemical sensors for monitoring changes in pH, sodium, potassium, calcium, oxygen and lactate (Weltin et al., 2014, Xu et al., 2014). Such markers are important for detecting hypoxaemia, chronic respiratory acidosis and ischemia for example. Detecting inflammatory markers such as C-reactive protein (CRP), cytokines such as the interleukins (IL) IL-6 and IL-8 and procalcitonin (PCT) with such devices is also important for the various comorbidities of COPD. Tactile sensors can also be fabricated for wearable monitoring of the respiratory cycle (monitoring lung hyperinflation, respiration rate, prolonged respiratory duration) in the form of resistive or capacitive sensors used in thoracic belts (Bingger et al., 2012). Airflow sensors can also be fabricated on flexible substrates and used to examine respiration cycles (Jiang et al., 2015b, Shikida et al., 2015). In addition, polarisable and non-polarisable electrodes can also be fabricated for the measurement of ECG (Dieffenderfer et al., 2015, Wu and Qu, 2015) and tissue bio-impedance. Tissue bio-impedance using a minimum of four electrodes, can be used for the assessment of the cardiac cycle and monitoring of various cardiodynamic parameters, such as stroke volume, heart rate, cardiac output, and others (impedance cardiography).

Optical devices, such as photodetectors and light emitting diodes (LED) and transistors can also be fabricated on flexible and stretchable substrates (Xu et al., 2014). Thus, preliminary signal conditioning can be performed in the vicinity of the sensors to ensure signal integrity, while systems performing pulse oximetry can also be realised to assess tissue perfusion (Chu et al., 2016, Xu et al., 2014). As mentioned previously, cardiovascular diseases are an important family of COPD comorbidities. Such devices can be implanted or used externally for the assessment of bodily fluids and tissue. The seamless integration of such devices would allow continuous monitoring, and thus early detection of exacerbation episodes, such as increased dyspnea, cough, and changes of the sputum.

Gastroesophageal Reflux Disease (GERD) is another COPD comorbidity. Implantable devices for GERD combining pH electrodes and impedance sensors have been proposed (Cao et al., 2012, Gonzalez-Guillaumin et al., 2007, Hammond et al., 2005).
A multiparametric flexible sensing system on a polyimide substrate for in vivo measurement of glucose, lactate, oxygen and the neurotransmitter glutamate, was presented in (Weltin et al., 2014). Such devices can be developed and optimized for COPD monitoring. A wrist-worn reflectance oximetry sensor with an enhanced signal to noise ratio is presented (Chu et al., 2016) for continuous monitoring of oxygen levels in COPD patients. Such devices are effective for the detection and prevention of respiratory failure and aide in the reduction of COPD symptoms and comorbidities. The device demonstrated a performance within medical-grade specifications.

A wearable hot-wire anemometry sensor attached to the upper lip underneath the nostrils is presented in (Jiang et al., 2015b). The sensor was fabricated on a polyimide substrate and consisted of two resistors with low thermal sensitivity and two with a high temperature coefficient of resistance configured into a Wheatstone bridge arrangement. Off-the-shelf front-end electronics and Bluetooth modules were used to interface with the sensor and transmit the data to an aggregator. All components of the wireless system, including batteries, were cast within a PDMS encapsulation to provide a compact flexible platform. The device was tested using protocols simulating normal breathing, hypopnea and apnoea and measurements were corroborated with SpO\textsubscript{2} measurements, demonstrating the applicability of the device for COPD monitoring applications.

A textile-based capacitive respiration sensor was presented, which comprised of a conductive textile and polyester layers forming a parallel plate capacitor belt in (Viventi et al., 2011). The distance between the two plates varied by the force applied to the belt due to the abdominal diameter changes following the respiratory movement of the thorax, thus allowing assessment of the respiratory cycle.

A wearable sensor system combining flexible substrates and off-the-shelf components for chronic respiratory disease monitoring, was presented in (Dieffenderfer et al., 2015). The intended use of the device is for asthma, but it is applicable to COPD. The system was comprised of a wrist-worn device measuring ambient ozone levels, heart rate, acceleration temperature and humidity and a chest patch measuring heart and respiration rates, acceleration and wheezing. The LEDs and photodetector for PPG measurements were assembled on a custom flexible polyimide substrate with copper traces. The Ag/AgCl electrodes for ECG measurements were fabricated on a nonwoven fabric. This was followed by a PET flexible film with conductive traces connecting the fabric electrodes to the recording electronics. A polyurethane layer served as a top passivation layer.
induced hyperinflation. These are suitable for heterogeneous emphysema. Endobronchial valves with various mechanics have been reported.

**Endobronchial valves**

Suitable for heterogeneous emphysema induced hyperinflation. These are directional valves that block the propagation of airflow into the diseased regions of the lung where there’s no collateral ventilation, leading to the lobe atelectasis. Trapped air and excreted fluid are allowed to escape from the sectioned area. Adjustment and replacement are sometimes required due to valve migration and air leaks. Example products include Zephyr/EBV (Pulmonx) and the Spiration Valve System (Olympus).

**Endobronchial coils**

These are shape memory alloys arranged as a coiled wire for guiding disease tissue folding and restoring elasticity. It is suitable for treating homogeneous emphysema induced hyperinflation in areas with collateral ventilation. This is a relatively new technology with few published data. Representative products include Repneu (PheumRx).

**Other bronchialoscopic interventions**

Endobronchial valves and coils are among the most studied non-surgical intervention for emphysema. There are a number of emerging alternatives reported. Among these is the Emphysema Lung Sealant, a hydrogel foam that polymerises when instilled into emphysematous alveoli. This seals off the targeted region preventing hyperinflation and is suitable for areas with collateral ventilation. However, preliminary clinical trials raised safety concerns and further studies are required to validate this approach.

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**Medical implants for COPD**

Since the first metallic hip replacement in the 1940s and the first implanted pacemaker in the late 1950s, chronic implants for organ replacement represent a major advance in modern medical technology. The first coronary stent scaffolds were used in 1986, while the first cochlea implant for the profoundly deaf was FDA approved in 1984. Since then, developments have focused on better biocompatibility, miniaturisation, longevity and patient safety. Current emerging implant research and development includes retinal implants for sight restoration, implanted insulin pumps, deep brain stimulators, and the electronic nose.

For COPD, the current generation of implants have several shortcomings, including readjustment and re-deployment due to air leaks or implant migration, the limitation of deployment for cases without lateral ventilation, and safety concerns from clinical trial outcomes. The next generation implants will focus on self-calibration and adaptation through context-aware sensing. Recent technological developments in micro-device fabrication, sensor functionalisation, and advances in endomicroscopy are moving closer to a next generation of implants for COPD. Here are some of those implant technologies:

**Active implants – miniaturisation and powering**

Active implants providing nerve stimulation particularly for loss-of-function compensation are already used in hundreds of thousands of cochlea implants and millions of pacemakers fitted worldwide. The underpinning technologies for active implants include integrated circuits fabrication, wireless battery charging, and electrode materials development. Integrated circuit (IC) technology has evolved exponentially in the past decades due to a high commercial demand. As a result, a chip can hold more circuits with lower power. The state-of-art fabrication allows transistors with feature sizes down to 14nm to be made. Over time, active implants, such as the pacemaker, deplete battery energy. Wireless powering technologies were developed to power up devices without surgical battery replacement. Inductive powering has been the preferred technique for subcutaneous implants. An external coil connected to a power source transmits energy through a varying magnetic field. This energy is received by an implanted coil for charging a battery and to power up the ICs in a stimulation implant. Recently, wireless implant powering by ultrasound has also been carried out on a pacemaker. Ultrasound powering complements the inductive approach by allowing energy to be delivered to more deep-seated implants, provided there are direct (non-cavity) paths between the external ultrasound power source and the implant receiver.

