At a Glance

Practical Implications p 175
Author Information p 180
Full text and PDF www.ajmc.com
Web exclusive eAppendix

Patient Preference for Treatment Administration in Cystic Fibrosis

Gregory S. Sawicki, MD, MPH; Dana P. Goldman, PhD; Wing Chan, MS; Alicia Casey, MD; Jonathan Greenberg, BS; and John A. Romley, PhD

ABSTRACT

Objectives: To assess the preference of patients with cystic fibrosis (CF) between treatments with different modes of administration.

Study Design: Survey of 73 adult CF patients receiving treatment in a major clinic regarding their willingness to trade off life expectancy for the ability to use a treatment that is less burdensome to administer.

Methods: We developed and fielded a time trade-off survey instrument that elicited patient preferences toward a dry powder inhaler and nebulized therapy. We quantified the number of life-years that patients would be willing to give up to have their preferred treatment and determined how the number of years willingly given up varied with patient characteristics. We used a second instrument that assessed patients' willingness to give up life expectancy to not have CF.

Results: Eighty-nine percent of patients preferred a dry powder inhaler to nebulized therapy (the rest were indifferent). The average patient would be willing to give up 5.3 years of life (out of a total of 40 years) to use the less burdensome inhaler. The number of years patients were willing to give up was positively correlated with self-reported treatment burden (P = .060). In terms of quality of life, a year with nebulized therapy was equivalent to 0.704 years without CF. The quality-adjusted life-year value for the dry powder inhaler was 0.797.

Conclusions: In the context of CF, a treatment that is less burdensome to administer can mitigate a substantial portion of the disease's impact on quality of life.

Am J Pharm Benefits. 2015;7(4):174-181

In healthcare, it is well recognized that quality of life is important, and as a conceptual matter, health embodies quality as well as quantity of life.[1-3] It is therefore generally accepted that quality of life merits consideration when payers and policy makers weigh the clinical and economic value of medical treatments. Such assessments typically focus on health states[2]; however, the concept of quality of life, and the impact of healthcare on quality of life, plausibly extend beyond conventional health states. There is growing evidence that patients care about nonclinical aspects of care. For example, many hospital patients elect to be treated relatively far from home, in part because distant hospitals offer better food, more attentive staff, or more pleasant surroundings.[4,5] For specific treatments, it is likewise possible that patients value not only clinical efficacy and side effects, but the overall experience, potentially including the burden of administering the treatment, for instance.

The treatment of cystic fibrosis (CF) is a test case for this proposition. CF is the most common lethal inherited disease affecting individuals of Caucasian descent[6] and is characterized as a multisystem disease that primarily results in chronic and progressive pulmonary dysfunction, nutritional abnormalities, and heightened inflammation secondary to chronic respiratory infections. Life expectancy with CF, while improving, remains substantially shortened, with a median predicted survival of 41 years.[7] CF affects not only life expectancy, but also functional capabilities such as exercise capacity, and significant lung disease can lead to multiple chronic physical and psychosocial symptoms.[8] As such, quality-of-life assessments of individuals with CF are increasingly useful adjuncts to standard clinical care pathways.[9]

Improvements in CF health outcomes have arisen in part because of the early introduction of chronic respiratory therapies to treat airway abnormalities and chronic infections. Many of these treatments require a significant time to complete, leading to high treatment burden for these individuals. Time may be especially valuable to individuals with shortened life expectancy, yet common treatments have been

time-consuming and otherwise burdensome. Studies have estimated that adults with CF spend approximately 2 hours per day on routine treatments,[10] and the treatment burden has been increasing over time[11]; moreover, this burden is also associated with a decline in quality of life.[10]

For individuals with CF and chronic infection with *Pseudomonas aeruginosa*, alternate-month nebulized administration of tobramycin is a guideline-recommended standard of care.[12] Chronic therapy with nebulized tobramycin has been associated with improvements in lung function and decreased mortality,[13-16] but despite this clinical efficacy, adherence to inhaled tobramycin in the population is low.[17] Multiple barriers to adherence have been studied in the CF population, and time for treatment administration is often cited. With a standard nebulizer model, delivery of this medication, together with setup and cleaning, takes 50 to 70 minutes daily. In addition, the equipment weighs in excess of 5 pounds and must be connected to a power source.

Recently, a new mode of administration for inhaled tobramycin has been introduced: an inhaler that delivers tobramycin as an inhaled dry powder.[18] The efficacy and safety of this formulation have been demonstrated in clinical trials[19-22]; this treatment requires only about 10-15 minutes daily, and the inhaler is compact and lightweight.

This study assesses patient preferences for treatment modalities, focusing specifically on treatment administration and burden. We developed and conducted a survey with adult CF patients undergoing chronic respiratory treatment. The survey applied the established and validated time trade-off (TTO) methodology to treatments that differed in treatment burden. Survey results were translated into the benchmark quality-adjusted-life-year (QALY) metric for the distinct treatments.

PRACTICAL IMPLICATIONS

Treatment for cystic fibrosis (CF) has been time-consuming and otherwise burdensome to administer. This study assesses the preferences of patients with CF for treatments that differ in administration mode.

- Approximately 9 out of 10 adults with CF prefer a dry powder inhaler to nebulized treatment.
- Patients with CF would be willing to give up a substantial number of life-years to be able to use a treatment that is less burdensome to administer.
- Clinicians, payers, and policy makers should recognize the importance to patients of the burden associated with specific treatments.

METHODS

Survey Overview

We surveyed CF patients receiving care in the adult CF clinic at Boston Children's Hospital between August and October 2013. Study participants were ≥18 years old, had previously been diagnosed with *P aeruginosa* lung infection, and had used nebulized antipseudomonal therapy; these criteria were verified with medical records. We reviewed the medical records of all study participants to document the most recent lung function (as measured by percent-predicted forced expiratory volume in 1 second [FEV_1]).

Study participants were administered the Cystic Fibrosis Questionnaire-Revised (CFQ-R), a validated and commonly used health-related quality-of-life measure that assesses the impact of CF on 9 domains, including overall health perceptions and perceived treatment burden. The reliability coefficients on the domains (measured by Cronbach's α) range from 0.18 to 0.94, with a majority exceeding the threshold of 0.70.[9] The CFQ-R also elicits patient characteristics such as age, gender, and marital/partner status. We obtained data on whether a participant had any children via a review of clinic administrative records. Our survey also included a module that elicited family income.

Assessment of Treatments

To assess patient preferences for treatment modalities that plausibly differ in treatment burden, we used the TTO approach, which presents a respondent with 2 situations and asks him or her how many years of life expectancy he or she would be willing to give up to have his or her preferred situation. This approach has been widely used to compare health states, often for the purpose of measuring quality of life in the specification of QALYs.[23] More recently, the method has been used to assess non-clinical aspects of treatment.[24,25]

We developed a TTO module for the survey. This module compared 2 treatments for respiratory lung infections caused by *P aeruginosa*. Therapy A corresponded to an unbranded nebulized therapy and therapy B corresponded to an unbranded dry powder inhaler. The treatments were contrasted in their burden of administration, vis-à-vis equipment used, setup and cleaning, medicine storage, and total treatment time per day; side effects were also compared. These treatment parameters were calibrated to real-world treatments based on existing clinical trial data and a literature review.[18] The module specified that the treatments would be equally effective in treating infection.

