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# Impact of increased single-inhaler triple therapy use in appropriate patients on COPD exacerbations, mortality, and medical costs: PROMETHEUS Spain.

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Short title: Impact of increased SITT use in Spain's COPD population

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Keywords: COPD, single-inhaler triple therapy, population model

**Abstract**

**Introduction**: COPD is the third cause of death in Spain. The ETHOS (NCT02465567) and IMPACT (NCT02164513) RCTs showed reduced exacerbations and all-cause mortality for single-inhaler triple therapy (SITT), but no studies have evaluated the potential impact on COPD outcomes of higher SITT adoption in Spain.

**Methods:** We used literature-based data on patient characteristics, incidence, COPD severity changes, treatment distributions/transitions, mortality, exacerbations, and medical costs, to inform a stochastic simulation of the Spanish COPD population for 2025-2034 under two scenarios: "Status Quo" and "Increased SITT", in which higher SITT use is driven by airflow limitation, exacerbation history (as per 2025 GOLD report) and SITT replacing multiple-inhaler triple therapy (MITT). Additionally, we present results separately for the subset of patients that met the criteria for SITT use, referred to as "flagged population."

**Results:** In our 10-year simulation, increased SITT use in the flagged population could lead to 51,000 deaths avoided resulting in a 14.6% reduction in mortality rates and extended patient life by 1.2 years per COPD flagged patient. Additionally, increased SITT use in the flagged population reduced severe and moderate exacerbations by 62,000 (an 11.5% reduction) and 366,000 (an 11.6% reduction), respectively, resulting in total medical savings of €384 million.

**Conclusion:** Based on our simulation, increased use of SITT in the Spanish COPD population, consistent with the most recent 2025 GOLD report recommendations, could reduce mortality and exacerbations and their corresponding medical costs. Increasing SITT utilization in patients with COPD may constitute a long-term strategy with relevant clinical and economic benefits.

## Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable lung disorder that gradually worsens and impairs lung function. COPD develops predominantly due to inflammation that can occur from the inhalation of lung irritants, such as cigarette smoke or other particles (1) (2). In addition to the known progressive decline in lung function associated with COPD, there are a host of other chronic diseases for which patients with COPD are at risk including cardiovascular and metabolic diseases, anemia, osteoporosis, and sleep and mental health conditions (2). COPD deaths in Spain have increased over time from 47.7 per 100,000 in 1990 to 67.9 per 100,000 in 2019, resulting in COPD being the 3rd leading cause of death, responsible for 7%, or 31,000 deaths, in 2019 (3). The overall prevalence of COPD in Spain in 2019 was 14.6% in males and 9.4% in females with an estimated underdiagnosis of 74.7%, which suggests a large population at risk of morbidity and mortality who are currently underdiagnosed (4). GOLD report placed an increased importance on exacerbations (5). While airflow limitations (% predicted FEV1) are still utilized to define GOLD 1-4 categories, the previous symptomology-based GOLD phenotypes -- A, B, C, D -- have been revised to combine C and D into a new group, GOLD E, representing patients with ≥ 2 moderate or ≥ 1 severe exacerbation (an exacerbation leading to hospitalization) annually (5).

Under GOLD report, patients who are GOLD E are recommended to initiate therapy with dual long-acting beta-agonist (LABA) + long-acting muscarinic antagonist (LAMA therapy). To escalate from dual to triple therapy by adding inhaled corticosteroids (ICS), patients would have to experience exacerbations or have a blood eosinophil count ≥ 100 according to GOLD report (5). Alternatively, for patients in GOLD E with a blood eosinophil count ≥ 300 or those with concomitant asthma, initial therapy with triple therapy may be initiated. The ETHOS and IMPACT studies have both demonstrated that patients treated with single inhaler triple therapy (SITT) have reduced rates of all-cause mortality and exacerbations (6) (7) relative to dual therapy, notably, patients were not excluded on the basis of their blood eosinophil count.

Triple therapy can be prescribed using multiple inhalers (MITT) or in a single inhaler (SITT) and although they contain the same medication, compliance may be higher with SITT therapy (8). A retrospective analysis using electronic health records in the Spanish National Healthcare System found that patients on SITT had higher therapy persistence (HR 1.37, P < 0.001) as well as a reduced risk of exacerbations (HR 0.68, P = 0.001) and lower all-cause mortality (HR 0.67, P = 0.027) (9). GOLD report also state that SITT may be more convenient and effective than MITT.

Exacerbations are important to the disease progression of COPD as they are associated with an increased decline in lung function, decline in functional status, higher risk of mortality, as well as additional costs related to receiving treatment and care (5). The AVOIDEX study evaluated patients with COPD in Spain to determine the burden of exacerbations (10).

As the Spanish COPD population ages and patients with COPD are living longer, these issues become increasingly important to the healthcare system. Indeed, an analysis of mortality trends from 1980-2020 found an increase in the average age at death in patients with COPD by 3 years in men to 77 years and by 2 years in women to 82 years (11).

In addition to mortality and morbidity, COPD is associated with medical costs. When patients with COPD are hospitalized, the average cost for a hospitalization was €3,212 with ICU admissions costing €8,214 (12). Looking specifically at costs related to exacerbations, the estimated cost for a moderate exacerbation is €71, while a severe exacerbation costs €4,350 in Spain (13). COPD also leads to noticeable indirect costs (via lost productivity) (14).