**Passive smart sensors**

Passive sensors in the form of resonators are invaluable for self-adapting implants in the future. To this end, sensor transduction is achieved by modulating the physical and electrical properties of a passive sensor. Pressure sensing can be achieved with a complete passive device consisting of copper coils printed and encapsulated on a flexible polymer substrate (Chen et al., 2014). Pressure applied to the device is translated to physical deformation of the coils and associated capacitance results in shifting radio resonance frequency. The device can then be wirelessly interrogated for a frequency shift, resulting in pressure readings. Resonance devices can be further functionalised to carry out biosensing. An example for this is cDNA sensing by immobilising ssDNA on gold electrodes of a surface acoustic wave (SAW) resonant structure (Kim et al., 2013). Hybridisation of a sensing target changes the surface characteristic of the SAW device and results in a resonance frequency shift readout.

**Smart materials and sensing**

Recent advances in material science have opened up the opportunity for deploying biocompatible, surface conformal, and bioresorbable implants. Microfabricated materials can also be functionalised for physical, optical, and biosensing of relevant molecular markers. This creates huge opportunities for self-adapting implants as well as enabling sensing for existing surgical instruments (see also section on flexible electronics).
An implant in the air passage of the bronchi airflow sensing system was demonstrated for COPD in (Shikida et al., 2015). The system includes two ring-shaped heating elements, detecting airflow by hot-wire anemometry, thus avoiding the use of moving elements. Flow-rate and flow direction could be detected. The sensors were fabricated on a flexible parylene substrate via photolithography and inserted in a flexible tube with legs on each side to allow attachment and fixation to the air passage without hindering its ciliary motion. The sensor was implanted in rabbit bronchi.

Implanted blood pressure monitoring was demonstrated in (Bingger et al., 2012), via a flexible capacitive strain gauge. This is wrapped around an arterial blood vessel to measure changes in its diameter, which are indicative of blood pressure. Silicone was used as the substrate and encapsulant and the conductive tracks were formed by PEDOT:PSS which was patterned without masks via a laser system. The gaps in the interdigital structure are 95 µm and the track width is 200 µm with a total of 95 finger pairs. Fabricated sensors showed sensitivity of between -0.18%/mmHg and could be elongated up to 15% without damage.

An implantable impedance system on a flexible substrate with on-board Au electrodes was presented in (Theodor et al., 2014). The battery powered system transmitted recording through an inductive link to an external device. The device was implanted and positioned directly on the femoral artery of a domestic pig. Blood pressure was increased artificially and bio-impedance measurements showed a clear correlation with blood pressure. Estimation of artery diameter through impedance measurements demonstrated a linear relationship with blood pressure, which correlated with blood pressure.
Typically, an endobronchial valve consists of a self-expanding metal strut enclosing a one-way valve to provide an airtight seal. Endobronchial coils on the other hand are placed as straight wires in the target area and subsequently coil up with the affected tissue.

Deployment is with a bronchoscope and a flexible delivery catheter for guidance towards a disease lobe. In the case of endobronchial valves, lobes without lateral airflow suitable for implantation are identified either through high-resolution CT or with an in vivo flow measurement system (e.g. Chartis – Pulmonx) consisting of a balloon catheter that provides resistance for lobe specific CV measurements. A number of clinical trials (Kemp and Shah, 2016) evaluated the effectiveness of commercially marketed valves and coil implants, with general outcomes suggesting an improvement in patients’ forced expiratory volume in 1 second (FEV₁) and six minute walk distance (6MWT) after six months. More adverse events such as exacerbations and hospital re-admissions, pneumothorax, and death, are however reported in the cases of patients with the implants. Further studies are needed to assess implant safety, possibly resulting in improvements to existing implant design and deployment practices.

Two randomised clinical trials of COPD patients without collateral ventilation for the Zephyr (Pulmonx) endobronchial valve implant have been reported recently.

1. The BeLieVer-HiFi (Davey et al., 2015) study is a randomised double-blinded sham controlled trial with 50 patients (50% control). Patients with less than 50% predicted FEV₁ and significant hyperinflation, as well as restricted exercise capacity were selected. Participating patients were assessed for lateral ventilation using the Chartis system as well as CT scanning. Outcomes on FEV₁ and 6MWT, as well as scores from the St. George’s Respiratory Questionnaire (SGRQ) were collected. Improvements from baseline to six months were recorded despite two deaths reported in the valve placement group.

2. The STELVIO (Klooster et al., 2015) study is a randomised, open label trial involving emphysema patients older than 35 years with post-bronchodilator FEV₁ less than 60% of the predicted value. The selected patients had stopped smoking more than six months earlier and been clinically assessed that lateral ventilation was not present. A total of 25 patients were in the endobronchial valve treated group, with 33 patients in the control group. Outcomes were followed from baseline to six months on FEV₁, forced vital capacity (FVC), and 6MWT. Greater improvements in the valve treated group were reported. However, 23 serious adverse events were reported in the valve treated group, compared to five in the controlled group. One death was reported due to end-stage COPD with respiratory failure.
Concrete evidence of improving outcomes is the major hurdle for translating new technologies to clinical use. To demonstrate the effectiveness of new technologies, extensive research and clinical studies have to be conducted with due consideration of ethics, data privacy, ergonomics and user acceptance. Typical clinical studies may take years to perform and the outcome of improvement may not always be clear. As such, the cost of studies often discourages many commercial companies from investing in healthcare technologies, but to focus only on fast growing consumer markets. Coupled with the complex procurement processes, adopting new technologies in clinical practice is often challenging. There are however a number of organisations in the UK that provide support to companies developing medical technologies and conducting healthcare research that can provide support across this pathway.

Cost-effectiveness and evidence of improving outcomes – There have been many attempts to use traditional telehealth systems to manage COPD. A recent meta-analysis showed there’s no evidence of benefit to early self-management support on admission, mortality, and other health outcomes. And only modest improvement in health-related quality of life was identified (Jordan, Majothi et al. 2015). Traditional telehealth has shown no benefits for patients with COPD (NHS 2015) and many intrinsic problems are associated with the devices used. Many of these devices require cumbersome user-interaction and each is only equipped with single, rather than multiple functions. As such, there is a major demand to address this challenge by using new smart sensing technologies.

Competitions – The fast growing wearable device market has led to numerous devices designed for fitness monitoring and measuring a user’s energy expenditure – a key measurement index for managing COPD. Although most devices haven’t been tested or validated clinically, some COPD research and clinical practices have started investigating using such devices for continuous monitoring of patients. This has blurred the boundary between consumable products and medical devices. This needs to be addressed carefully in terms of efficacy, safety and legal considerations. The UK’s Medicines and Healthcare products Regulatory Agency (MHRA), has recently published guidance to assist manufacturers in determining when software applications (including Apps and in vitro diagnostic medical devices (IVDMDs)) are considered to be a medical device and how they are regulated https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/564745/Software_flow_chart_Ed_1-02.pdf. Health related apps and software that are not medical devices fall outside the scope of the MHRA and within the UK, work in this area is being developed by the National Information Board in their Workstream 1.2.

