# Modulator Treatments for Cystic Fibrosis: Effectiveness and Value

**Modeling Analysis Plan**

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**Institute for Clinical and Economic Review**

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# 1. Approach

This analysis plan details our modeling approach and outcomes to be assessed for the economic evaluation of cystic fibrosis transmembrane conductance regulator (CFTR) modulator treatments plus best supportive care for cystic fibrosis patients compared to best supportive care alone. Please refer to the research protocol for details on the systematic review of the clinical evidence on this topic.

The primary aim of this analysis will be to estimate the cost-effectiveness of four treatments for cystic fibrosis using a decision analytic model. For patients who are candidates for Kalydeco® (ivacaftor, Vertex Pharmaceuticals, Inc.) based on current indications, we will compare Kalydeco plus best supportive care to best supportive care alone. For patients who are homozygous for the *F508del* mutation and patients who are heterozygous for the *F508del* mutation with a residual function mutation, we will compare Symdeko® (tezacaftor/ivacaftor, Vertex Pharmaceuticals, Inc.) plus best supportive care, Trikafta™ (elexacaftor/tezacaftor/ivcafactor, Vertex Pharmaceuticals, Inc.) plus best supportive care, and best supportive care alone. We will not consider lifetime treatment with Orkambi® (lumacaftor/ivacaftor, Vertex Pharmaceuticals, Inc.) for the former population or ivacaftor monotherapy for the latter population because Symdeko has been shown to be clinically superior to both in trials with these populations. For patients who are heterozygous for the *F508del* mutation with a minimal function mutation we will compare Trikafta plus best supportive care and best supportive care alone. The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only) and potentially present the societal perspective as a joint base case for treatments for which ICER's ultra-rare disease framework apply (i.e., Kalydeco and Symdeko). A societal perspective will be included as a co-base case for ultra-rare diseases if it is anticipated that the impact of the treatment on patient and caregiver productivity, education, disability and nursing home costs are large relative to health care costs. In our last review we did not find that impact of the therapies on societal costs were large relative to the impact on health care costs; however, we will re-evaluate the balance of these costs with updated evidence. For scenarios where the ultra-rare framework doesn't apply (i.e., Trikafta), productivity losses and other indirect effects will be considered in a scenario analysis, if data allow. Outcomes will be estimated over a lifetime time horizon using one-year time increments from treatment initiation until death. Costs and health outcomes will be discounted at 3% per year. The models have been developed in TreeAge software version 2018 (Williamstown, MA).