Study participants were asked which treatment would be preferred if the out-of-pocket costs were the same. Next, each participant was asked whether he or she would choose to live a certain number of years with his or her

Table 1. Characteristics of Patients Who Participated in the Time Trade-off Survey Module (N = 73)

Demographic and Clinical Characteristics	Mean ± SD	%	Min	Max
Age, years	30.2 ± 11.3		18	73
Female		58%		
Had spouse/partner or child		36%		
Annual family income >$50k[a]		55%		
FEV_1	64.9 ± 23.6		26	115
CFQ-R health perceptions score	60.9 ± 19.0		11.1	100
CFQ-R treatment burden score	51.4 ± 19.0		11.1	88.9

CFQ-R indicates Cystic Fibrosis Questionnaire-Revised; FEV_1, percent-predicted forced expiratory volume in 1 second.
[a]Income was elicited in ranges in the survey instrument and dichotomized in the table for expositional purposes; income was available for 56 of 73 survey participants.

preferred treatment, or a longer time (40 years) with the alternative treatment—in either case, these years represent remaining life expectancy. The "ping pong" method was used to specify life-years with the preferred treatment.[26] If a participant chose (or alternatively, did not choose) the preferred treatment at a given life expectancy level, his or her life-years with the preferred treatment were decreased (or alternatively, increased) until he or she expressed indifference about the treatments and their life expectancies. Forty years of possible life expectancy was chosen to limit anxiety about mortality, and because this value has become more realistic for this population.[7]

To determine QALY values associated with each treatment, study participants were presented with a second TTO between a shorter life span without CF and 40 years with the disease while using their preferred treatment. In addition, the survey qualitatively assessed the 2 treatments by asking each study participant to agree or disagree with statements such as, "Therapy B is an improvement over therapy A." Additional details are presented in the **eAppendix** (available at **www.ajmc.com**).

Data Analysis

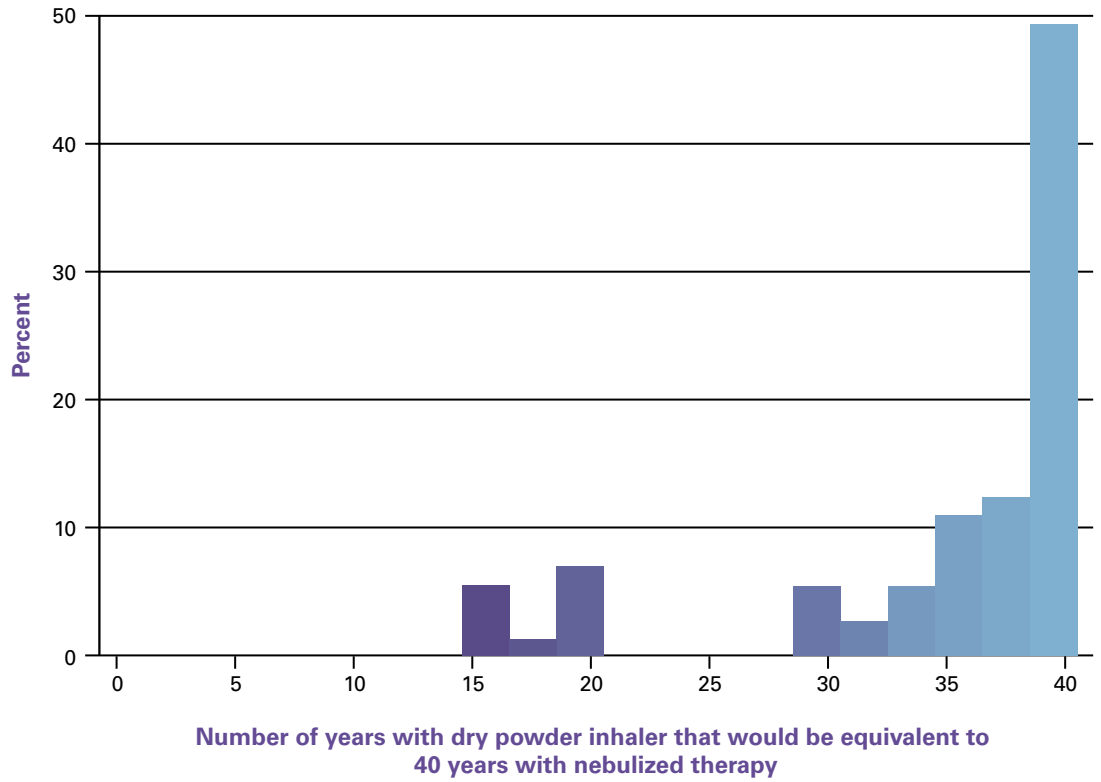
We quantified the number of years of life (if any) that patients with CF would give up to have their preferred treatments instead of the alternative. We also quantified willingness to give up life-years to be in perfect health, instead of having CF and using the preferred treatment. We calculated pairwise correlations between the numbers of life-years willingly given up and patient characteristics, including age, gender, having a partner or child, family income, percent-predicted FEV_1, current inhaled tobramycin use, and CFQ-R scores on 2 domains: health perceptions and treatment burden (each scale is scored 0-100). Because income was elicited in ranges, we created a continuous variable using midpoints for closed intervals (eg, $20,000 for $15,000-$24,999) and $200,000 for the highest value ($150,000 or more). We also performed multivariate linear regressions of the number of years that respondents would willingly give up for their preferred treatment on patient characteristics such as age. Income was excluded in sensitivity analysis because of occasional nonresponse. Statistical significance was assessed based on a 10% level.

RESULTS

We approached 100 adults with CF to participate in the study. Of these 100 patients, 75 were approached after the TTO module had been finalized. One patient declined to participate, and 1 did not complete the survey. Descriptive statistics for the 73 patients who completed the finalized TTO module are presented in **Table 1**. (There were no significant differences at a 10% level in measured characteristics between this sample of patients and those patients not in the TTO sample.) The average age in the TTO sample was 30.2 years (SD ± 11 years), and a majority of participants were female (58%). More than a third had a partner or child, and more than half reported an annual family income in excess of $50,000. In terms of patient health, the average FEV_1 was 64.9% predicted. On the CFQ-R questionnaire, the average score on the health perceptions domain was 60.9, while the treatment burden score averaged 51.4.

Of the 73 patients, 65 (89%) would prefer therapy B (the dry powder inhaler) over therapy A (nebulized therapy) if their out-of-pocket costs were the same. The 8 remaining patients were indifferent about the treatments. **Figure 1** shows the number of years with the dry powder inhaler that would be equivalent to 40 years with a nebulized therapy. Eleven percent of patients would have been equally happy with 40 years with a dry powder formulation or 40 years with a nebulized therapy, whereas another 36% viewed 39.5 years with a dry powder formulation as equivalent to 40 years with a nebulized therapy. Fifty-three percent would be as happy having the dry powder

Figure 1. Distribution of Number of Life-Years With Dry Powder Inhaler That Would Be Equivalent to 40 Years With Nebulized Therapy[a]



[a]N = 73, includes respondents indifferent about treatments. Bar width is 2 years.

inhaler for 38.5 years or less as with nebulized therapy for 40 years. That is, these respondents would be willing to give up at least 1.5 years of life expectancy to have the dry powder formulation. On average, respondents viewed 34.7 years with a dry powder formulation as equivalent to 40 years with a nebulized therapy and would have been willing to give up 5.3 years of life expectancy to have the dry powder inhaler instead of nebulized therapy.