Despite the growing body of evidence in favor of more progressive and widespread triple therapy prescribing, specifically SITT, long term data on its impact on patient outcomes is lacking due to its more recent approval and availability in Spain. In this study, we developed a multi-year stochastic microsimulation model that evaluates the impact of widespread SITT use in a real-world Spanish COPD population.

## Methods

### Model Approach

The model structure was based on the PROMETHEUS study, which estimated the impact of increased SITT use in a United States COPD population (15). The multi-year stochastic microsimulation model projects outcomes over a 10-year period and incorporates new COPD entrants (incident cases). Patients that represent the real-world Spanish COPD population are assigned characteristics (i.e. age, gender, incidence, changes in COPD severity, treatment, mortality, and exacerbations) that reflect the COPD literature. Refer to

the supplemental data for a description of the characteristics utilized in the modeling and the sources for each assumption. Based upon the percent of predicted forced exhalation volume in 1 second ($FEV_1$), we assigned Patients to GOLD stages 1-4. Patient's COPD severity progression was made by applying a decline in $FEV_1$ and this progression was determined annually as well as additional declines for concomitant smoking.
A baseline (or status quo) model was developed by incorporating population growth in line with the projected growth of the Spanish population over the 10-year projection period.

**Simulation Overview, Model Populations, and Simulation Scenarios**
Our projection modeled 1,000 simulations over 10 years from 2025 to 2034, with annual, probabilistic changes made to patient characteristics. Annually, the probability of events such as $FEV_1$ decline were applied to produce COPD disease progression, smoking quit rates, COPD medication changes, mortality, and moderate and severe exacerbations. Patients who continued smoking or had moderate or severe exacerbations had higher probabilities of progression. Medication therapy was also linked to disease progression and exacerbations. Detailed information on the assumptions can be found in the supplemental data (please refer to "Supplemental Data: References for baseline model patient characteristics" for a detailed list of assumptions and the sources utilized for each). Newly diagnosed (incident) patients with COPD were added annually and some patients exited annually through death or reaching 100 years of age. We modeled two scenarios – "Status Quo" and "Increased SITT".

- **"Status Quo"** (Baseline): this model simulated the current Spanish COPD population, assuming any new triple therapy users would be prescribed SITT rather than MITT, with no changes in current SITT prescribing patterns (Figure 1). Treatment patterns and probabilities were mapped based on the patterns observed in the AVOIDEX study.
- **"Increased SITT"**: this model assumed that an increase in SITT prescribing would occur over the projection timeframe, based on both 2023 and 2025 GOLD prescribing report recommendations (Figure 2). This model was created utilizing GOLD 2023 report, however, modeled outputs are valid under GOLD 2025 as well, as the prescribing recommendations utilized have not changed (16). Assumptions used in the "*Increased SITT"* modeled population are largely the same as those used in the "*Status Quo"* population except for the annual medication change algorithm that transitions additional patients to SITT.

We reported results for two populations within each scenario – Total and Flagged – where Flagged represents the subset of the Total population who met the criteria for SITT prescribing based on GOLD report (regardless of actual modeled medication use). Of note, each scenario was simulated separately, and therefore there may be slight variation in the outcomes for the non-Flagged population.

We estimated the number of years of life (ie, life-years) extended for the total and flagged populations under higher SITT adoption scenarios compared to the current situation. We initially determined the expected years of life by using standard mortality tables and considering the distribution of their age and sex. We adjusted the standard mortality rates to account for the increased mortality associated with COPD and then estimated the expected future years of life for each population. Cost data for moderate and severe exacerbations was determined using literature-based assumptions of €72,76 per-moderate exacerbation cost and €4466,09 per-severe exacerbation cost (17). We first trended these costs to 2023 using observed annual inflation rates and then further trended these costs to the 10 years modeled using the average annual consumer price index (CPI) inflation rate.

**Statistical Analyses**

In the 10-year model, we determined projected deaths and severe and moderate exacerbation rates (and counts) for the total population as well as the flagged population under both the "Status Quo" and the "Increased SITT" models. In addition, we determined the change in mortality, life years and exacerbation rate and counts between both models in the total and flagged populations, separately. We also calculated the number needed to treat (NNT) for the "Increased SITT" model to increase life expectancy by one year. Statistical analyses were performed using Python PySpark and included the use of a stochastic microsimulation model, calculation of descriptive statistics including means for continuous variables, and calculation of frequency percentages for categorical variables.

**Results**

At the start of our model at year 0, the baseline average age of patients with COPD was 69.3 years old and 34% were female, representing approximately 3.0 million total years of life. Regarding the severity of the baseline population, 8.2% of patients had an FEV1 >80% predicted (least severe), 46.2% had an FEV1 ≥50% and <80% predicted, 35.9% had an FEV1 ≥30% and <50% predicted, and 9.8% had an FEV1 <30% predicted (most severe). Additional baseline demographics are shown in Table 1 and are described for the study population prior to start of sampling (year 0) and across all 10 years of the projection.