# 2. Methods

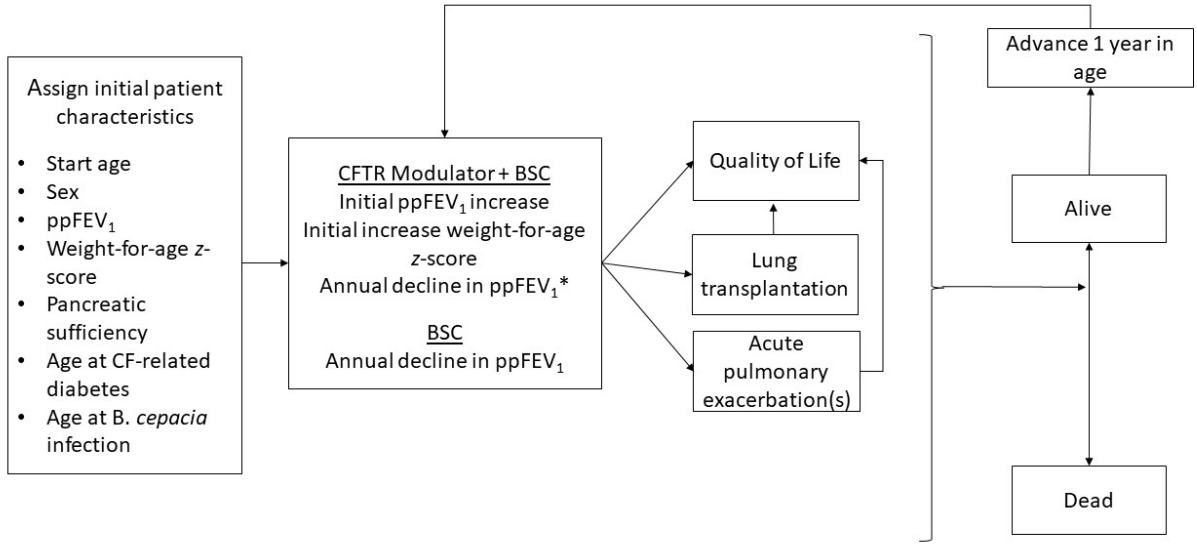
## 2.1 Overview and Model Structure

We will update previously developed *de novo* microsimulation models for this evaluation. The primary model variable is percent predicted forced expiratory volume in 1 second ($ppFEV_1$), modeled as a continuous variable. This model type was chosen to account for the continuous nature of $ppFEV_1$ and to capture the primary effect of the drugs (i.e., to increase $ppFEV_1$). CF patients begin the model at the age that they are eligible for a CFTR modulator treatment and are assigned a starting $ppFEV_1$ value. Each year, simulated patients experience annual age-specific declines in their lung function. Simulated individuals are assigned a heterogeneity parameter that determines whether the person progresses faster or slower in their lung function ($ppFEV_1$). Without assuming a heterogeneity parameter (the value of which can increase or decrease the rate of lung function progression for a simulated person), age and $ppFEV_1$ track together one to one. By changing the variance of the heterogeneity parameter (drawn from a Gamma distribution with a mean of 1), we are able to fit to both the median life expectancy and the median $ppFEV_1$ by age. Simulated individuals will be matched to observed statistics of CF patients: median age of survival, percent in lung function categories (≤40% $ppFEV_1$, severe; between 40% and 70% $ppFEV_1$, moderate; ≥70% pp $FEV_1$, mild) by age, and median $ppFEV_1$ by age.[1] In addition to $ppFEV_1$, we will also track other variables for each simulated person: sex, weight-for-age *z*-score, number of acute pulmonary exacerbations per year, pancreatic sufficiency, lung transplantation, and diagnosis of CF-related diabetes mellitus or *B. cepacia* infection. During any given year, a simulated person may experience a change in their $ppFEV_1$, may experience one or more pulmonary exacerbations, may be diagnosed with CF-related diabetes mellitus or *B. cepacia* infection, or undergo lung transplantation (conditional on their $ppFEV_1$ being less than 30%). The annual risk of death is a function of all these variables.

For the treatment arms, we allow the $ppFEV_1$ value at age of treatment initiation and weight-for-age *z*-score to change based on trial results. We will also allow for the occurrence of treatment-related side effects and assign costs and disutilities accordingly.

Figure 1 shows a diagram of the model, with the risk of pulmonary exacerbation and lung transplantation dependent on $ppFEV_1$ level. Persons are simulated for their lifetime and each year we accumulate life years, quality-adjusted life years (QALYs), and costs. All patients can transition to death from all causes from any of the alive health states. In addition, patients can die from CF-related causes as determined by a mortality model (described below).

**Figure 1. Model Schematic**




*Annual decline in ppFEV1 begins two years after treatment with CFTR modulator arm and is half that of BSC

## 2.2 Key Model Choices and Assumptions

Our model includes several assumptions, stated below.

**Table 1. Key Model Assumptions**

| Assumption | Rationale |
|---|---|
| **ppFEV$_1$ does not increase over time in the absence of CFTR modulator therapy.** | We make this assumption because it is true in general that lung function declines with age. |
| **Best supportive care is assumed to be the same in all treatment arms, though the intensity of therapy increases with decreasing lung function category (≥70%, 40%-69%, <40%).** | Modulator therapy will have an impact on costs associated with acute pulmonary exacerbations and lung transplantation, but all other costs of care not associated with lung function will not be affected by modulator therapies within a given lung function category. |
| **The weight for-age *z*-score is constant over the lifetime of a patient, with a one-time increase with CFTR modulator therapy.** | There is limited evidence for how weight for-age *z*-score changes over time and this assumption has been used in the United Kingdom's (UK) National Institute for Health and Care Excellence (NICE) economic evaluations. |
| **The risk of *B. cepacia* infection over time does not depend on lung function severity.** | The occurrence of of *B. cepacia* infection is incorporated because it is part of the CF-specific mortality risk. |
| **The CFTR modulator drug effect is modeled as an increase in ppFEV$_1$, and increase in weight for age *z*-score, and a decrease in the annual number of acute pulmonary exacerbations.** | These are well-documented effects of CFTR modulator drugs from clinical trials. |
| **CFTR modulator drugs decrease the annual number of acute pulmonary exacerbations through the increase in ppFEV$_1$ (i.e., the risk of exacerbations depends on lung function). There is also an independent effect of drugs on acute pulmonary exacerbation, independent of the lung function effect.** | We do not observe the rate ratio reported in the clinical trials by only assuming that the reduction in the number of acute pulmonary exacerbations are due to the increase in ppFEV$_1$ associated with the drug. This assumption is needed in order to match the risk reductions observed in the clinical trials. |
| **We will assume the same treatment discontinuation as reported in the trials and assume that there is no further discontinuation after the end of the trial time horizon.** | Because we are using trial effectiveness estimates, we assume the same percentage of patients are taking the drug in the model as in the trials. |
| **We will start patients on a CFTR modulator drug at the age that they are first eligible and then allow them to switch to a more effective drug when they become age eligible. The increase in ppFEV$_1$ will be determined by the difference in the effectiveness of the new drug relative to the original drug.** | It is reasonable to assume that patients will start on a modulator drug as soon as they are eligible but that they will switch to a more effective one over time. We do not assume that drugs will be given off label. |