Adoption and NHS procurement
The NHS in the UK is the “largest single healthcare delivery organisation in the world” (NHS National Innovation Centre 2012). Medical devices may be procured at national, regional and local levels, usually depending on the value, size and complexity requirements of a device and the NHS will consider the clinical and cost effectiveness of medical devices before they will be procured. From a medtech industry perspective, the NHS represents a major opportunity for medical devices, but in the same time a significant challenge in navigating the system’s structures and requirements. The Accelerated Access Review, which aims to speed up access to innovative drugs, technologies and diagnostics for NHS patients included the publication of an innovation pathway covering the entire development lifecycle from product idea to adoption and uptake by the NHS, which is a useful aid for those navigating the pathway and includes details of a number of key organisations, including the NIHR, which can provide support along this pathway. It has been noted that less attention is often given to ‘how-to’ compared with ‘principles’ knowledge at the early stages of the product development process and that this has contributed to incomplete implementations or discontinuations after initial adoption (Kyratsis, Ahmad et al. 2012). Organisations such as Academic Health Science Networks (AHSNs) and the NIHR, can help to bridge the gap between developers and the NHS to enable due consideration of how product functionality aligns with clinical needs and care pathway considerations.

Clinical evaluation and CE marking of medical devices - In the case of devices to be placed on the market in Europe, manufacturers need to determine whether their product is a ‘medical device’ as defined by the Commission Directives [https://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework_en]. Products falling within the scope of these directives, will need to demonstrate compliance with the applicable essential requirements as part of the CE-marking process before they can be placed on the market. As part of the process of ‘clinical evaluation’ required by the Directives, that is the assessment of clinical data relating to the device to demonstrate its safety and performance, a specific clinical study or ‘clinical investigation’ may be required. Where this is the case, manufacturers must notify the relevant competent authority in advance. For studies taking place in the UK, this will be the MHRA (https://www.gov.uk/guidance/notify-mhra-about-a-clinical-investigation-for-a-medical-device). Further guidance is available at https://www.gov.uk/topic/medicines-medical-devices-blood/medical-devices-regulation-safety. For novel products particularly those that challenge the current regulatory framework, the MHRA Innovation Office, provides a single point of access to free expert regulatory advice and guidance which is available to all types and sizes of organisation.

Approval and set-up of research in the NHS - For manufacturers wishing to conduct device related research in the NHS in England, including both clinical investigations for CE-marking purposes as well as other clinical research studies of devices, they will need to apply for Health Research Authority (HRA) Approval before they can begin. The HRA is one of a number of organisations that work together in the UK to regulate and approve different aspects of health and social care research. HRA Approval brings together an assessment of governance and legal compliance, with the independent REC opinion provided through the UK Health Departments’ Research Ethics Service and replaces the need for local checks of legal compliance and related matters by each participating organisation in England. Participating NHS organisations now focus
their resources on assessing, arranging and confirming their capacity and capability to deliver the study. Through its Study Support Service, the NIHR CRN can help researchers and the life sciences industry to plan, set up and deliver high quality research in the NHS in England, this includes early feasibility advice and help to identify appropriate study sites as well as provide support with performance oversight to support successful delivery of the study to its recruitment targets.

**Data ownership and privacy** - In the fast growing data driven wearables sector there are important considerations for supporting the appropriate sharing of information whilst ensuring personal data is adequately protected. With reform of the EU’s data protection framework underway, including the introduction of the new General Data Protection Regulation (Regulation (EU) 2016/679) in 2016 which will apply from May 2018, device manufacturers will need to give due consideration to the principles of data protection by design and by default throughout the product development lifecycle. In addition, the recent publication of the proposal for a Regulation on Privacy and Electronic Communications, intended to update and replace the existing Directive (2002/58/EC), means that manufacturers need to stay up-to-date with developments in this area. Whilst some data sharing between patients and healthcare workers is already in place, it is likely this will grow further. Therefore there are important considerations for the future on the development of such data sharing, and access to clear guidance and standards, particularly for supporting small and medium enterprises, will be key.

**Design and ergonomics** – Patient compliance is a major challenge in developing wearable technologies for health monitoring. The aesthetic of a wearable device will directly affect the compliance of the user. Like clothing, a wearable device can represent personal identity and influence self-image (McCann 2014). Even device colour can affect the user’s choice and self-image. As a body-worn device, sensor positioning and fitting could directly affect the sensitivity of the device. Often the best location may not be the most preferred for the user, (e.g. nostrils can be ideal locations for sensing respiration, but patient acceptance can be an issue in free-living conditions). Some devices are designed as patches to enable stable attachment to the body, and others designed to fit on limbs, legs, ears, waist, and chest. Similar to fashion, the style of the devices is often dictated by the trends and the preferences of the target market. However, style is very personal, and perception of a ‘stylish’ design tends to be subjective (Willis 2013). Designing a ‘stylish’ device that appeals to the majority is often difficult. Apart from the device’s appearance, the material used has to be biocompatible and comfortable to wear. For any medical device that comes into contact with human tissue, the material has to comply with the ISO standard 10993-1.

To ensure comfort for long term use and biocompatibility, fabrics or e-textiles are a popular choice for wearable devices.

**Environmental concerns** – With increasing awareness of the environmental impacts from electronics and devices, new products and devices have to adopt an eco-design approach. From electronic components, circuit design, package design, and materials, to manufacturing processes, transportation, recycling, and product end-of-life, ‘green’ approaches can be implemented across the whole product cycle. There are life-cycle assessment (LCA) tools, which support the design and production of ‘green electronics’ (Griese, Schischke et al. 2003, Mueller, Griese et al. 2004, Stevels 2007) and further advice on environmental management systems is available from the Institute of Environmental Management and Assessment. Although very few regulations apply for using only ‘green’ approaches, (e.g. RoHS Directive 2002/95/EC and WEEE Directive 2002/96/EC, REACH No. 1907/2006) any changes to requirements in this area could have significant impacts on the cost of production and manufacturing processes.
Market opportunities for COPD

**Care costs** – COPD costs the NHS over £800 million a year, and treating severe cases of COPD costs 10 times more than mild diseases (NHS Medical Directorate, 2012). 24 million working days are lost each year to COPD – equivalent to around £2.7 billion worth of productivity (DH, 2010). The average annual COPD management cost per patient, excluding medication, was £2,108, and £1,523, £2,405 and £3,396 for patients experiencing no, one or multiple moderate to severe exacerbations, respectively (Punekar, 2014).

So far, one in eight emergency admissions to hospital is for COPD, and the average cost for an inpatient admission for COPD is about £1,960 (NICE, 2011). The total annual cost of COPD was £3,008 for LAMA initiators, £2,783 for LABA initiators and £3,376 for LABA+ICS initiators.

**Pulmonary rehabilitation** – Studies have shown pulmonary rehabilitation can improve the quality of life of COPD patients. In the rehabilitation programme, patients usually attend the rehabilitation unit on three half days per week for six weeks. The first third of the time is spent on education, teaching patients how to manage their condition. This is then followed by an exercise session and a personalised prescribed training programme (Griffiths et al., 2000). The estimated NHS cost of the six-week rehabilitation programme (for 17 patients) is about cost £12,120 in 2001. Overall cost saving of £152 per patient per pulmonary rehabilitation programme (Griffiths et al., 2001).

**Market size** – The respiratory care market is estimated to be EUR1.5 billion with a growth rate of 6-8% (Shafer, 2012). The global COPD and asthma devices market will reach US$34.3 billion by 2020, and the European market US$10 billion by 2020 (Research, 2014). Over 97% of COPD patients using mobile phone technology to manage their condition felt highly satisfied, and 94% of patients have shown better treatment compliance (Taylor, 2015).