The baseline treatment distribution reflected 3.5% of patients received no COPD maintenance treatment, 17.5% received LABA or LAMA, 3.3% received ICS only, 22.8% received ICS+LABA or ICS+LAMA, 26.6% received LABA+LAMA, 9.5% received MITT, and 16.7% received SITT. Medication distribution for patients at baseline and over 10 years for the "Status Quo" and "Increased SITT" populations are shown in Figure 3. Notably, over the 10 years, 25% of patient years are using triple therapy in the "Status Quo" model versus 34% in the "Increased SITT" model.

As shown in Table 2, the reduction in moderate and severe exacerbations and mortality were larger in the flagged population, as this a subset of the total population that isolates those that met the criteria for SITT use. For the flagged population the severe exacerbation rate was reduced from 8.9% in the "Status Quo" model to 7.5% in the "Increased SITT" model, representing a 15.8% reduction in severe exacerbations. The flagged population's moderate exacerbation rate was reduced from 47.2% in the "Status Quo" model to 39.7% in the "Increased SITT" model, representing a 16.0% reduction. In addition, all-cause mortality rate was reduced from 7.5% in the "Status Quo" model to 6.4% in the "Increased SITT" model for the flagged population, resulting in a mortality rate reduction of 14.6%.

Over the 10-year study period, the "Increased SITT" model led to a reduction in the severe exacerbation count for the flagged population of 62,100 exacerbations, equating to savings of €350.7 million (Table 2). The moderate exacerbation count was reduced by 365,700, equating to savings of €33.5 million. This represents a total cost saving of €384.2 million from reduced exacerbations for the flagged population. Mortality was also reduced; deaths were reduced by 2.3% in the total population and by 10.7% in the flagged population. The annual "Status Quo" costs as well as the annual incremental cost avoided due to increased SITT use are shown in Figure 4.

For the flagged population under the "Increased SITT" model, over the 10 years, the years of life remaining was extended 1.8 years for ages 41-49, 1.7 years for ages 50-59, and 1.4 years for ages 60-69, and 1 year or less for those over 70 (Figure 5). Across all ages over the 10 years, the average years of life extended per patient with COPD were 0.2 and 1.2 (or 7.2 million cumulative life years across all patients with COPD) for the total and flagged populations, respectively. As seen with other outcomes, the extended life years per patient with COPD is greater for the flagged population compared to the total population. Over the modeled

10-years, the number needed to treat to extend the average patient life by 1 year was 57 for the total population and 12 for the flagged population.

**Sensitivity Testing**

We conducted sensitivity testing to understand the impact of variations in our assumptions on our "Increased SITT" deaths and exacerbation counts, and exacerbation cost outcomes. We tested four variables; 1) the base case GOLD stage distribution, 2) the exacerbation rates, 3) the COPD population growth, and 4) the FEV1 % of predicted cutoff required to consider patients for SITT therapy under the Increased SITT model.

For the GOLD distribution, we assumed that the COPD population was more or less severe than the base case population by shifting 10% of the patients in each baseline GOLD stage to a higher or lower stage. For the exacerbation rate sensitivity testing, we took the base case exacerbation rates and increased or decreased them by 10%. The incidence rates of COPD were varied up and down by 1%, and lastly the FEV1 % of predicted cutoff for the "Increased SITT" model was modified from 65% to 80%. The 80% cutoff aligns with the IMPACT study and is also the cutoff in the recently published Canadian Thoracic Society COPD management guidelines (18) (7).

Figure 6 below displays the difference in "Status Quo" and "Increased SITT" results in the flagged population under the sensitivity analysis for the four varying assumptions described above. We found that adjusting the FEV1 % predicted threshold for considering patients for increased SITT therapy from 65% to 80% had the most significant impact on the results. Raising the FEV1 % predicted threshold to 80% (from 65% in the base case) leads to more patient life years being included in the flagged population, and therefore a higher reduction in death counts, severe and moderate exacerbations under "Increased SITT" compared to "Status Quo" for both the flagged and total populations. Conversely, altering the assumptions for COPD population growth rates had the smallest impact on the results across all populations and modeled scenarios. Further details on the impacts of assumption changes are also provided in Supplemental Table 1.

If exacerbation costs are lower or higher than expected, then the savings presented in these results would also be proportionally lower or higher, respectively. For example, based off of Sicras at. al., if we raised the medical costs for moderate exacerbations from the current base case assumption of approximately €80 to around €370 as noted in the study, the moderate exacerbation costs would increase approximately 4.5 times, equating to savings of €147.9 million over the 10 years (compared to the base case savings of €33.5 million) only for this type of exacerbations (20). For the flagged population, the total savings, considering both types of exacerbations, would amount to €498.6 million, as opposed to the base case savings of €384.2 million.

**Limitations**

Due to the lack of available clinical and biological markers such as symptom severity and blood eosinophils, we used predicted forced exhalation volume in 1 second (FEV1) to determine disease severity, assigning patients to GOLD stages 1-4. We note that eosinophil data is used for treatment escalation and de-escalation decisions and the unavailability of eosinophil data may lead to an overestimation of the impact of triple therapy addition. Patients' COPD severity progression was modeled by applying an annual decline in FEV1 with additional declines for concomitant smoking or asthma. The FEV1 % of predicted cutoff of 65% was chosen to model this paper on the ETHOS and PROMETHEUS studies; utilizing a different cutoff would yield different results, as noted in our sensitivity analysis. Our assumptions relied on data from both prospective clinical trials as well as real-world data from retrospective observational studies. Both of theses data sources have inherent biases and limitations as they also rely on assumptions in their methodology. We also note that we used unpublished data available to AstraZeneca to model the baseline treatment distribution. These data, routinely obtained by pharmaceutical companies from third-party providers, are generally not published but are commonly used in similar analyses due to their reliability.