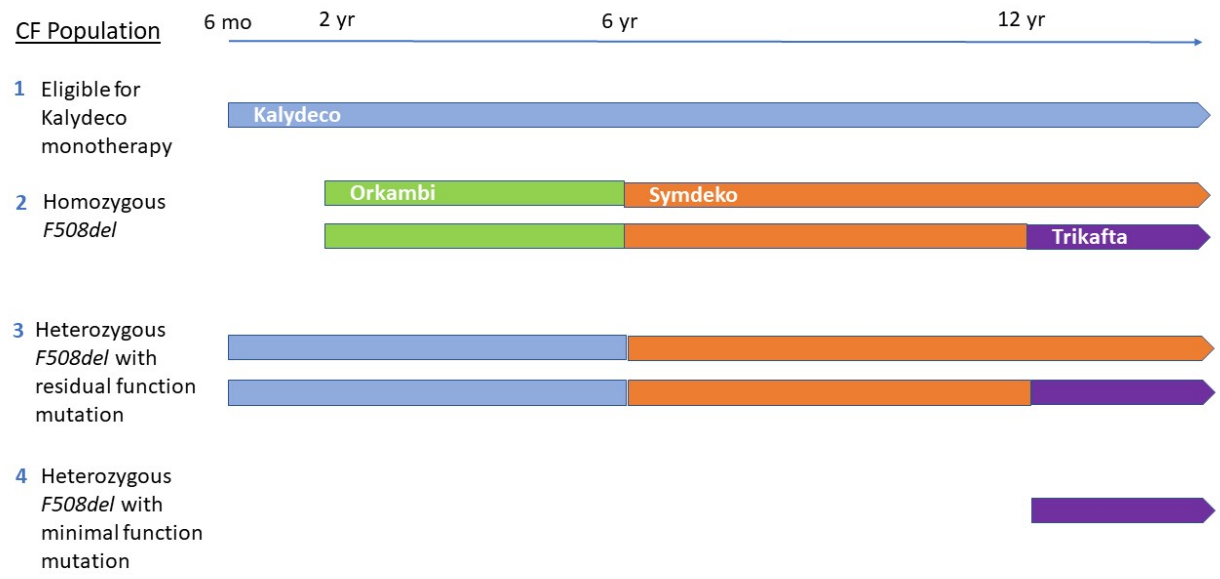
## 2.3 Populations

We will evaluate four possible therapeutic options for four CF populations as follows. Some analyses will be updates of our prior analysis and some will be new, as noted below.

1. For patients who are candidates for Kalydeco monotherapy based on the current indications, we will compare ivacaftor plus best supportive care to best supportive care alone (updated analysis).
2. For patients who are homozygous for the *F508del* mutation, we will compare Symdeko plus best supportive care, Trikafta plus best supportive care, and best supportive care alone as competing alternatives (updated and new analyses). Patients in the first two treatment strategies will be treated with Orkambi starting at age 2 years until they turn 6 (Figure 2).
3. For patients who are heterozygous for the *F508del* mutation with a residual function mutation, we will compare Symdeko plus best supportive care, Trikafta plus best supportive care, and best supportive care alone (updated and new analyses). Patients in the first two treatment strategies will be treated with Kalydeco monotherapy starting at age 6 months until they turn 6 years old (Figure 2). We will use the efficacy for Trikafta from the population who are heterozygous for the *F508del* mutation with a minimal function mutation to model Trikafta in this population, which differs from the study populations of the clinical trials.
4. For patients who are heterozygous for the *F508del* mutation with a minimal function mutation, we will compare Trikafta plus best supportive care and best supportive care alone (new analysis).

Because the recommended start age varies by drug, we will model sequential drugs in relevant populations (Figure 2). For example, for patients who are homozygous for the *F508del* mutation we will assume that all patients on a CFTR modulator strategy will start with Orkambi at age 2 and then switch to Symdeko at age 6. Patients assigned to Trikafta therapy will switch to this therapy at age 12. At switching we will allow for an improvement in lung function based on the difference between the two drugs and will allow this improvement to be constant for two years.

**Figure 2. Schematic of the CFTR Modulator Strategies**




The target populations will vary in terms of their prognosis.[2] On average, CF patients who are homozygous for *F508del* or have two minimal function mutations (such as *F508del*) have a more severe prognosis than patients with one or no minimal function mutation. McKone et al. classified patients into high-risk and low-risk groups based on the effects of the functional class of their phenotype. They found that the median age of death was much younger for the high-risk genotypes (24.2 years vs. 37.6 years). Sawicki et al. showed that *F508del* homozygous patients had a faster rate of decline in their lung function compared with patients with a residual function mutation heterozygous for *F508del.*[3] We will adjust the lung function declines in our model to represent these different subgroups of patients.