**Global wearable market** – The global market for wearables is accelerating, and showing no signs of slowing down. This brings unique opportunities for managing chronic diseases, and COPD in particular. The forecast unit sales of wearable devices worldwide will reach 116 million units in 2016. More than four times the forecast of 28 million made in 2014 (GfK, 2016). In particular, the forecast unit sales of health and fitness trackers grew from four million units in 2014 to 7.1 million units in 2015 in Western Europe (GfK, 2016). In the UK, 39% of wearable technologies were health and fitness trackers in 2014. It’s expected that wearable device users in the UK will double from 7% in 2015 to 14% in 2016 (eMarketer, 2015). The International Data Corporation (IDC) forecasts that by 2019, the worldwide shipment of wearable devices will reach 214.6 million units, resulting in a five-year compound annual growth rate (CAR) of 28% (Shirer et al., 2015). The wearable market will be worth US$25 billion by 2019, up from US$15 billion in 2015 (CCS Insight, 2015).

![Figure 9: The global market for wearable technologies for healthcare.](image)
Patients’ involvement is crucial to predicting and preventing diseases. They need to take part in each step of the treatment: from research to deployment towards the delivery of personalised treatment.

5. Patient involvement and stratified patient management

Leroy Hood first introduced P4 medicine, which aims to provide wellness through predictive, personalised, preventative and participatory treatments (Hood and Friend, 2011). This ongoing revolution is underpinned by:

1) the redefinition of medicine as an informative science
2) the interconnected domains composing complex diseases
3) the emerging technologies allowing different approaches to understand and access patient’s data
4) new and powerful analytical systems (Hood and Friend, 2011).

Compartmeting illness origin from either the patient’s genome or environmental factors helps to explain biological processes. All the above information provides a global network of processes that have led to the patient’s current biological state. P4 medicine aims to provide a full understanding of it.

A number of trials involving COPD patients have looked at ways of improving the delivery of different care programmes. Long-term effectiveness of integrated disease management delivered in primary care was investigated with over one thousand COPD patients, randomly assigned from 40 practices in the Netherlands. At one year follow-up, no significant benefit in the general health status or physical activity was measured compared to the usual care (Kruis et al., 2014). Although the usual care seems optimal, a study involving 200 randomised COPD patients showed that a six-week outpatient rehabilitation multidisciplinary programme does improve the general patient’s wellbeing (Griffiths et al., 2000).

When hospitalised, patients recover faster (about 10 days compared to 21 days for patients not following the programme). Similarly, they needed half as many care home visits than the usual rehabilitation programme and improved their overall physical activity. A close follow-up with multidisciplinary care can reduce patients’ need for healthcare services, while improving physical activity. Observing how a close multidisciplinary programme can reduce the need for healthcare services, a study investigated the potential benefit of home care.

Comparisons between home and hospitalised care was assessed with 150 AECOPD patients (50 hospitalised patients) (Davies et al., 2000). No significant difference was found in the re-hospitalisation (37% of patients receiving home care against 34% of patients in hospital) and mortality rates (9% of patients receiving home care against 8% of patients in hospital) at three months. Similarly, there was no significance difference in force expiratory volume in 1 second (FEV1) measured at three months between the groups (41.5% confidence interval 8.2% to 74.8% against 41.9%, 6.2% to 77.6%). Consequently, home care can be an alternative to hospitalisation in cases of AECOPD in selected patients.

Patients’ involvement is crucial to predicting and preventing diseases thanks to the comparison of large amounts of data about environmental factors and genomes. To do so, patients need to take part in each step of the treatment: from research to deployment. This will eventually allow the delivery of personalised treatment.

In surveyed patients, as many as 51% are limited in their ability to function at work.

70% say it limits physical activity.
6. Research and innovation in the National Health Service

A thriving medical technology and diagnostic sector is essential for shaping the NHS for delivering world-class healthcare. The medtech sector has produced a wide range of products benefiting patients, the healthcare systems and the economy at large. In the UK, this sector is predominantly made up of SMEs (Small and Medium Size Enterprises), that are often seen as responsible for driving innovation, with approximately 25% of SMEs being actively involved in research and development activities (NOCRI, n.d.).

In the development process of innovative medical technologies, research is crucial in identifying unmet clinical needs and generating supporting evidence of clinical utility. The UK government body that coordinates and funds research for the NHS is the National Institute for Health Research (NIHR). Funded through the Department of Health, NIHR was established with the vision to ‘improve the health and wealth of the nation through research’. NIHR represents the most integrated clinical research system in the world, supporting high quality health research and driving a faster translation of research from bench to bedside and into tangible benefits for the patients and the public (NIHR, 2016a). The NIHR clinical research infrastructure brings together world-leading experts working in dedicated facilities using state-of-the-art technologies. The NIHR infrastructure provides an opportunity to work in partnership with the medtech sector, helping companies to produce innovative technologies successfully and accelerating their development.

6.1 Dedicated NIHR infrastructure

The NIHR infrastructure (NIHR, 2016b) is designed to support the NHS needs and provides facilities for innovative research. Within its structure, the following organisations are particularly relevant to the innovation pathways of implantable and wearable devices for COPD:

Biomedical Research Centres (BRCs) and Biomedical Research Units (BRUs)
The BRCs and BRUs are partnerships between leading NHS organisations and universities with a focus on conducting and supporting ‘translational research to transform scientific breakthroughs into life-saving treatments for patients’ (NIHR, 2016b).

Clinical Research Network (CRN)
The role of CRN is to facilitate participation of patients and health professionals in research. CRN offers support with the set-up and timely delivery of clinical studies in the NHS in England, provides advice on study feasibility, facilitates an effective patient recruitment and streamlines NHS permissions (NIHR, 2016b).

Collaborations for Leadership in Applied Health Research and Care (CLAHRCs)
CLAHRCs are collaborations between universities and their NHS organisations including primary care, NHS commissioners, relevant local organisations and the Academic Health Science Network. The aim of these collaborations is to enable applied health research that is transferable across the NHS (NIHR, 2016b).

Diagnostic Evidence Co-operatives (DECs)
DECs are centres of expertise that bring together specialists from across the NHS and industry, clinicians, patients, NHS commissioners and researchers to investigate specific clinical areas. The aim of DECs is to ‘catalyse the generation of evidence on in vitro diagnostic medical devices’ (NIHR, 2016b).

Healthcare Technology Co-operatives (HTCs)
HTCs work collaboratively with industry, charities, academics, patients and patient groups to develop concepts, demonstrate proof of principle and devise research protocols for new medical devices, healthcare technologies or technology dependent interventions (NIHR, 2016b).
6.2 Funding streams
There is a recognised gap between proof-of-concept funding and funding for conducting larger studies to support uptake in the NHS. NIHR aims to address the gap between development and adoption by creating a health research system in which the NHS supports cutting edge research driven by patient needs. The NIHR offers translational funding streams via its Invention for Innovation and Health Technology Assessment (HTA) Programmes.

The Invention for Innovation (i4i) Programme is focused on preclinical and clinical development of innovative medical technologies. i4i aims to ‘de-risk early stage projects that have a strong potential for commercialisation and acceptance for use in the NHS, and to make them attractive to follow-on funders and investors’ (NIHR, 2015).

The HTA Programme is focused on the clinical, cost effectiveness and broader impact of healthcare treatments and tests. HTA research is suitable for a development stage where ‘some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard NHS intervention to see which works best’ (NIHR, 2015).