Table 2 shows how the number of years of life that patients would be willing to give up for the dry powder inhaler is related to their clinical characteristics and reported quality of life. No association was observed with age, gender, or living situation. The correlation coefficient between the number of years given up and the CFQ-R score for treatment burden is –0.221 (P = .060); because a higher score corresponds to a lower burden, respondents who reported a higher burden from CF treatment were willing to give up more life-years for the dry powder formulation than patients with a lower burden. This relationship remains significant (P = .052) in the multivariate regression that includes income: a 1-SD increase in treatment burden is associated with a 0.104-SD increase in the number of years a respondent would give up for the dry powder inhaler. In the larger analysis sample that excludes income, the association is somewhat smaller in magnitude and statistically insignificant. In 1 of the 2 specifications, FEV_1 is negatively related (at a 10% significance level) to years given up. Specifically, a 1-SD decrease in lung function is associated with a 0.074-SD increase in years willingly given up for the dry powder formulation. In additional analysis (available from the authors upon request), individuals with an FEV_1 above the sample median of 62 would be willing to give up an average of 3.9 years out of 40 years of life expectancy to have the dry powder formulation rather than nebulized therapy (the confidence around 3.9 years does not include zero); individuals with an FEV_1 below the median would give up 6.7 years (P = .11 for the difference).

Figure 2 shows the number of years with perfect health (no CF) that survey respondents viewed as equivalent to 40 years living with CF while using the dry powder inhaler. Twenty-five percent of patients would have been equally

Table 2. Relationship Between Patient Characteristics and Number of Life-Years Patients Would Be Willing to Give Up for Dry Powder Inhaler (N = 73)[a]

Variable	Correlation	Regression 1[b]	Regression 2[b]
Age, years	–0.002	–0.052	–0.156
Female	0.015	–0.034	–0.059
Has partner or child	0.041	0.016	0.009
Income (log)	0.079	Not included	0.094
FEV_1	–0.124	–0.106	–0.235[c]
CFQ-R health perceptions score[d]	–0.127	–0.037	–0.045
CFQ-R treatment burden score[d]	–0.221[c]	–0.212	–0.295[c]

CFQ-R indicates Cystic Fibrosis Questionnaire-Revised; FEV_1, percent-predicted forced expiratory volume in 1 second.
[a]Patients who were indifferent about treatments were treated as willing to give up 0 years of life for dry powder inhaler.
[b]Regression coefficients are standardized; standard errors are robust to heteroscedasticity. N = 56 for regression 2 because of missing values for income.
[c]Indicates statistical significance at 10% level.
[d]Health perceptions and treatment burden are composite scores from CFQ-R. Higher scores correspond to better perceived health and lower burden.

happy with 39.5 years of perfect health, or 40 years with CF while using the dry powder inhaler; all respondents would have given up some life expectancy (1 half year or more) to not have CF. At the extreme, 5% of patients would give up 25 or more years of life to not have CF. On average, respondents viewed 31.9 years with perfect health as equivalent to 40 years with CF while using the dry powder inhaler, and would have been willing to give up 8.1 years to not have CF.

Table 3 shows how the number of years of life that patients would be willing to give up for perfect health is related to their clinical characteristics and quality of life. Age, gender, and living situation were not associated with this outcome. The correlation coefficient between the number of years willingly given up and the CFQ-R score for health perceptions is –0.278 (P = .025). That is, patients who reported lower overall health perceptions were willing to give up more life-years to not have CF than were patients who were healthier.

Applying the chained TTO approach, the average QALY value for having CF and using nebulized therapy (therapy A) was 0.704. The average QALY for having CF while using a dry powder inhaler (therapy B) was 0.797. These values exclude the 8 patients who were indifferent about the treatments and were not administered the second TTO. If we use multivariate regression to predict the second TTO value for these patients, the average QALY values are very similar (0.693 and 0.797, respectively).

In the qualitative assessment of CF treatments, 78% of patients in the TTO sample agreed with the statement, "Therapy B is an improvement over therapy A"; 52% strongly agreed with this statement. (Responses of "Don't know/refuse" are treated as disagreement for this purpose.) Sixty-two percent agreed with the statement, "If I could use therapy B, my life would be better." In terms of treatment attributes, 95% of respondents rated time spent on treatment as important; 90% rated ease of setup and cleaning as important; and 88% rated the portability of equipment and ability to administer treatment anywhere as important.

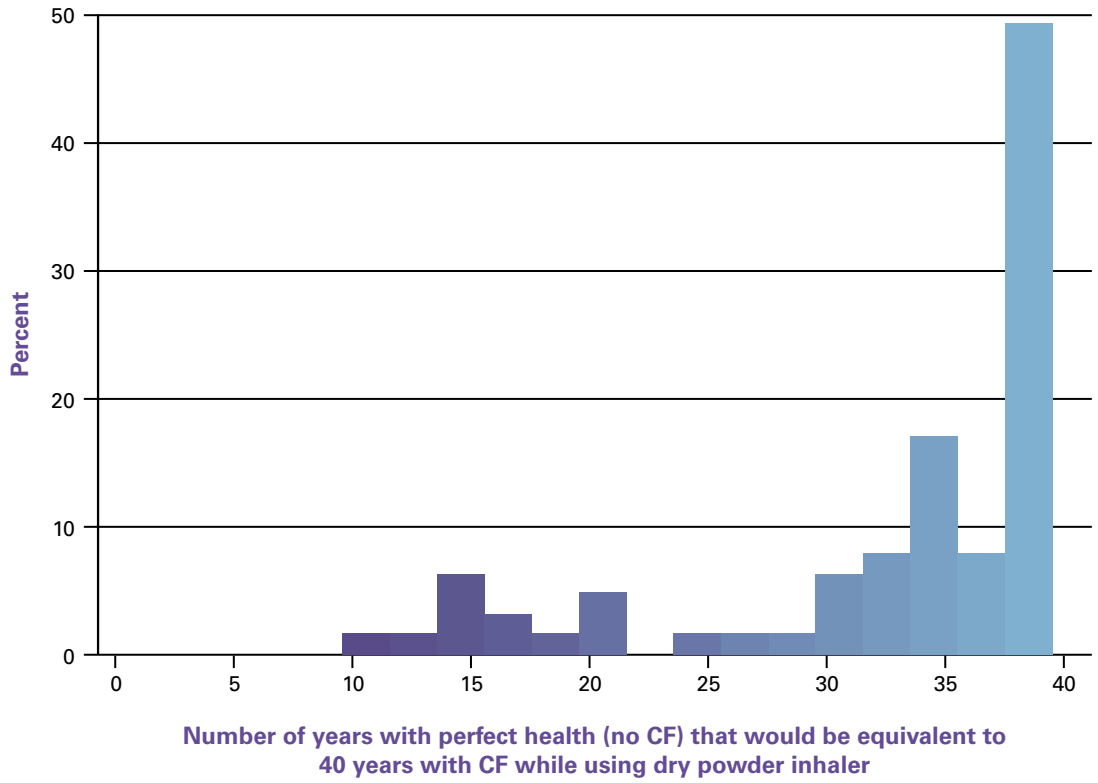
DISCUSSION

In this study, we assessed how treatment burden affects quality of life in patients with CF, from the patient point of view. To do so, we surveyed adults with CF about their attitudes toward treatments that differed in burden of administration. We applied the established and validated TTO methodology and translated the results into the benchmark QALY metric for the distinct treatments.