## 2.4 Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include. The full list of interventions is as follows:

- Kalydeco
- Orkambi
- Symdeko
- Trikafta

### Comparators

All CFTR modulator drugs plus best supportive care will be compared with best supportive care alone. We will assume that best supportive care includes combinations of the following therapies: dornase alfa, inhaled tobramycin, inhaled aztreonam, azithromycin, hypertonic saline, oxygen, pancreatic enzyme replacement therapy, and supplemental feeding. Patients with diabetes will require diabetes-related treatments and diabetes-specific follow-up care.

## 2.5 Input Parameters

### Clinical Inputs

We will use clinical inputs from the clinical evidence review, details of which can be found in the research protocol.

#### *Transition Probabilities*

We will model the $ppFEV_1$ trajectories through age-specific annual declines (Table 2).[4,5] The annual risk of having acute pulmonary exacerbation is a function of $ppFEV_1$ and age.[6,7] The annual risk of lung transplant is a function of age and is 0 for $ppFEV_1$ >30%.[8] The annual risk of diabetes as a function of age and sex is shown in Table 2.[9] We will adjust these overall rates to account for differential risk by CFTR mutation class (RR of I/II vs. III/IV/V = 1.7).[9] Over 95% of CF patients with severe genotypes (class I-III) have pancreatic insufficiency at diagnosis or progress to pancreatic insufficiency after diagnosis.[10] We will assume that 95% of the simulated cohort has pancreatic insufficiency and that this is stable over their lifetime. We assume that any improvement in pancreatic insufficiency with CFTR modulators is reflected in weight gain. We will assume that weight-for-age *z*-score is constant for each person throughout their life (in the absence of modulator therapy).[11] The other clinical outcomes (rates of infections) will be derived from age-specific prevalence values from the Cystic Fibrosis Foundation (CFF) Registry,[1] and will not depend on lung function severity. Base-case values are listed in Table 2.

**Table 2. Base-Case Values for CF Outcomes**

| | Baseline Value | Source |
|---|---|---|
| **Annual decline in ppFEV$_1$*** | | |
| Age 6-8 years<br>(assume applies to age 0-6 years) | -1.12<br>(-2.0 for higher risk mutations) | Konstan, 2007[5]<br>Konstan, 2012[4] |
| Age 9-12 years | -2.39 | |
| Age 13-17 years | -2.34 | |
| Age 18-24 years | -1.92 | |
| Age ≥25 years | -1.45 | |
| **Annual risk of acute pulmonary exacerbation by age and ppFEV$_1$** | | |
| Age <18 | 8.5938*exp(-0.035*FEV) | Goss, 2007[6]<br>Whiting, 2014[7] |
| Age ≥18 | 3.7885*exp(-0.026*FEV) | |
| **Number of pulmonary exacerbations per year (1, 2, 3, conditional on 1+)** | | |
| Age < 5 | 0.76, 0.19, 0.05 | Goss, 2007[6] |
| Age 5-10 | 0.68, 0.20, 0.12 | |
| Age 11-17 | 0.54, 0.22, 0.24 | |
| Age 18-29 | 0.48, 0.23, 0.29 | |
| Age ≥30 | 0.53, 0.27, 0.20 | |
| **Annual risk of lung transplantation** | | |
| ppFEV$_1$ >30 | 0 | Thabut, 2013[12] |
| ppFEV$_1$ ≤30 | 0.647 | |
| **Annual risk of diabetes (male, female)** | | |
| Age 0-9 | 0.008, 0.016 | Adler, 2008[9] |
| Age 10-19 | 0.039, 0.060 | |
| Age 20-29 | 0.049, 0.071 | |
| Age 30-39 | 0.065, 0.072 | |
| Age 40+ | 0.051, 0.029 | |
| **Weight-for-age *z*-score** | | |
| Male | -1.3 | Lai, 1999[11] |
| Female | -1.1 | |

* Represents overall CF population. Lung function declines are averages and may be higher or lower for individual patients (based on the heterogeneity parameter).

## Treatment Efficacy

To model the treatment effect, we will assume that there is an immediate increase in ppFEV$_1$ and improvement in weight-for-age *z*-score, as observed in the trials or based on clinically reasonable assumptions in case of weight-for-age *z*-score (Table 3). When a person switches drugs they will experience the net increase in ppFEV$_1$ between the two drugs (Table 3) and experience no decline for 2 years. The improvement in lung function will decrease the risk of experiencing pulmonary exacerbations and ultimately lung transplantation, increase a person's health-related quality of life (HRQoL), and decrease the mortality risk. We will also incorporate an additional decrease in the risk of pulmonary exacerbation, independent of the effect of lung function improvement. We will

model various assumptions about the treatment effect beyond the time horizon of the trials: 1) no ppFEV$_1$ decline as long as patient is on drug, 2) no ppFEV$_1$ decline on drug for 2 years and then 50% of the standard care rate thereafter, 3) no ppFEV$_1$ decline on drug for 2 years and then equal to the standard care rate thereafter. We anticipate using the second assumption in the base-case analysis, where 50% is in the range of the CFTR modulator effect on lung function decline.[13,14]