6.3 Innovation pathway
The Accelerated Access Review of Innovative Medicines and Medical Technologies (Accelerated Access Review, 2016), which aims to speed up access to innovative drugs, devices and diagnostics for NHS patients, published a detailed ‘how to’ guide to navigating the innovation pathway in England. The guide is designed to support innovators and the life sciences and health tech industry, particularly aiming to assist the small and medium-sized enterprises by providing an overview with recommendations, checklists and main organisations and contacts for all the stages in the innovation pathway starting from the idea generation, followed by development stages, regulation, reimbursement, endorsement and health technology assessments through commissioning and adoption. The guidance has a dedicated section to medical devices and is particularly relevant for technologies to be used in the NHS in England - full details can be found in Deloitte MCS Limited report on Accelerating NHS patient access to medical innovations - A guide to navigating the innovation pathway in England (Monitor Deloitte, 2016). Key points along the innovation pathway are extracted from the aforementioned report and highlighted as follows.

Idea generation and identification of the unmet need
- innovators should consider at the earliest design stage if the proposed technology will address an unmet clinical need and evaluate the potential solution;
- it is important to identify end users at this point and consider whether NHS will be interested in purchasing the novel technology;
- innovators can access NIHR’s infrastructure and expertise for help in identifying unmet needs;
- an early stage concept testing is recommended whereby the concept should be tested with patients, healthcare professionals and regulators before taking the idea to the development stage;
- patient involvement from the early stages, particularly in the specification stage will warrant relevance of the final product and will strengthen the business case;
- Academic Health Science Networks (AHSNs) can provide further information and assist with many stages of the development pathway;
- consider financial requirements for companies selling to the NHS.

Development
- prototype development is an iterative process that refines the product and prepares it for the subsequent regulatory step;
- adoption of a ‘designing for usability’ approach, whereby the unmet need remain the focus of the development and end-users are involved and provide feedback throughout this stage;
- medical devices are classified according to their complexity and risk as Class I, Class IIa, Class IIb and Class III - please refer to the European Commission MEDDEV 2. 4/1 Rev. 9 guidance for medical devices (EC, 2010);
- the product testing requirements for each medical device are dependent on its class;
- evidence of cost effectiveness is required to support the value proposition of the device;
- safety and performance of the device needs to be demonstrated through a clinical evaluation;
- requirements for the clinical evaluation depend on device class and/or available evidence;
- NIHR can help with clinical research and advise on an appropriate design for clinical testing; for in vitro diagnostic devices DECs are a good resource;
- engagement with regulators and external stakeholders is recommended to confirm that trials will satisfy requirements and support the value proposition.

Regulation
- need to demonstrate conformity to the relevant requirements (e.g. medical devices directive, active implantable medical devices) before the device can be freely marketed;
- acquire CE mark as an indicator of compliance with EU legislation;
- guidance on requirements and assessment process can be obtained from MHRA;
- prepare technical documents to record evidence of conformity;
- ensure sufficient clinical evidence;
- register with a competent authority (MHRA) or involvement with a Notified Body that will assess conformity to the EU standards
- consider reimbursement assessment requirements and a suitable route to reimbursement.
National endorsement
- NHS considers the evidence of clinical and cost-effectiveness of a device before deciding reimbursement;
- depending on the product, reimbursement can be done at national, regional or organisational level;
- most of the medical devices do not need national assessment for local commissioning;
- NICE assessment is not mandatory;
- a health technology assessment performed by NICE can be requested, as the published guidance can support decision making and uptake;
- if requesting NICE assessment, the medical technology advisory committee will evaluate the new and innovative medical devices along with their clinical and cost effectiveness evidence before routing the application to a relevant assessment programme such as the medical technologies programme;
- specialised services or devices are reimbursed at national level with a funding mandate for specialised commissioners - NHS England conducts an assessment process and publishes guidance for these products (Monitor Deloitte, 2016).

For details on specialised commissioning routes and procedures please refer to (Monitor Deloitte, 2016).

Commissioning and adoption
- commissioning is conducted by the local Clinical Commissioning Groups (CCGs);
- not all medical devices require CCG evaluation for local adoption;
- CCG only needs to consider the product where a change in commissioned services or tariff is required - such as innovative devices or procedures, large investments or the introduction of the new technology change the patient pathway and requires a new service design and/or amendments.

6.4 NHS adoption and procurement

Procurement is an ‘all-encompassing term to describe the activities of obtaining the right goods, works and services from third parties at the right price, at the right time’ and includes all components that enable an organisation to operate successfully – e.g. ‘supply chain management, sourcing, purchasing, contracting, contract and supplier management, supplier relationship management, supplier development’ (DH, 2016).

The NHS in the UK is the ‘largest single healthcare delivery organisation in the world’ (NHS NIC, 2012). From a medtech industry perspective, the NHS represents a major opportunity for medical devices, but in the same time a significant challenge in navigating the system’s complex structures and requirements.

Medical devices may be procured at national, regional and local levels, depending on the value, size and complexity requirements of a device. The NHS will evaluate both the clinical effectiveness and the cost effectiveness of medical devices. One way of demonstrating that a product is appropriate for patient use is through a NICE evaluation that issues recommendations based on a review of clinical and economic evidence. The most suitable route to reimbursement will depend on the type of medical device and its addressable population (Monitor Deloitte, 2016).

The NHS Supply Chain is an agent of the NHS Business Services Authority and follows EU procurement regulations. In line with these regulations, medical devices must be procured through tenders and listed on a framework agreement. New suppliers of medical devices are required to wait for the relevant tender to be announced and published. Tenders are then evaluated based on financial criteria, clinical acceptability and ease of use of the device. To be able to sell to the NHS companies must also abide to the NHS Supply Chain Code of Conduct must provide management accounts for the required time period (Monitor Deloitte, 2016).

eProcurement was introduced in 2014 to make the procurement process faster and more efficient, and employs an increased use of technology to deliver cost efficiencies and ‘to automate the exchange of procurement information throughout the supply chain’ (DH, 2014). Compliance with eprocurement, mandates the use of the global GS1 coding and PEPPOL standards and requires suppliers to place their product data in a GS1 certified data pool (Graham, 2014). eProcurement strategy enables the use of master procurement data, automates the exchange of information and allows NHS trusts to benchmark their procurement expenditures against other trusts.

6.5 Patient and public involvement

Patients and the general public have important roles to play in shaping research as both direct participants to research studies as well as being involved in research commissioning and management processes. Researchers are expected to actively engage the public in their research and to consider patient’s participation at every step of a project from the conception through deployment.

Members of the public are encouraged to be involved in reviewing funding applications and being part of decision-making committees and panels, actively contributing with recommendations on research funding.
CRN has a key role in supporting researchers and healthcare industry in developing, setting up and delivering high quality research in the NHS. Selective examples of successful stories of research delivery in the remit of respiratory conditions are covered below.

**Wearable health monitoring technologies**

Dedicated self-monitoring medical devices have the potential to give greater control to the patients and their carers, empowering them to better manage their health condition. Recognising this potential, the CRN: Wessex has recently supported an innovative med-tech collaborative study that aimed to provide a new solution for management of chronic respiratory conditions such as COPD, bronchiectasis and asthma.

The SENSOR (SElf-management checks to predict exacerbatioNs of Pseudomonas aeruginosa in patients with long-term reSpiratORy conditions) project brought together a consortium of partners including Portsmouth Hospitals NHS Trust, University of Portsmouth and a UK based healthcare company Aseptika Ltd. The project received funds from NHS England's Small Business Research Initiative Healthcare, managed by Health Enterprise East on behalf of the Eastern Academic Health and Sciences Network (Aseptika, 2014c).