Additionally, we did not factor in the costs of maintenance COPD drugs in our model. Less or more expensive therapies may represent an increased or decreased savings, respectively, to what is described here. In Spain, SITT therapy is more expensive than dual therapy, but is less expensive than MITT therapy.

**Discussion**

PROMETHEUS and this subsequent modeling approach for the Spanish COPD population incorporate real-world evidence – such as treatment patterns, GOLD stage distribution, and other patient characteristics – to help model changes over a long timeframe in a large population. Ideally, prospective studies could provide these insights, but they would require time and may also not be able to isolate the impact of a singular change as the treatment of COPD evolves.

SITT therapy has traditionally been reserved for patients with a higher severity and higher symptom burden. Exacerbations represent a significant burden in patients with COPD and to the healthcare system. They not only add costs and drive hospital and healthcare utilization, but they also increase morbidity of patients who experience them. While not in the scope of this work, other modeling studies have evaluated the impact of dual to triple therapy escalation on disease progression (21). The results of our study show that more progressive SITT prescribing than currently observed over the 10 year study is projected to significantly decrease hospitalizations due to exacerbations and increase the average life expectancy by 0.2 years for the total population and by 1.2 years for the flagged population. To extend the average patient's life by one year, the estimated number needed to treat is 57 for the total population and 12 for the flagged population. We note that we did not identify or model any differences in adverse events (and their potential related costs) in this model. Overall, across all 10-years of the model, we found that increased SITT utilization would save €384.16M in cost due to avoiding a total of 365.7K moderate and 62.1K severe exacerbations for the flagged population. Additionally, there would be a 14.6% reduction in mortality rate. The results of our sensitivity testing also indicate that even if our assumptions were modified, the overall direction of the results would not change. This adds to the credibility to the assumptions used in this modeling.

These results reinforce studies such as ETHOS and IMPACT that demonstrated meaningful impact on the reduction of exacerbations and mortality, as well as lowering medical costs. This in turn, improves patient outcomes and reduces the burden to the healthcare system. Other countries have moved towards adoption of more progressive SITT prescribing guidance, aligning with the results observed in ETHOS and IMPACT. Adopting a similar strategy could be beneficial, as demonstrated by our modeling. The potential substantial benefits in reducing exacerbations and mortality from implementing SITT could complement other strategies aimed at improving COPD outcomes, such as comprehensive management in line with guidelines, smoking cessation, supplemental oxygen therapy, and pulmonary rehabilitation.

**Conclusion**

In conclusion, an increase in SITT utilization rates in Spain could lead to lower rates of mortality, exacerbations and a reduction in the associated medical costs in patients with COPD. Increasing SITT utilization in patients with COPD may constitute a long-term strategy with relevant clinical and economic benefits as SITT therapies lessen the burden of exacerbations and mortality in patients with COPD.

**Acknowledgement**

We thank Steven Wright for his work in building the stochastic model.

**Statement of Ethics**

Study approval was not required as this was a modeling study based on published literature. No ethics board approval was required. No human participants were involved in this work and no informed consent was required.

**Conflict of Interest**

MM-O and JM-F have been remunerated for validating assumptions, sources, and interpreting results of the present work.

JS-C, CCG, NM-M and JB are employees of AstraZeneca and may hold stock and/or stock options in the company. MC, JC, PB and BP are employees of Milliman, which was contracted by AstraZeneca to conduct this study.

The American Academy of Actuaries requires its members to identify their credentials in their work product. Bruce Pyenson, Jennifer Carioto, and Melissa Caplen are members of the American Academy of Actuaries and meet its relevant qualification requirements.

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This study was sponsored by AstraZeneca. AstraZeneca was involved in the review of selected literature sources for inclusion in the modeling but had no role in the data analysis. AstraZeneca was also involved in manuscript review.

**Author Contributions**
JS-C, CCG, NM-M, JB, MC, JC, PB, BP, MM-O, and JM-F were all involved in the review of assumptions, the review of modeling results, and manuscript drafting or review.

**Data Availability**
Published literature was utilized for this modeling study. Details on the sources utilized for each assumption are described in the supplementary materials.

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**Figures**

***Figure 1:*** *"Status Quo" medication transition*

*Note: If a patient started on SITT, no further transitions were made, ED = emergency department, IP = inpatient admission*

*SITT = single-inhaler triple therapy, LABA = long-acting beta 2 agonist, LAMA = long-acting anticholinergic*

***Figure 2:*** *"Increased SITT" medication transition*

*Note: If a patient started on SITT, no further transitions were made, ED = emergency department, IP = inpatient admission, OP = outpatient visit, OCS = oral corticosteroids, ABX = antibiotics*