**Table 3. Treatment Efficacy (From Evidence Review)**

| | Increase in ppFEV$_1$ | PEx RR | Change in Weight-for Age *Z*-Score | Source and Calculations |
|---|---|---|---|---|
| **Population 1 - Eligible for Kalydeco Monotherapy** | | | | |
| Kalydeco | 10.0 | 0.56 | 0.35 | Davies, 2013[15]; Ramsey, 2011[16] Borowitz, 2016 [17] McKone, 2014[18] |
| **Population 2 - Homozygous *F508del*** | | | | |
| Orkambi (ages 2-5) | 2.8 | 0.44 | NR | Wainwright,2015[19] |
| Symdeko | 4.0 | 0.54 | -0.04 | Taylor-Cousar, 2017[20] |
| Symdeko vs. Orkambi | 1.2* | | | ppFEV$_1$ effect is calculated |
| Trikafta vs. Symdeko | 10.0 | NR | NR | Heijerman, 2019 [21] |
| **Population 3 - Heterozygous *F508del* with residual function mutation** | | | | |
| Kalydeco | 4.7 | 0.46 | | Rowe, 2017[22] |
| Symdeko | 6.8 | 0.54 | NR | Rowe, 2017[22] |
| Symdeko vs. Kalydeco | 2.1* | | | ppFEV$_1$ effect is calculated |
| Trikafta | 13.8 | | | Assumption (same as Pop 4) |
| Trikafta vs. Symdeko | 7.0† | | | ppFEV$_1$ effect is calculated |
| **Population 4 - Heterozygous *F508del* with minimal function mutation** | | | | |
| Trikafta | 13.8 | 0.38 | NR (BMI) | Middleton, 2019 [23] |

PEx = acute pulmonary exacerbation; RR = relative risk; NR = not reported

*Values used to model drug switching

†Value used to model drug switching, assuming that the overall effect vs. placebo for Population 3 would be the same as observed in the trial with Population 4 (13.8)

### *Discontinuation*

We will incorporate the discontinuation rates reported in the trials and assume that those who do not discontinue in the short run will remain on therapy for their lifetime.

### *Mortality*

Each year patients will face a risk of dying. This will be a combination of their age-specific mortality rate based on the US life tables[24] and the CF-specific rate. CF-specific mortality rates are a function of sex, ppFEV$_1$, weight-for-age *z*-scores, pancreatic sufficiency, number of acute pulmonary exacerbations, and diagnosis of diabetes mellitus or *B. cepacia* infection.[25] The Liou analysis also found that *S. aureus* infection was an independent predictor of mortality; however, the impact of infection was to decrease the mortality rate. Because we found no explanation as to why infection with *S. aureus* would be associated with better survival, and because of the rise in methicillin resistant *S. aureus* [1], we opted to not include this characteristic in the mortality rate function. The following equation will be used to model the annual mortality rate for age *a* ($h_a$) for non-transplanted patients[25]:

$$h_a = b_a e^{(K)}$$

$$K = 0.15(SEX - 0.47) - 0.042(ppFEV_1 - 67.7) - 0.028(WFA + 0.85) + 0.350(\#PE - 1.1) + 0.440(DIAB - 0.061) - 0.140(PS - 0.053) + 1.410(BAI - 0.032) - 0.280(\#PE - 1.1)(BAI - 0.032)$$

The patient-specific parameters that affect mortality among non-transplanted patients are *SEX* (0 male, 1 female), *ppFEV$_1$* (%), *WFA* (weight-for-age *z* score), *#PE* (number of acute pulmonary exacerbations in the current year), *DIAB* (0 no diagnosis of diabetes, 1 yes), *PS* (0 no pulmonary sufficiency, 1 yes), *BAI* (0 no *B. cepacia* infection, 1 yes). The age-specific baseline hazard ($b_a$) will be a product of the age-specific rates from the US life tables [24] and an adjustment factor that is needed to match the life expectancy targets of a CF cohort. Survival after lung transplant is a function of time since transplant and is better than prior to transplant.[12]

### *Adverse Events*

In our prior analysis we found that adverse events were generally comparable across treatment groups and often higher in the placebo arms. Therefore, we will assume that the reported discontinuation rates include discontinuation due to adverse events and will not assign a cost or disutility for adverse events.