With support from CRN: Wessex the project developed and set-up a clinical trial to evaluate ‘new ways to help people with respiratory disease learn about means to maintain their health’ (Aseptika, 2014c). The study was conducted on 30 participants from the Portsmouth area that volunteered to monitor at home their activity levels, pulse, body mass, peak flow and blood pressure using a tailored suite of medical devices offered by Aseptika under its Avtiv8rlives rage products. Participants also provided samples of sputum, which was subsequently analysed using Aseptika’s new biomarker test that measured the bacterial activity level used to predict exacerbations.

Patients’ adherence to the monitoring requirements has been extremely good – with levels as high as 99%, mainly attributed to the sense of empowerment among patients and their enthusiasm for participating in clinical research. Also contributing to high levels of adherence were the simple-to-use devices, the training and education provided through SENSOR events, and a responsive technical support from Aseptika (NIHR CRN, 2015).

The observational trial required patients to use a dedicated SENSOR App to record and upload 42 clinical parameters each day (Aseptika, 2014b). The ultimate aim of this work is to combine information collected and develop a system capable for early detection of flare ups, meaning that patients could be treated earlier at home, reducing the decline in their lung function but also improving their quality of life and in the same time decreasing hospitalisation costs.

**Implantable technologies for COPD**

Emphysema is a respiratory condition characterised by baggy lungs, full of holes that do not empty properly when the person breathes out. This is called “gas trapping” and the air trapped inside the lung makes it harder to breathe. Surgical treatment relies on lung volume reduction procedures in which the worst affected areas of the lung are resected to stop them from trapping gas and getting in the way of the remaining healthy lung. Evidence shows that in properly selected individuals lung volume reduction increases life expectancy, improves lung capacity, reduces breathlessness and helps patients to walk further. However, it remains a significant operation with risks of complications (HRA).

In the recent years a fibre optic camera (bronchoscope) was used to insert small valves into the airways of the lung (Davey et al., 2015, Toma et al., 2003). These small valves block air entering the diseased area of the lung causing it to eventually collapse. The effects and benefits of the bronchoscopic intervention are similar to those of traditional removal surgery.

The CELEB trial stands for Comparative Effectiveness of Lung volume reduction surgery for Emphysema and Bronchoscopic lung volume reduction with valve placement. It is a programme funded by the UK National Institute for Health Research through a Research for Patient Benefit scheme and is aiming to compare the two lung reduction approaches and evaluate which is more effective. With support from the CRN, the study recruited 76 patients with severe emphysema. Half of the patients have lung volume reduction surgery and the other half have bronchoscopic lung volume reduction with valves. The study aims to identify which approach is better value for patients and the healthcare system (HRA).

**Emerging novel point-of-care technologies**

As we know, COPD patients have frequent exacerbations, which irreversibly damage their lungs and affect their quality of life. However, if exacerbations are diagnosed and treated early the damage to the lung can be reduced with lung function being preserved. Driven by the recognised need and importance of early detection of COPD exacerbations, the COPD-SPOC monitor aims to develop a simple portable device that allows patients to assess their condition at home and help identify exacerbations early from onset (HRA). Compared to blood or sputum biosamples, saliva was found to be a more acceptable and easier to produce biosample for home monitoring (Spiteri, 2013).

Spiteri and team developed a sensitive analyser that measures three saliva biomarkers: C-reactive protein, procalcitonin and neutrophil elastase (Patel et al., 2015). They have demonstrated that the levels of these biomarkers depend on the severity of COPD inflammation, and thus could be used to warn early of a developing exacerbation. Throughout the research study, patients were considered as ‘experts by experience’, and were actively involved during all stages of the process from the design phase, through development and clinical testing of the monitoring device (HRA).
7. Recommendations and conclusions

COPD is a condition with a significant burden on patients, as well as the economy and society. The present report looked at how wearable and implantable devices can help to alleviate this burden and reviewed promising technologies with the potential to address some of the unmet care needs, and help at different stages of the disease. These range from diagnosis, treatment and rehabilitation to monitoring during exacerbations, monitoring disease evolution, and management of comorbidities. All these are important aspects of the natural history of COPD.

Prevention – COPD is now considered a preventable disease, particularly where the cause is cigarette smoking. So prevention of COPD through appropriate education and smoking cessation programmes should be the strategic focus for minimising the burden of COPD. Good nutrition, timely vaccination and regular exercise should complement the education programmes and also form the basis of all preventative measures. Technological interventions for stopping smoking revolve around wearables that can address both the psychological (via motivational and personalised behavioural support) and physiological symptoms of addiction (through optimised programmable transdermal nicotine delivery platforms).

Early screening and diagnosis is another priority as COPD disease develops slowly and asymptptomatically. Many patients are unaware they have the condition until it manifests as a medical emergency. The reason COPD is often diagnosed late is because people often miss early signs and think shortness of breath is part of the natural aging process. However, while there’s no cure for COPD, much can be done to mitigate and manage the disease if it’s detected early. Raising awareness among those at risk and training patients to self-monitor their health and functional status using wearable/ portable technology could prevent exacerbation episodes and significantly improve long-term outcomes.

Exacerbations – for patients diagnosed with COPD, prevention and early detection of exacerbations continue to be an unmet clinical need. Effective tools such as decision-making platforms that can predict exacerbations based on multi-parameters measurements of biological markers are highly desirable. Current wearable and portable devices can monitor sputum production, cough and adventitious sounds (crackles, wheezes, etc), and respiration and identify shortness of breath. Physical activity, pulse rate, oxygen saturation and blood pressure can be continuously measured to provide early alerts for health status deterioration. Indoor and outdoor pollution monitors can be used to complete the picture of potential external triggers, and at the same time provide patients with additional important information.

Healthcare in the community – the long term nature of COPD care requires commitment for continuous disease management and behaviour changes. With the exception of a few people who require hospitalisation for treatment, COPD should be managed in the community, and medical devices tailored for home use. This empowers patients to monitor their own condition. This approach fits with the proposed shift from the current reactive care to a preventative medicine that is predictive, personalised and participatory, where patients self-manage their condition. However, despite the commercial availability of numerous wearable devices, there’s still a lack of viable tools to enable patients to self-manage COPD. While the necessary sensing technology is available and sufficiently mature, dedicated integrated system performing meaningful amalgamation of useful metrics and real-time feedback are still being developed and trialled. Further advances should integrate biological markers data with info from wearables.

Pulmonary rehabilitation – physical inactivity is a predictor of poor outcomes across several aspects of COPD and is generally associated with increased morbidity and mortality. Pulmonary rehabilitation is the most effective therapy, with a positive effect on exercise capability. It requires an interdisciplinary approach, bringing together respiratory clinicians, rehabilitation therapists, and social and behavioural scientists. Pedometers and activity monitoring devices can play an important role in supporting pulmonary rehabilitation and their use, promoting better compliance and levels of physical activity.

Psychological impact management – anxiety and depression are important comorbidities in COPD. They are associated with worse outcomes and reflected in increased mortality, higher exacerbation rates, longer hospitalisations, and a lower quality of life, accompanied by deteriorated functional abilities. The underlying mechanism of linking COPD with anxiety and depression is poorly understood but it’s accepted as a complex, bidirectional relationship. Treatment options range from pharmacological interventions to psychological therapies that include relaxation, cognitive behavioural therapy and self-management. Pulmonary rehabilitation and the collaborative care model show promising results in reducing anxiety and depression symptoms in patients with COPD. Wearable and smartphone technologies have the potential to sense human behaviour and act as a medium for delivering support, feedback, and customised behavioural therapy to users.