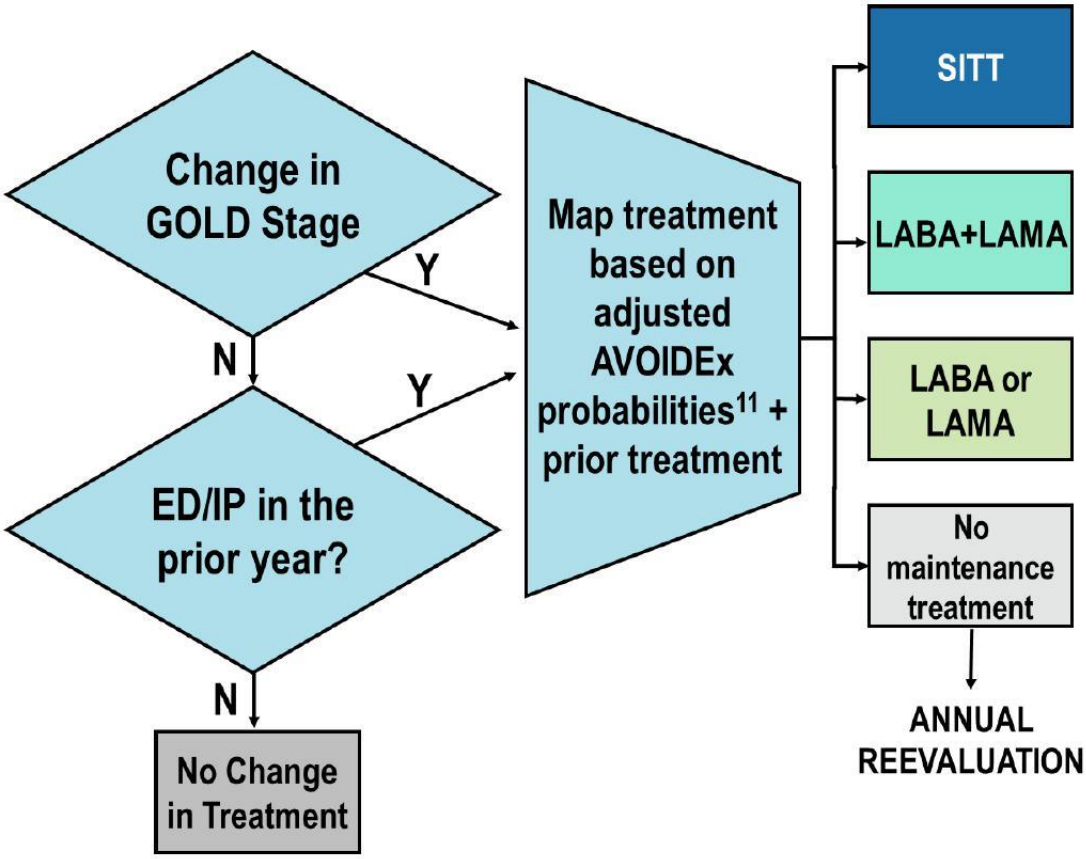
*SITT = single inhaler triple therapy, LABA = long-acting beta 2 agonist, LAMA = long-acting anticholinergic*

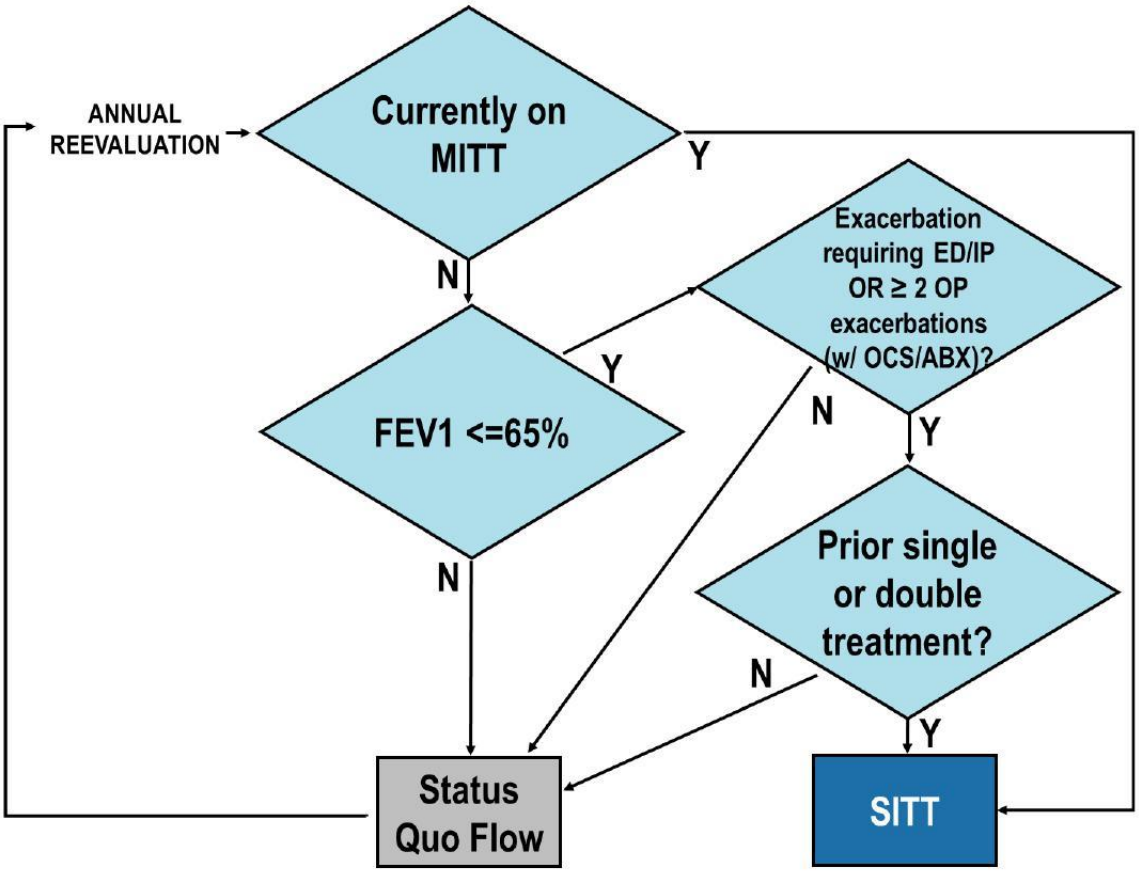
***Figure 3:*** *Medication Distribution, patient years*