The vast majority of survey participants would prefer a dry powder inhaler to nebulized therapy if their out-of-pocket costs were the same. In our survey, the key distinction between the dry powder inhaler and the nebulized therapy was that the inhaler took substantially less time out of the patient's day and was otherwise less burdensome to administer. In terms of the TTO, the average adult with CF would willingly give up 5.3 years of life, out of a possible 40 years, to have the less burdensome treatment. In terms of QALYs, having CF and using the less burdensome treatment had an average value of 0.797, compared with an average value of 0.704 for the treatment that is more burdensome to administer. Thus, the less burdensome treatment mitigated one-third of the quality-of-life impact of having CF.

We also found that assessments of the treatments varied with patient characteristics in reasonable ways. For example, there was some evidence that patients who reported that their treatment burden was relatively high were willing to give up more life-years to have the less burdensome treatment than were patients with a low treatment burden. It is also noteworthy that nearly all patients

Figure 2. Distribution of Number of Life-Years With Perfect Health (no CF) That Would Be Equivalent to 40 Years With CF While Using Dry Powder Inhaler[a]



CF indicates cystic fibrosis.
[a]N = 65, excludes respondents indifferent about treatments. Bar width is 2 years.

deemed important the time spent on treatment, as well as ease of setup and cleaning, and the ability to administer treatment anywhere.

Altogether, our findings about patient preferences toward CF treatments are consistent with trial evidence of improved patient satisfaction with administration of tobramycin by dry powder inhaler instead of as a nebulized solution.[21] It is noteworthy that comparable quality-of-life impacts have been found for a preferred mode of treatment (inhalation rather than injection) among patients with diabetes.[25] Our findings raise the possibility that use of a dry powder might lead to improvement in adherence to chronic therapy, a critical issue in CF care.[27-29]

Limitations

Nevertheless, our study does have a number of limitations. We analyzed a sample of 73 individuals, using a 10% significance level; these individuals did not have direct experience with a dry powder inhaler at the time of the survey. Moreover, the generalizability of our findings to the broader population of US adults with CF is a natural concern. It is somewhat reassuring that the measured characteristics of our study sample are comparable to the average health characteristics of the adult CF population as reported by the US CF Foundation.[7] From a methodological point of view, there is ongoing debate about the strengths and weaknesses of alternative approaches to eliciting patient utilities/valuations, and indeed debate about the implications of varied implementations of the TTO approach.[23] Although QALY estimates with CF are not widely available, the agreement between our QALY value for CF with nebulized therapy and the QALY value for CF from a prior TTO assessment (0.70) lends some validity to our results.[30] A comparable value (0.75) has also been used in cost-effectiveness analysis of neonatal screening for CF.[31] This study has not addressed the value of reduced treatment burden in economic terms. It is also not clear whether our key finding—that the burden of administering the CF treatments studied matters a good deal to CF patients—applies broadly to other therapies and diseases.

Table 3. Relationship Between Patient Characteristics and Number of Life-Years Patients Would Be Willing to Give Up for Not Having Cystic Fibrosis (N = 65)

Variable	Correlation	Regression 1[a]	Regression 2[a]
Age, years	0.004	0.014	–0.039
Female	–0.024	–0.042	–0.014
Has partner or child	0.009	–0.044	–0.057
Income (log)	–0.023	Not included	0.017
FEV_1	–0.138	–0.104	–0.182
CFQ-R Health perceptions score[b]	–0.278[c]	–0.226	–0.166
CFQ-R treatment burden score[b]	–0.189	–0.124	–0.229

CFQ-R indicates Cystic Fibrosis Questionnaire-Revised; FEV_1, percent-predicted forced expiratory volume in 1 second.
[a]Regression coefficients are standardized; standard errors are robust to heteroscedasticity. N = 50 for regression 2 because of missing values for income.
[b]Health perceptions and treatment burden are composite scores from CFQ-R. Higher scores correspond to better perceived health and lower burden.
[c]Indicates statistical significance at 10% level.

Implications

The implications of this research are significant, as the importance of the patient perspective is increasingly being recognized in US healthcare. In its report entitled *Crossing the Quality Chasm*, the Institute of Medicine offered 6 criteria by which to judge the performance of the healthcare system.[32] Among them, healthcare should be "patient centered," that is, "respectful of and responsive to individual patient preferences, needs and values." Consistent with this view, CMS has sponsored the development of survey instruments for patient experience of care, and publicly reports on the performance of providers and even pays for "value" partly on this basis.[33] More recently, the Affordable Care Act established a Patient Centered Outcomes Research Institute, which funds research that "is inclusive of an individual's preferences, autonomy and needs."[34]

CONCLUSIONS

This study suggests that the burden of administering treatments is of concern to adults with CF, and that non-clinical aspects of treatments may be important more generally. Clinicians should assess patient preferences for treatment delivery systems, certainly when recommending chronic respiratory therapies for patients with CF, and potentially in other settings. Payers should be cognizant of the potential importance to patients of the burden that can be imposed in administering treatments, because coverage decisions may have competitive consequences in insurance markets. Finally, health technology assessment thought leaders and practitioners should seriously consider the possibility that non-clinical aspects of treatment play a role in these assessments.

Author Affiliations: Division of Respiratory Diseases, Boston Children's Hospital (GSS, AC, JG), Boston, MA; Leonard D. Schaeffer Center for Health Policy and Economics (DPG, JAR), Los Angeles, CA; Novartis Pharmaceuticals Corporation (WC), East Hanover, NJ.

Funding Source: This study was funded by Novartis Pharmaceuticals Corporation. Support for Dr Sawicki was provided in part by the National Heart, Lung and Blood Institute (5K23HL105541).

Author Disclosures: Dr Sawicki is a consultant for Novartis and is on their advisory board, as well as that of Gilead. Dr Goldman is a founder of Precision Health Economics, which had a research contract with Novartis. Ms Chan is an employee of Novartis Pharmaceuticals Corporation, which approved the antibiotic treatment for cystic fibrosis patients. Dr Romley was a consultant to Novartis on the study. Dr Casey and Mr Greenberg report no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (GSS, DPG, WC, JAR); acquisition of data (GSS, DPG, AC, JG, JAR); analysis and interpretation of data (GSS, WC, JAR); drafting of the manuscript (GSS, WC, JG, JAR); critical revision of the manuscript for important intellectual content (GSS, WC, JAR); statistical analysis (JAR); provision of study materials or patients (JG); obtaining funding (DPG); administrative, technical, or logistic support (WC, AC, JG, JAR); and supervision (DPG, AC, JAR).