Technological features and recommendations – in order to maximise their clinical potential and impact, COPD medical devices need to be comfortable to wear and easy to use. They also need to be reliable and provide clinically relevant, accurate information that improves diagnosis, treatment, and better disease management. Furthermore, devices need to be unobtrusive, miniaturised, and have low or optimised power management.

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for long term use. They also need to cope with potential noise and interference. Devices and monitoring systems need to be affordable and ergonomically designed, also fully exploit wireless devices such as smart phones already adopted by users. When combined with communication systems, user privacy and data protection need to be considered carefully. The advantage of smart sensing wearable and implantable technology is that it can offer a holistic picture of health monitored in a quantitative way.

**Translational considerations** – medical devices have to comply with rigorous FDA and EU regulations and must have the CE-mark to base clinical decisions on their measurements. Some critical challenges in translating these technologies include safety aspects, long-term reliability and stability of device performance, minimising follow-up calibration and maintenance, as well as cost of device production and of the surgical procedure (applicable for the implantable devices). Ultimately, wearable and implantable devices need to be accepted and adopted by the medical community and users, embedded in the COPD pathways and show a return on investment in healthcare systems if they are to make a significant impact on the quality of life of COPD patients.

**Figure created from data in reference:** Lopez A, Shibuya K, Rao C et.al. Chronic obstructive pulmonary disease: current burden and future projections. Eur respir J 2006; 27:397-412

**DALY = YLD + YLL**

DALY – Disability Adjusted Life Years  
YLD – Years Lived with Disability  
YLL – Years of Life Lost (Premature Mortality)
## Appendix – biomarkers

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<th>Biomarkers</th>
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<tr>
<td><strong>Sputum biomarker</strong></td>
<td>• Analysis of micro particles in sputum to reflect pathophysiological conditions inherent to COPD</td>
<td></td>
<td>• COPD monitoring</td>
<td>• Non-invasive sample collection</td>
<td></td>
<td>(Lacedonia et al., 2016, Snell and Newbold, 2008, Woodruff, 2011, Lin et al., 2010, Cazzola and Novelli, 2010, Whiteman et al., 2008)</td>
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<tr>
<td></td>
<td>• Using Fourier transform infrared spectroscopic monitoring</td>
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<td>• Analysing the effects of drugs</td>
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<td></td>
<td>• Surfactant protein A (SPA) [lung-derived protein of high concentration in COPD patients]</td>
<td></td>
<td>• Inflammation monitoring</td>
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<td></td>
<td>• Soluble decoy receptor advanced glycation end product [participate in excitation of new molecules linked to inflammation; low levels correlate with COPD]</td>
<td></td>
<td>• Asthma monitoring</td>
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<td></td>
<td>• Sputum myeloperoxidase (MPO) [marker of neutrophil activity; high levels are found in COPD patients]</td>
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<tr>
<td></td>
<td>• Neutrophil gelatinase-associated lipocalin (NGAL) [white blood cell; higher levels are found in COPD patients]</td>
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<td><strong>Expired gas biomarkers</strong></td>
<td>• Carbon monoxide [gas with anti-inflammatory and anti-oxidant properties; low level can be used for therapeutic purposes]</td>
<td></td>
<td>• COPD monitoring</td>
<td></td>
<td></td>
<td>(Borrill et al., 2008, Snell and Newbold, 2008, Kharitonov and Barnes, 2006, Lin et al., 2010, Woodruff, 2011) (Kubáň and Foret, 2013, Phillips et al., 2014)</td>
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<tr>
<td></td>
<td>• Nitric oxide [pulmonary vasodilator gas that can be used as treatment of stable COPD]</td>
<td></td>
<td>• Assessment of the effects of the drugs</td>
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<tr>
<td></td>
<td>• Leukotriene [used as a treatment for retrieving normal response to inflammatory episodes]</td>
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<td>• Inflammation monitoring</td>
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<td></td>
<td>• Hydrogen peroxide [molecule secreted during infections; used as a treatment for emphysema]</td>
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<td>• Asthma monitoring</td>
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<td></td>
<td>• 8-isoprostane [protein secreted during oxidative stress; measured in breath condensate as a marker to prevent AECOPD]</td>
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<tr>
<td></td>
<td>• Prostaglandin [protein that induces senescence and inflammation; can be used as a biomarker to prevent AECOPD]</td>
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<tr>
<td><strong>Urine biomarkers</strong></td>
<td>• Matrix metalloproteinase 8 (MMP8)</td>
<td></td>
<td>• COPD monitoring</td>
<td></td>
<td></td>
<td>(Lindberg et al., 2011, Ma et al., 2011, Eisner et al., 2009, Gaki et al., 2007)</td>
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<tr>
<td></td>
<td>• Matrix metalloproteinase 9 (MMP9)</td>
<td></td>
<td>• AECOPD assessment</td>
<td></td>
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<tr>
<td></td>
<td>• Desmosinces (DES) [protein involve in elastin cross linking; increased level suggests AECOPD]</td>
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<td>• Monitoring of the effects of the drugs</td>
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<td></td>
<td></td>
<td></td>
<td>• Inflammation monitoring</td>
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<td></td>
<td></td>
<td></td>
<td>• Asthma monitoring</td>
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</table>

*Neutrophil elastase is a substance responsible for decreasing the lung elasticity, which reduces lung function if not controlled. It is produced mostly by neutrophils and macrophages during inflammations.*
### Appendix – biomarkers

<table>
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<th>Technic</th>
<th>Description of hypothesis (count of)</th>
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<th>References</th>
</tr>
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</table>
| Blood and plasma biomarker | • Eosinophil (type of white blood cell that confirm COPD diagnosis as they create inflammatory response)  
• AoVal (plasma substance allowing recognition of pre-inhibition of neutrophil elastase* responsible for decrease of lung function)  
• C-Reactive Protein (CRP) (plasma substance produced by the liver in response to inflammation)  
• HSP27 (heat shock protein 27 is present in the serum at early stage of inflammation)  
• ARHGEF1 (Rho guanine nucleotide exchange factor 1 decrease worsen lung function as it decreases the number of leukocytes)  
• A1AT (α1-antitrypsin is an inhibitor of neutrophil elastase* responsible for decrease of lung function)  
• α2-macroglobulin (coagulator inhibitor)  
• Ceruloplasmin (protein participating in the fixation of iron on haemoglobin; high level suggests COPD or possible exacerbation)  
• Hemopexin (protein participating in iron preservation and oxidation protection; low levels indicate anaemia)  
• Uric acid (it is the final product of purine degradation and increases during hypoxia)  
• Hydrogen sulphide (gasotransmitter which level is linked to COPD stage)  
• Hyaluronic acid (protein participating in anti-inflammatory responses)  
• Heparan sulphate (participate in the regulation of biological processes as well as the reception of respiratory viruses; increased level is correlated with AECOPD)  
• Plasma periostin (participated in tissue development; increased level correlates with lung function improvement)  
• Matrix Metalloproteinase-9 (MMP9) (involved in wound healing or pathological processes; increased level suggests inflammation)  
• Chemokine ligand 18 (inflammatory protein which level increases during AECOPD)  
• Surfactant protein D (protein produced by lungs which level correlates with AECOPD)  
• Interleukin-6/8 (protein secreted by fibroblast; its level is negatively correlated to lung function)  
• Procalcitonin (protein activated in response to bacterial infection; can predict AECOPD)  
• Endothelial micro particle (membrane vesicles circulating in blood; their level increase during AECOPD and inflammation) | Early stage COPD diagnosis  
• AECOPD monitoring  
• Routine COPD monitoring  
• Improving antibiotics prescription  
• Inflammation monitoring  
• COPD mortality prediction | Biochemical reactions with potential accurate and reliable results | • Blood or tissue sample required  
• Bio-chemical result calibration  
• In the case of self-monitoring, the patient needs to act  
• No real time or continuous analysis | More studies are required to determine the potential impact and benefit of those technics in a clinical setting. Preliminary feasibility studies showed promising results. Acceptance by clinicians depends on the potential clinical value and impacts on treatment delivery. Not all bio-markers are relevant for monitoring of COPD or AECOPD evolutions. Some methods require sample extraction, which might increase morbidity. To diagnose COPD, a combination of bio-markers is necessary. | (Bafadhel et al., 2012, Carter et al., 2013, Duvoix et al., 2013, Ankersmit et al., 2012, Packard et al., 2013, Bartziokas et al., 2014, Elmalek et al., 2014, Aida et al., 2011, Jash, 2014, Sun et al., 2012, Wu, 2013, Salto et al., 2014, Rovina et al., 2014, Park et al., 2016, Aldonyte et al., 2004, Karadag et al., 2008, Woodruff, 2011, Lin et al., 2010, Cazzola and Novelli, 2010)  