## Health State Utilities

We will use the linear interpolation of EQ-5D utilities by ppFEV$_1$ used by Schechter et al. (Table 4).[26] The interpolation was based on EQ-5D estimates for wider ppFEV$_1$ groups (0.864 for >70%, 0.810 for 40%-69%, and 0.641 for <40%). We will also use similar assumptions as Schechter at al. [26], and apply a utility decrement of 0.174 to acute pulmonary exacerbations and a utility of 0.32 for the

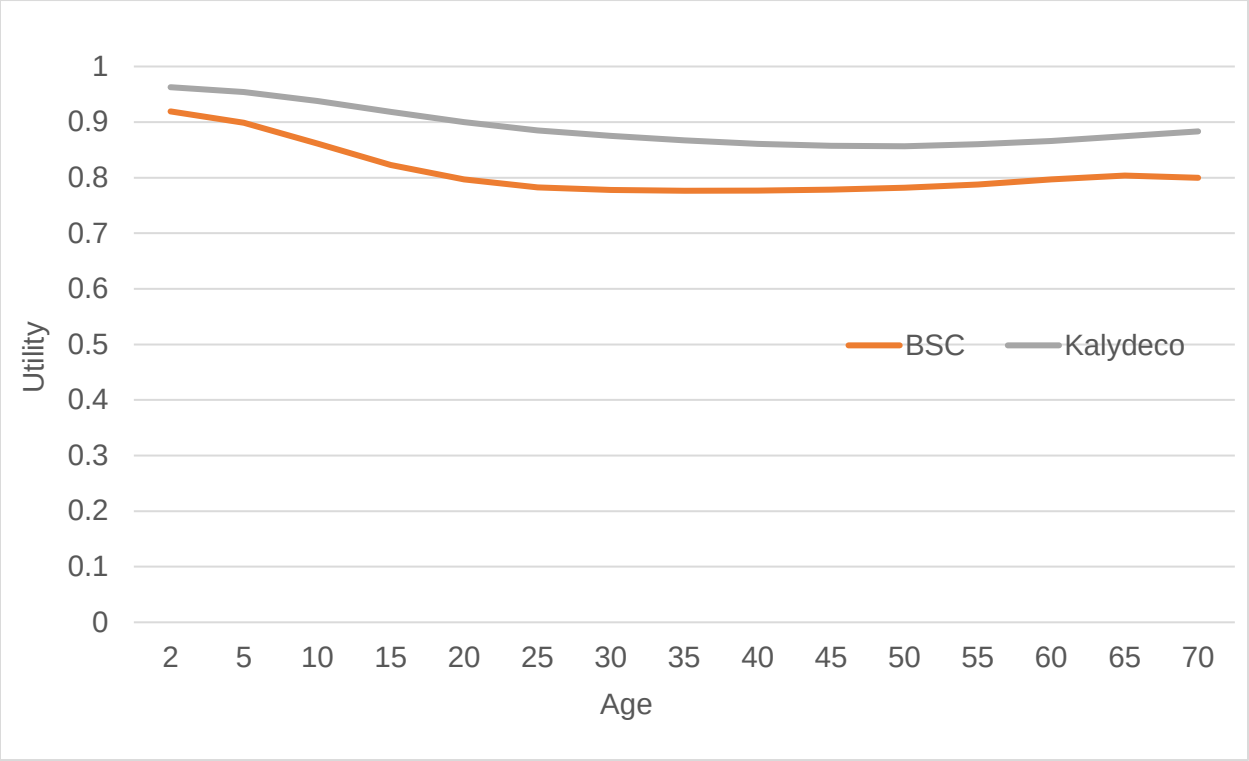
first year post-lung transplantation. (Subsequent years will be set equivalent to $ppFEV_1$ of 70%-79%.)

**Table 4. EQ-5D Utility Values by $ppFEV_1$**

| $ppFEV_1$ | Utility |
|---|---|
| >90 | 0.920 |
| 80-89 | 0.873 |
| 70-79 | 0.838 |
| 60-69 | 0.801 |
| 50-59 | 0.765 |
| 40-49 | 0.729 |
| 30-39 | 0.692 |
| 20-29 | 0.653 |
| 15-19 | 0.625 |

As validation for using these utility estimates, we simulated a cohort of patients treated with Kalydeco compared with a group receiving best supportive care only. Each year of the simulation, we calculated the mean EQ-5D utility among those simulated people who were still alive and had not undergone lung transplantation. We compared the simulated mean utilities to a study conducted by Bell et al. who compared HRQoL measures between cystic fibrosis patients with a *G551D* mutation who were treated with Kalydeco and patients homozygous for the *F508del* mutation who were treated with standard of care alone.[27] The mean age of patients who participated in the study was 23.9 years in the Kalydeco group and 24.6 years in the standard of care group.[27] Patients in the Kalydeco treatment group had a significantly greater mean EQ-5D score than patients in the standard of care treatment group (0.90 vs. 0.81, $p < 0.01$).[27] In our validation exercise we found that, at age 25, modeled patients on Kalydeco plus BSC and BSC alone had mean utility values of 0.88 and 0.78, respectively (Figure 3).