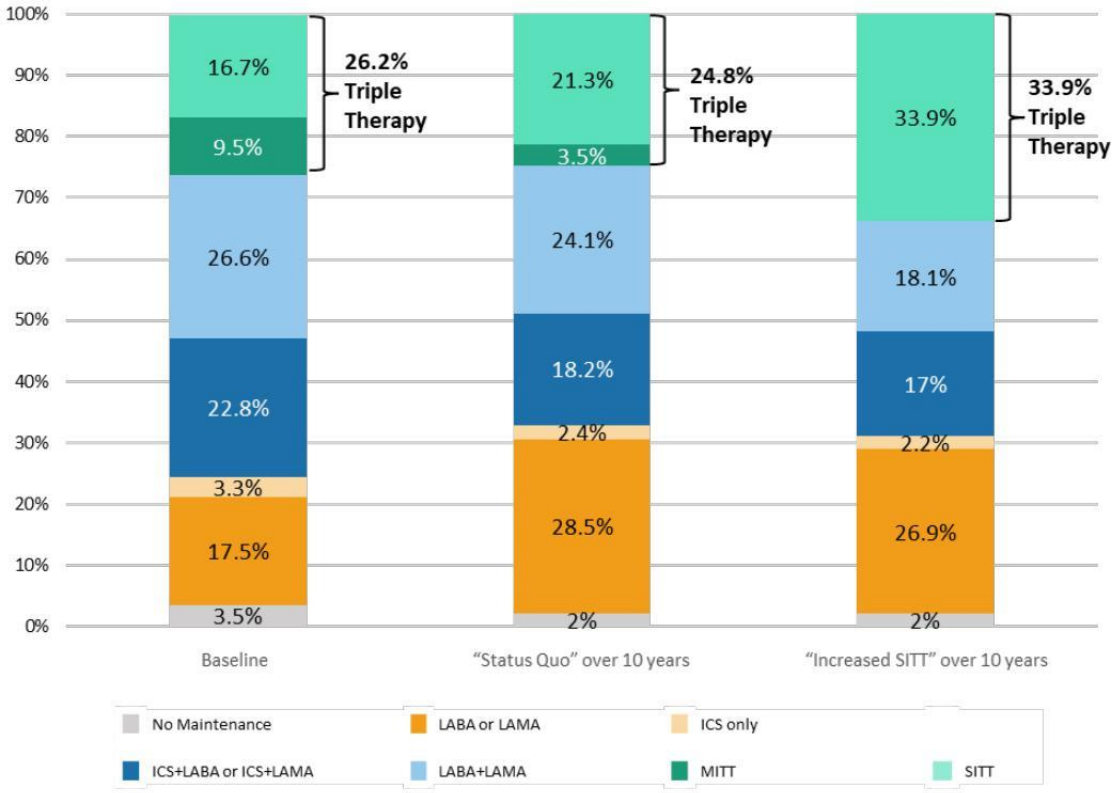
***Figure 4:*** *Cumulative exacerbation costs avoided under Increased SITT adoption over 10 years – Flagged Population*

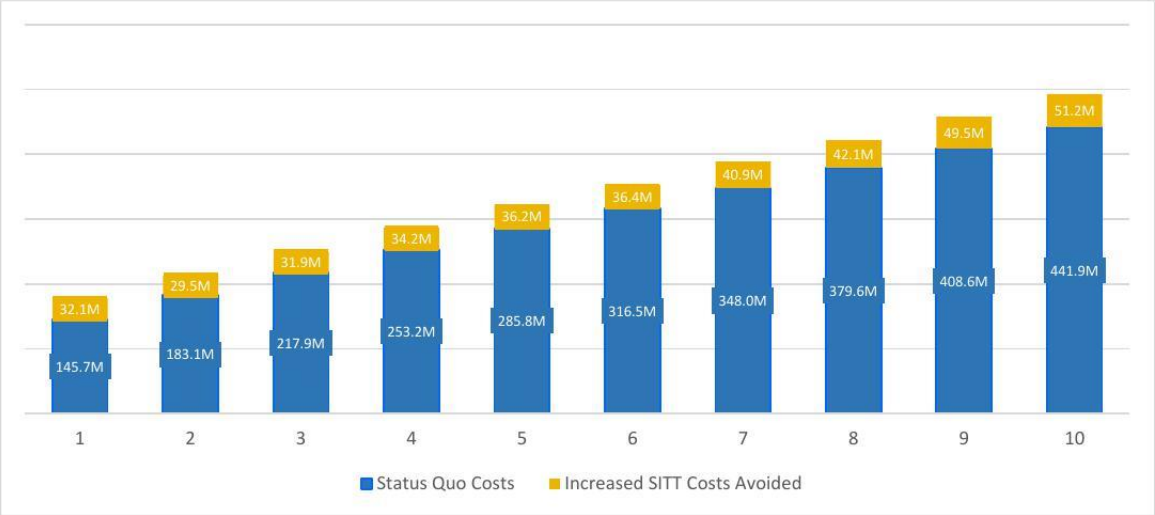
***Figure 5:*** *Average years of life remaining and extended life-years per patient with COPD, by age band – Over 10 years*