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<table>
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<tr>
<th>Method</th>
<th>Description of Hypothesis</th>
<th>Medical Applications</th>
<th>Advantages</th>
<th>Limitations</th>
<th>Papers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pulse, step activity and vital signs monitoring. Wrist/ fingertip</td>
<td>PPG, step count activity and position recognition</td>
<td>• COPD monitoring</td>
<td>• Wireless system with application and server</td>
<td>• Bulky system&lt;br&gt;• Need clinical input for data analysis</td>
<td>(M2D2, n.d.)</td>
</tr>
<tr>
<td>Wheeze, respiratory rate and blood oxygenation monitoring</td>
<td>2PPG sensors, pneumogram belt, ambient microphone</td>
<td>• COPD monitoring&lt;br&gt;• Asthma&lt;br&gt;• Allergy</td>
<td>• Home monitoring&lt;br&gt;• Continuous monitoring</td>
<td>• Wired system&lt;br&gt;• Maximum 24 hour monitoring&lt;br&gt;• Clinician input for data analysis</td>
<td>(iSonea 2012)</td>
</tr>
<tr>
<td>Blood flow and oxygenation monitoring</td>
<td>PPG sensor</td>
<td>• COPD monitoring&lt;br&gt;• AECOPD monitoring</td>
<td>• Integrated into a watch-like device&lt;br&gt;• Wireless system with telemedicine</td>
<td>• Clinical input for data analysis</td>
<td>(medGadget 2013)</td>
</tr>
<tr>
<td>Blood oxygenation saturation, heart rate, walking, temperature</td>
<td>PPG, temperature sensor</td>
<td>• COPD monitoring</td>
<td>• Wireless system with server</td>
<td>Limitation use of the hand</td>
<td>(Aseptika 2014a)</td>
</tr>
<tr>
<td>Vibration response imaging technology</td>
<td>Accelerometer</td>
<td>• COPD monitoring</td>
<td>• Wireless system&lt;br&gt;• Real-time data</td>
<td>• User interaction for data collection&lt;br&gt;• Can be Cumbersome to use</td>
<td>(Breeze 2011)</td>
</tr>
<tr>
<td>Respiration and movement monitoring</td>
<td>Accelerometers which reproduce respiratory waveforms</td>
<td>• COPD monitoring</td>
<td>• Wireless system with server&lt;br&gt;• No patient input needed&lt;br&gt;12 months battery life&lt;br&gt;Real-time</td>
<td>Patch placement accuracy</td>
<td>(Lorna et al., 2012)</td>
</tr>
<tr>
<td>Spirometer and electronic diary linked to server</td>
<td>Daily measurement of lung air capacity</td>
<td>• COPD monitoring&lt;br&gt;• AECOPD early detection</td>
<td>• Real-time data access by the clinical team</td>
<td>• Need patient input</td>
<td>(Sund et al., 2009, Taube et al., 2011, Giraud et al., 2016)</td>
</tr>
<tr>
<td>Wireless body sensor network</td>
<td>Pulse oximeter and accelerometer sensor (measuring time spent in sitting, standing and lying positions)</td>
<td>• COPD monitoring&lt;br&gt;• AECOPD early detection</td>
<td>• Near real-time data analysis&lt;br&gt;• Possible telemedicine</td>
<td>45 hour monitoring&lt;br&gt;• Patient needs to switch the device on or off&lt;br&gt;• Bulky system (pulse oximeter on finger)</td>
<td>(Noury et al., 2014, Perriot et al., 2014, Dinesen et al., 2012, Vooijs et al., 2014, Patel et al., 2009)</td>
</tr>
<tr>
<td>Home oxygen deliverance system</td>
<td>Portable device for delivering oxygen in such a way that the SpO2 measured remains &gt;90%</td>
<td>• Treatment of stable COPD patient</td>
<td>Portable system</td>
<td>Bulky system</td>
<td>(Rice et al., 2011)</td>
</tr>
<tr>
<td>Forced oscillation technique (FOT) with server</td>
<td>Home device for self-measurement of lung air capacity with tidal breathing and telemedicine</td>
<td>• COPD monitoring</td>
<td>Self-assessment of lung air capacity</td>
<td>Discrete assessment&lt;br&gt;• Only home use, not portable</td>
<td>(Dellacà et al., 2010, Teulier et al., 2013)</td>
</tr>
<tr>
<td>Electro myograph (EMG)</td>
<td>The neural respiratory drive index (NRDI) is calculated from EMG</td>
<td>• COPD monitoring&lt;br&gt;• Predict respiratory changes and AECOPD&lt;br&gt;• Monitoring of treatment response</td>
<td>Possible translation into a mobile device</td>
<td>Electrodes placement might require medical training</td>
<td>(Murphy et al., 2011)</td>
</tr>
</tbody>
</table>

Table 2: Emerging Wearable Devices for COPD
<table>
<thead>
<tr>
<th>Method</th>
<th>Description of Hypothesis</th>
<th>Medical Applications</th>
<th>Advantages</th>
<th>Limitations</th>
<th>Papers</th>
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</thead>
<tbody>
<tr>
<td>Blood pulse, step activity and vital</td>
<td>Monitoring. Wrist/fingertip PPG, step count activity and position</td>
<td>COPD monitoring</td>
<td>Wireless system with application and server</td>
<td>Bulky system</td>
<td>(M2D2, n.d.)</td>
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<td>signs monitoring</td>
<td></td>
<td>Asthma</td>
<td>Home monitoring</td>
<td>Continuous monitoring</td>
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CHILDERS, N. 2013. Data Protection Regulation: Keeping Health Research Alive in the EU. Medical Sciences Committee of Science Europe.


GFK 2016. Forecast unit sales of health and fitness trackers worldwide from 2014 to 2015 (in millions), by region. Statista, Inc.


GULLICK, J. 2012. Psychosocial dimensions of COPD for the patient and family, INTECH Open Access Publisher.


NHS 2015. Inhaled therapy in chronic obstructive pulmonary disease (COPD). PrescQIPP. NHS.


NIHR CRN. 2015. Using health technology to empower patients. Insight [Online].


PUNEKAR, Y. S. 2014. COPD management costs according to the frequency of COPD exacerbations in UK primary care. International Journal of Chronic Obstructive Pulmonary Disease, 9, 65-73.


Implantable and Wearable Medical Devices for COPD