Send correspondence to: John A. Romley, PhD, 3335 S. Figueroa St, Unit A, Los Angeles, CA 90089-7273. E-mail: romley@healthpolicy.usc.edu.

REFERENCES

1. Jennett B. Health technology assessment. *BMJ.* 1992;305(6845):67-68.
2. Velasco M, Perleth M, Drummond M, et al. Best practice in undertaking and reporting health technology assessments. working group 4 report. *Int J Technol Assess Health Care.* 2002;18(2):361-422.
3. Frost MH, Sloan JA. Quality of life measurements: a soft outcome--or is it? *Am J Manag Care.* 2002;8(18 suppl):S574-S579.
4. Goldman DP, Vaiana M, Romley JA. The emerging importance of patient amenities in hospital care. *N Engl J Med.* 2010;363(23):2185-2187.
5. Romley JA, Goldman DP. How costly is hospital quality? a revealed-preference approach. *J Ind Econ.* 2011;59(4):578-608.
6. Walter T, Szabo S, Kazmaier S, et al. Effect of clopidogrel on adhesion molecules, hemostasis, and fibrinolysis in coronary heart disease. *J Cardiovasc Pharmacol.* 2008;51(6):616-620.
7. Cystic Fibrosis Foundation Patient Registry Annual Data Report for 2010. Bethesda, MD: Cystic Fibrosis Foundation; 2011. http://www.cff.org/UploadedFiles/LivingWithCF/CareCenterNetwork/PatientRegistry/2010-Patient-Registry-Report.pdf [cache]. Accessed March 12, 2014.
8. Sawicki GS, Sellers DE, Robinson WM. Self-reported physical and psychological symptom burden in adults with cystic fibrosis. *J Pain Symptom Manage.* 2008;35(4):372-380.
9. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of The Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest Journal.* 2005;128(4):2347-2354.
10. Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. *J Cyst Fibros.* 2009;8(2):91-96.

11. Sawicki GS, Ren CL, Konstan MW, Millar SJ, Pasta DJ, Quittner AL. Treatment complexity in cystic fibrosis: trends over time and associations with site-specific outcomes. *J Cyst Fibros.* 2013;12(5):461-467.

12. Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med.* 2013;187(7):680-689.

13. Konstan MW, Wagener JS, Pasta DJ, Millar SJ, Morgan WJ. Clinical use of tobramycin inhalation solution (TOBI®) shows sustained improvement in FEV1 in cystic fibrosis. *Pediatr Pulmonol.* 2014;49(6):529-536.

14. Murphy TD, Anbar RD, Lester LA, et al. Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease. *Pediatr Pulmonol.* 2004;38(4):314-320.

15. Sawicki GS, Signorovitch JE, Zhang J, et al. Reduced mortality in cystic fibrosis patients treated with tobramycin inhalation solution. *Pediatr Pulmonol.* 2012;47(1):44-52.

16. Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med.* 1999;340(1):23-30.

17. Briesacher BA, Quittner AL, Saiman L, Sacco P, Fouayzi H, Quittell LM. Adherence with tobramycin inhaled solution and health care utilization. *BMC Pulm Med.* 2011;11:5.

18. Vandevanter DR, Geller DE. Tobramycin administered by the TOBI(®) Podhaler(®) for persons with cystic fibrosis: a review. *Med Devices (Auckl).* 2011;4:179-188.

19. Galeva I, Konstan MW, Higgins M, et al. Tobramycin inhalation powder manufactured by improved process in cystic fibrosis: the randomized EDIT trial. *Curr Med Res Opin.* 2013;29(8):947-956.

20. Geller DE, Konstan MW, Smith J, Noonberg SB, Conrad C. Novel tobramycin inhalation powder in cystic fibrosis subjects: pharmacokinetics and safety. *Pediatr Pulmonol.* 2007;42(4):307-313.

21. Konstan MW, Flume PA, Kappler M, et al. Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: the EAGER trial. *J Cyst Fibros.* 2011;10(1):54-61.

22. Konstan MW, Geller DE, Minić P, Brockhaus F, Zhang J, Angyalosi G. Tobramycin inhalation powder for P. aeruginosa infection in cystic fibrosis: the EVOLVE trial. *Pediatr Pulmonol.* 2011;46(3):230-238.

23. Arnesen T, Trommald M. Are QALYs based on time trade-off comparable?--a systematic review of TTO methodologies. *Health Econ.* 2005;14(1):39-53.

24. Huang ES, Brown SE, Ewigman BG, Foley EC, Meltzer DO. Patient perceptions of quality of life with diabetes-related complications and treatments. *Diabetes Care.* 2007;30(10):2478-2483.

25. Chancellor J, Aballéa S, Lawrence A, et al. Preferences of patients with diabetes mellitus for inhaled versus injectable insulin regimens. *Pharmacoeconomics.* 2008;26(3):217-234.

26. Measurement and Valuation of Health Group. *Time Trade-Off User Manual: Props and Self-Completion Methods:* York, UK: University of York; 1994.

27. Bucks RS, Hawkins K, Skinner TC, Horn S, Seddon P, Horne R. Adherence to treatment in adolescents with cystic fibrosis: the role of illness perceptions and treatment beliefs. *J Pediatr Psychol.* 2009;34(8):893-902.

28. Geller DE, Madge S. Technological and behavioral strategies to reduce treatment burden and improve adherence to inhaled antibiotics in cystic fibrosis. *Respir Med.* 2011;105(suppl 2):S24-S31.

29. Daniels T, Mills N, Whitaker P. Nebuliser systems for drug delivery in cystic fibrosis. *Cochrane Database Syst Rev.* 2013;4:CD007639.

30. Haddow JE, Bradley LA, Palomaki GE, et al. Issues in implementing prenatal screening for cystic fibrosis: results of a working conference. *Genet Med.* 1999;1(4):129-135.

31. Simpson N, Anderson R, Sassi F, et al. The cost-effectiveness of neonatal screening for cystic fibrosis: an analysis of alternative scenarios using a decision model. *Cost Eff Resourc Alloc.* 2005;3:8.

32. Committee on Quality of Health Care in America, Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century.* Washington, DC: The National Academies Press; 2001.

33. Hospital value-based purchasing. CMS website. http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/hospital-value-based-purchasing/index.html. Modified December 18, 2014. Accessed July 21, 2015.

34. Patient-centered outcomes research. Patient-Centered Outcomes Research Institute website. http://www.pcori.org/research-we-support/pcor/. Updated November 7, 2013. Accessed 2014. ajpb

eAppendix. Additional Detail on Assessment of Treatments

The "chained" series of time trade-off approaches (TTOs) helped to isolate the value of treatment attributes from the value of good health.[1] The second TTO was administered only to participants who were *not* indifferent about the treatments given equal out-of-pocket costs. (The first TTO was not administered to these patients, because indifference implied that 40 years with one treatment was equivalent to 40 years with the other.)