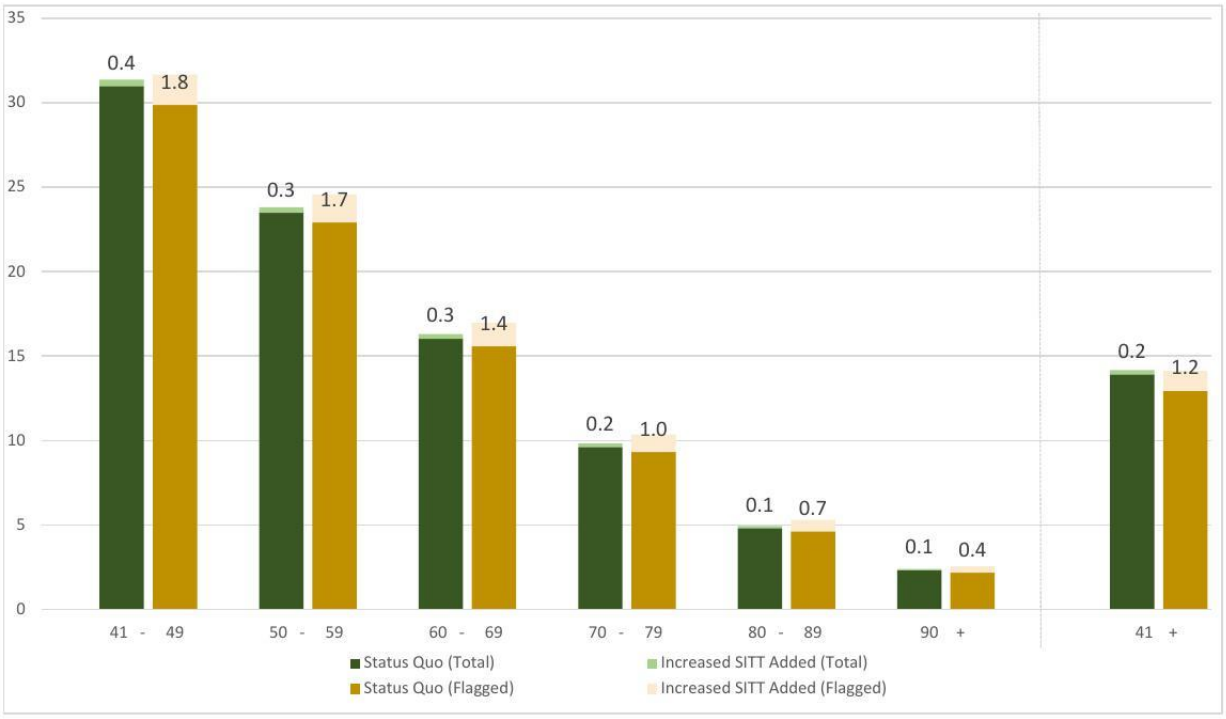
***Figure 6:*** *Status Quo and Increased SITT outcomes in sensitivity testing scenarios for the flagged population*