**Figure 3. Cystic Fibrosis Patients Eligible for Kalydeco Monotherapy, Mean Utility by Age**




## Drug Utilization

Table 5 shows the inputs that will be used to model drug utilization and associated costs. We will assume lifetime treatment duration.

**Table 5. Treatment Regimen Recommended Dosage**

| Generic name | Ivacaftor | Lumacaftor /Ivafactor | Tezacaftor /Ivafactor | Elexacaftor/ Tezacaftor/ Ivafactor |
|---|---|---|---|---|
| **Brand name** | Kalydeco | Orkambi | Symdeko | Trikafta |
| **Manufacturer** | Vertex Pharmaceuticals, Inc. | Vertex Pharmaceuticals, Inc. | Vertex Pharmaceuticals, Inc. | Vertex Pharmaceuticals, Inc. |
| **Route of administration** | oral | oral | oral | Oral |
| **Dosing** | One 150 mg tablet twice daily (age 6+); by weight twice daily (6mo – 6 yr)* | Lumacaftor 150 mg, ivacaftor 188 mg twice daily (≥14 kg, 2-5 yr)† | One tablet (tezacaftor 100 mg/ivacaftor 150 mg) twice daily (age 12+ or 30 kg+)‡ | Two tablets (elexacaftor 100 mg, tezacaftor 50 mg, ivacaftor 75 mg, morning) Ivacaftor 150 mg (evening) |

* 5-7 kg, 25mg twice daily; 7-14 kg, 50mg twice daily; 14kg or greater 75 mg twice daily

† Weight <14 kg, lumacaftor 100mg, ivacaftor 125 mg

‡ One tablet (tezacaftor 50 mg, ivacaftor 75mg) twice daily (age 6-11 yr and <30 kg)

## Cost Inputs

The model will include direct medical costs, including but not limited to costs related to drug administration, monitoring of disease severity, acute pulmonary exacerbations, and lung transplantation. Indirect costs, such as productivity loss, will be included in a scenario using a societal perspective, as data allow.

### *Drug Costs*

Estimated annual net drug acquisition costs for each medication will be used in the model. We cannot calculate net prices for all drugs using our standard source (SSR Health, LLC),[28] as this source does not include consistent publicly disclosed net sales figures for the specialty drugs in this review. In addition, there was no discount for the Federal Supply Schedule (FSS) prices [29], so we used wholesale acquisition cost (WAC) as net prices (Table 6). The FSS is a price schedule set forth by the US General Services Administration (GSA) that is used in negotiation with manufacturers of drugs, medical equipment, and supplies and service contracts for the VA and other federal organizations. As Trikafta was only recently approved by the FDA, information on its net pricing is not yet available; we assumed its net pricing will be as for the other CFTR drugs, and used the WAC in our analyses. Lower doses (for younger patients) have the same FSS price as adult doses, so no age adjustments will be done. We will assume that there are no additional costs associated with the administration and monitoring of the CFTR drugs above best supportive care.

**Table 6. Drug Costs**

| Drug | WAC per day* | Annual Drug Cost |
|---|---|---|
| **Kalydeco** | $853.40 | $311,704 |
| **Orkambi†** | $746.40 | $272,623 |
| **Symdeko** | $800.00 | $292,200 |
| **Trikafta** | $853.50 | $311,741 |

*WAC as of December 2, 2019

†Costs for dosing for ages 2-5

Please refer to the ICER Reference Case for more details on drug pricing

***Non-CFTR Drug Costs***

We will use an approach similar to that taken by Dilokthornsakul et al. in their cost-effectiveness analyses.[30,31] Health care costs are assumed to include an annual disease management cost based on severity of disease, plus an incremental cost associated with antibiotic treatment for acute pulmonary exacerbations. The cost of an acute pulmonary exacerbation is based on categories of age (reflecting higher percentage of total treatment time spent in the hospital for children) and lung function (reflecting an increasing length of treatment associated with more severe disease). Estimates are derived from the CF literature [32] and adjusted to match CFF registry data for current treatment durations associated with pulmonary exacerbations (i.e., applying the longer treatment durations observed in current patients).[1] Because these estimate were derived from health maintenance organization (HMO) data, we inflated the costs (in addition to adjusting for inflation) in order to be consistent with two studies conducted using private insurance fee for service (FFS) data.[33,34] We then assume a 60%/40% insurance mix (private/other) to generate the cost estimates shown in Table 7. As validation, we will compare the annual hospital costs for patients treated with Kalydeco to those treated with best supportive care and compare the simulation results to the estimates generated using the Truven Health Analytics MarketScan Commercial Research database.[35] Transplant costs include the one-time cost of receiving a lung transplant followed by an annual cost associated with the post-transplant condition. We will compare our costs with those reported by van Gool et al.[36] to inform our sensitivity analysis.