For each respondent, we calculated the quality-adjusted life-year (QALY) value of the preferred treatment by dividing by 40 years the number of years with the treatment that was equivalent to 40 years not having CF. The value of the treatment that was not preferred was calculated by multiplying the former QALY value by the number of years with the preferred treatment that was equivalent to 40 years with the treatment that was not preferred, divided by 40 years.

The survey qualitatively assessed the 2 treatments by asking each study participant to agree or disagree with statements such as "Therapy B is an improvement over therapy A" using a 5-point Likert scale. Participants were also asked to rate the importance of time spent on therapy and other aspects of treatment administration. These survey questions followed the TTO module, so as not to prime respondents to respond favorably to the less burdensome treatment.[2]

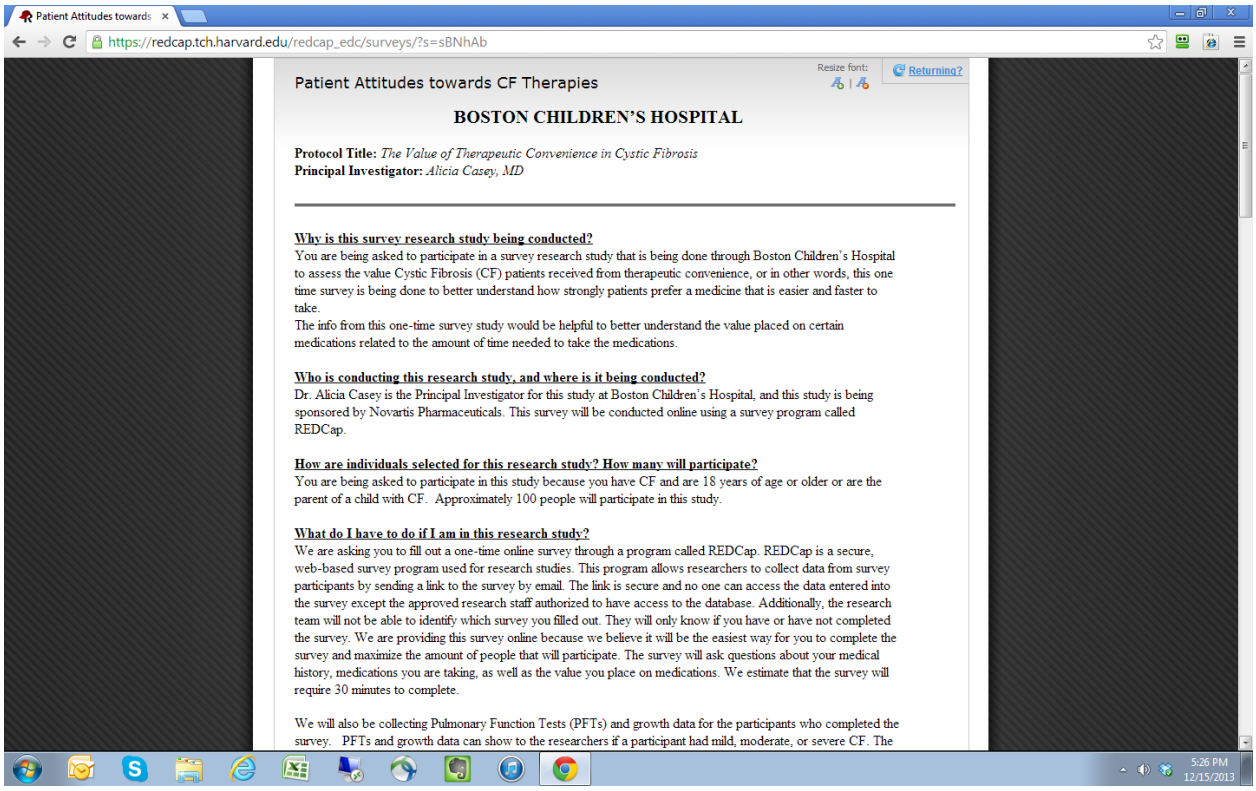
Surveys were administered through an internet browser on a table computer during routine clinic visits; a staff member was available to provide assistance. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Boston Children's Hospital.[3] Screen captures from the survey are shown below.

The survey was piloted to 5 patients, and the TTO module was assessed for clarity of the treatment comparison and general comprehensibility. The survey instrument and study protocol were reviewed and approved by the hospital's institutional review board; informed consent was obtained from study participants.