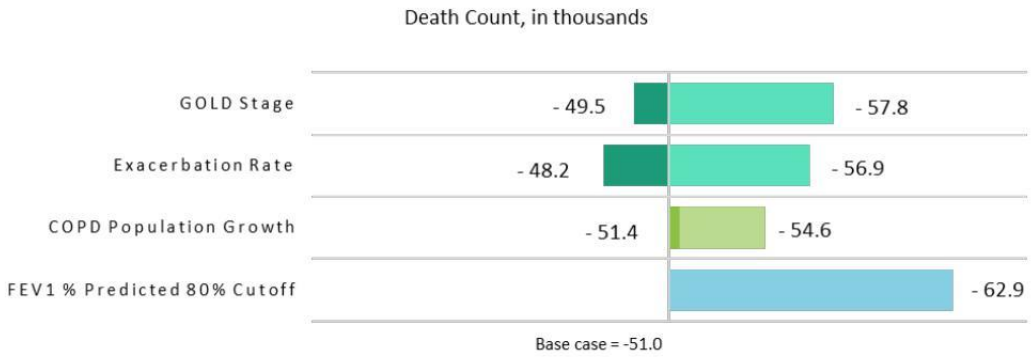














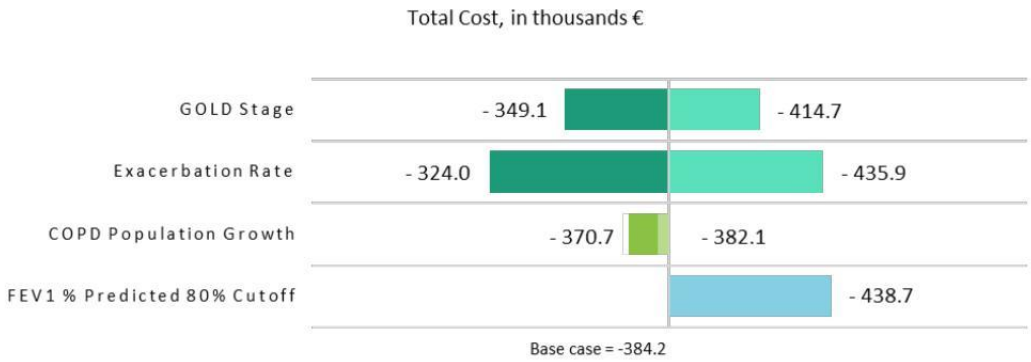



*Table 1: Study Population Demographics, COPD Severity and Medication Therapy by Scenario*

| | Baseline | Across All 10 Years | | | |
|---|---|---|---|---|---|
| | Total Population | Total Population | | Flagged Population | |
| | | Status Quo | Increased SITT | Status Quo | Increased SITT |
| Average Age | 68.3 | 69.8 | 69.9 | 70.4 | 70.7 |
| Female, n (%) | 1.02M (34.0%) | 11.8M (35.2%) | 11.9M (35.2%) | 2.24M (35.5%) | 2.33M (35.4%) |
| Asthma Comorbidity, n (%) | 360.4K (12.0%) | 3.67M (11.0%) | 3.71M (11.0%) | 727.9K (11.5%) | 763.9K (11.6%) |
| **Smoking Status Distribution** | | | | | |
| Current, n (%) | 927.7K (30.9%) | 7.48M (22.3%) | 7.53M (22.3%) | 1.28M (20.3%) | 1.33M (20.2%) |
| Former, n (%) | 1.26M (42.1%) | 16.98M (50.7%) | 17.13M (50.7%) | 3.35M (53.0%) | 3.5M (53.0%) |
| Never, n (%) | 809.9K (27%) | 9.05M (27.0%) | 9.13M (27.0%) | 1.69M (26.7%) | 1.77M (26.8%) |
| **FEV1% of Predicted Distribution** | | | | | |
| GOLD 1: >80%, n (%) | 245.4K (8.2%) | 3.04M (9.1%) | 3.05M (9.0%) | 122.8K (1.9%) | 129.4K (2.0%) |
| GOLD 2: ≥50% and <80%, n (%) | 1.38M (46.2%) | 16.42M (49.0%) | 16.51M (48.8%) | 2M (31.6%) | 2.08M (31.5%) |
| GOLD 3: ≥30% and <50%, n (%) | 1.08M (35.9%) | 8.47M (25.3%) | 8.56M (25.3%) | 2.1M (33.2%) | 2.19M (33.1%) |
| GOLD 4: <30%, % | 293.9K (9.8%) | 5.57M (16.6%) | 5.68M (16.8%) | 2.1M (33.2%) | 2.21M (33.5%) |

*M = millions (1000 thousands), K = thousands (10 hundreds)*

*Table 2: Mortality, life years, and exacerbation outcomes by population over 10 years*

| | Total Population | | | Flagged Population | | |
|---|---|---|---|---|---|---|
| | **Status Quo** | **Increased SITT** | **Absolute / Percent Change** | **Status Quo** | **Increased SITT** | **Absolute / Percent Change** |
| Total Patient Years | 30.94M | 31.25M | 317.2K<br>1.0% | 6.07M | 6.39M | 311.0K<br>5.1% |
| Death counts | 2.36M | 2.31M | -53.3K<br>-2.3% | 476.5K | 425.6K | -51.0K<br>-10.7% |
| **CLINICAL OUTCOMES** | | | | | | |
| Mortality rate (%) | 7.4% | 7.1% | -0.2%<br>-3.1% | 7.5% | 6.4% | -1.1%<br>-14.6% |
| Severe exacerbation counts | 2.05M | 1.99M | -61.1K<br>-3.0% | 541.3K | 479.2K | -62.1K<br>-11.5% |
| ≥1 severe exacerbation rate (%) | 6.6% | 6.4% | -0.3%<br>-4.0% | 8.9% | 7.5% | -1.4%<br>-15.8% |
| Moderate exacerbation counts | 15.28M | 14.92M | -366.0K<br>-2.4% | 3.15M | 2.79M | -365.7K<br>-11.6% |
| ≥1 moderate exacerbation rate (%) | 45.4% | 43.9% | -1.5%<br>-3.4% | 47.2% | 39.7% | -7.5%<br>-16.0% |
| **COST OUTCOMES** | | | | | | |
| Severe exacerbation cost, € | € 11.52B | € 11.18B | -€ 345.03M<br>-3.0% | € 3.07B | € 2.72B | -€ 350.68M<br>-11.4% |
| Moderate exacerbation cost, € | € 1.40B | € 1.36B | -€ 33.48M<br>-2.4% | € 290.84M | € 257.37M | -€ 33.48M<br>-11.5% |

*Note: Each scenario was simulated separately, and therefore there may be slight variation in the outcomes for the non-Flagged population*

*B = billions (1000 millions), M = millions (1000 thousands), K = thousands (10 hundreds)*