The societal perspective captures the impact of modulator treatments on patient and caregiver productivity. A large impact of caregiver productivity from modulator treatment would require that caregiver burden be associated with lung function (e.g., characteristics for which modulator treatments change). However, Neri et al. [37] found no relationship between caregiver burden, as measured by the General Strain Index, and patient factors such as ppFEV$_1$ or occurrence of acute pulmonary exacerbation. There are mixed results in terms of the degree to which ppFEV$_1$ is an independent predictor of a person with CF being employed.[38-42] Thus, for the societal perspective we will assume that lung function affects the probability that a person with CF is employed.

Changes in lung function due to CFTR modulator drugs would increase the chance that a person is employed. Productivity costs will be quantified using average US wage rates.

All costs will be presented in 2019 dollars, with adjustments made using the Personal Health Care (PHC) Expenditure deflator developed by the Centers for Medicare and Medicaid Services (CMS).

**Table 6. Direct costs by disease severity (2017 US dollars) [36]**

| | ppFEV$_1$ ≥70% | ppFEV$_1$ 40%-69% | ppFEV$_1$ <40% |
|---|---|---|---|
| **Disease management** | $10,000 | $13,000 | $22,000 |
| **PEx (age <18)** | $21,000 | $33,000 | $49,000 |
| **PEx (age 18+)** | $19,000 | $30,000 | $43,000 |
| **Lung transplant** | $389,000 | | |
| **Post-transplant (year 1)** | $338,000 | | |
| **Post-transplant (year 2+)** | $128,000 | | |

* PEx = acute pulmonary exacerbation

## 2.6 Model Outcomes

Model outcomes will include number of pulmonary exacerbations averted, life years (LYs) gained, QALYs gained, equal value life years gained (evLYG), and total costs for each intervention over a lifetime time horizon. All costs and outcomes will be reported as discounted values, using a discount rate of 3% per annum.

Model outcomes of interest (for each target population and eligible treatments) will include:

- By intervention:
    - Total health care costs (discounted)
    - Total direct and indirect costs (discounted)
    - Number of acute pulmonary exacerbations
    - Number of lung transplantations
    - Life-years (LY, discounted and undiscounted)
    - Equal value life years gained (evLYG, discounted)
    - QALYs (discounted and undiscounted)
- Pairwise comparisons:
    - Incremental cost-effectiveness ratios (cost/LY, cost/QALY, and cost/evLYG) of modulator treatment plus best supportive care versus best supportive care
    - Incremental cost per acute pulmonary exacerbation averted

## 2.7 Model Analysis

Cost-effectiveness will be estimated using the incremental cost-effectiveness ratios, with incremental analyses comparing a particular CFTR modulator drug plus best supportive care to best supportive care alone, from a health sector perspective in the base-case analyses. For therapies eligible for the ultra-rare disease framework, a modified societal perspective will be presented as a co-base case if the impact of treatment on indirect costs such as productivity and education is substantial, and these costs are large in relation to health care costs. Additionally, we will present a cost per acute pulmonary exacerbation averted.

We will also incorporate a new effectiveness measure – the equal value life years gained (evLYG). This metric evenly measures any gains in length of life, independent of the treatment's ability to improve patient quality of life. If treatment adds a year of life to a person with compromised health (i.e., a lower quality of life) the treatment will receive the same evLYG as a different treatment that adds a year of life for healthy members of the community.

### Sensitivity Analyses

We will conduct one-way sensitivity analyses to identify the impact of parameter uncertainty and key drivers of model outcomes. Probabilistic sensitivity analyses will also be performed by jointly varying all model parameters over 5000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. We will also perform threshold analyses for drug costs across a range of incremental cost-effectiveness ratios (from $50,000 to $150,000 per QALY, or from $50,000 to $500,000 under the ultra-rare disease framework).

### Scenario Analyses

If data allow, we will consider conducting scenario analyses that include:

1. Modified/restricted societal perspective that includes components such as productivity losses and caregiver costs.
2. Assumptions about treatment effectiveness beyond the time horizon of trials, ranging from no ppFEV$_1$ decline as long as patient is on drug to no ppFEV$_1$ decline on drug for 2 years and then equal to the standard care rate thereafter.
3. Assumptions about the impact of treatment on HRQoL (independent of lung function), where we will assume a 0.05 increase in EQ-5D utility.

## Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to a patient groups and several clinical experts (the manufacturer declined to participate in this review). Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. As part of ICER's efforts to increase modeling transparency, we will also offer to share the model with participating manufacturers for external verification around the time of publishing the draft report for this review. Finally, we will compare results to other cost-effectiveness models evaluating CFTR modulator drugs in CF patients. The outputs from the model will also be validated against relevant observational analyses.

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