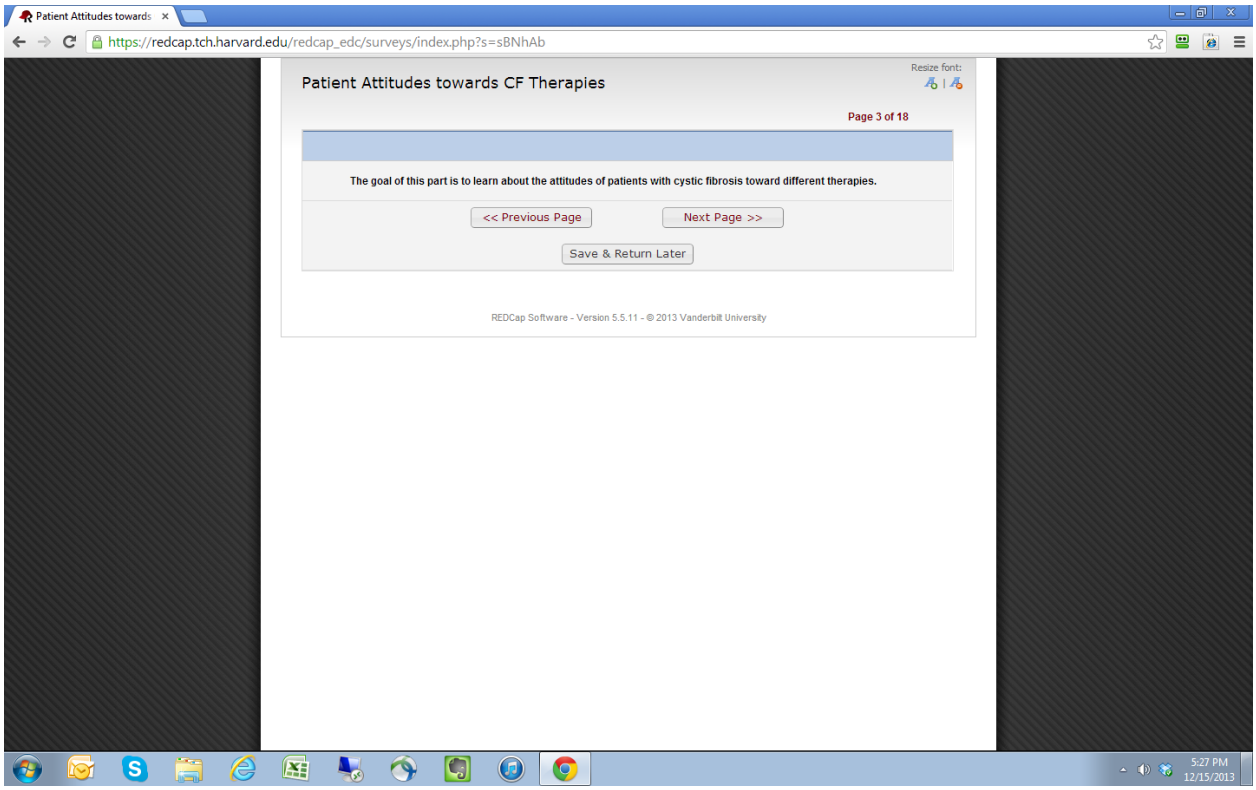
REFERENCES

1. Chancellor J, Aballea S, Lawrence A, et al. Preferences of patients with diabetes mellitus for inhaled versus injectable insulin regimens. *Pharmacoeconomics.* 2008;26(3):217-234.
2. Holyk G. Context effect. In: Lavrakas PJ, ed. *Encyclopedia of Survey Research Methods*. Vol 1. Thousand Oaks, CA: Sage; 2008: 143
3. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381.

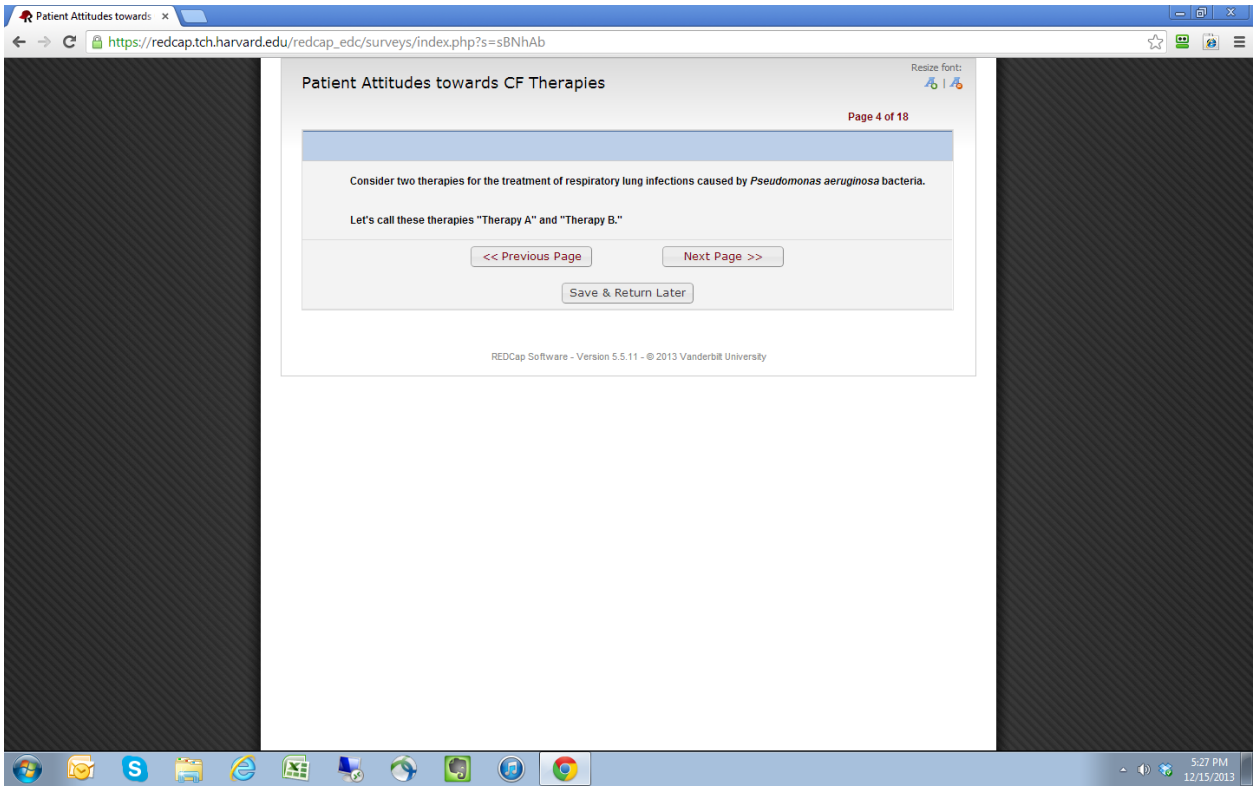
eAppendix Figure. Selected Screen Captures from Patient Survey



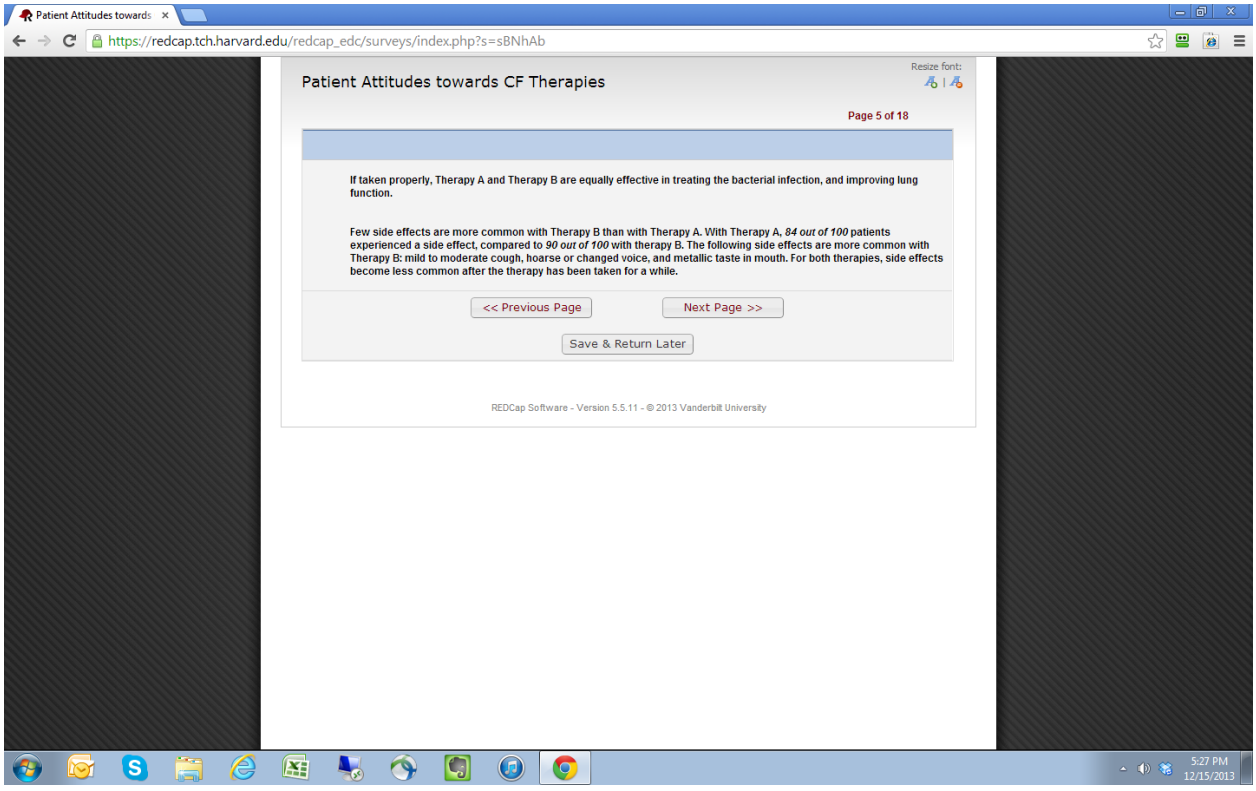
Survey overview



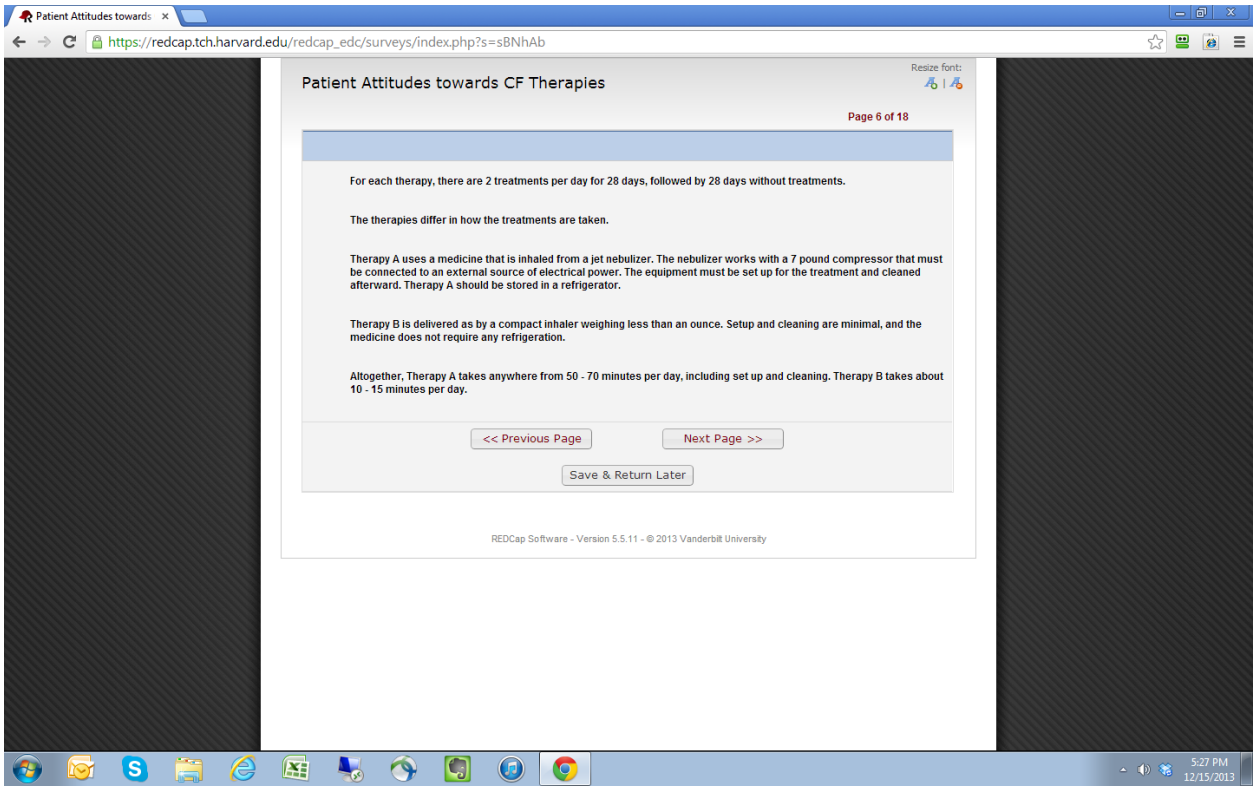
Framing of TTO module



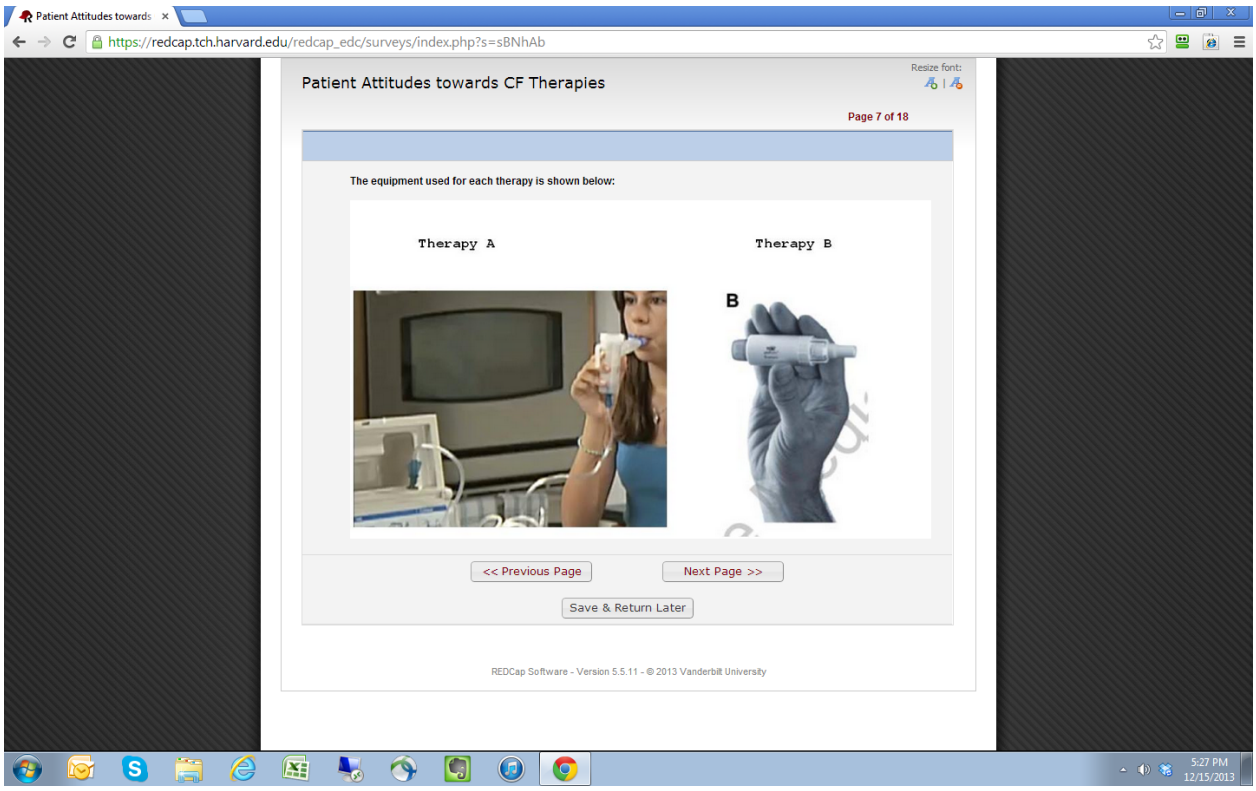
Introduction of therapies



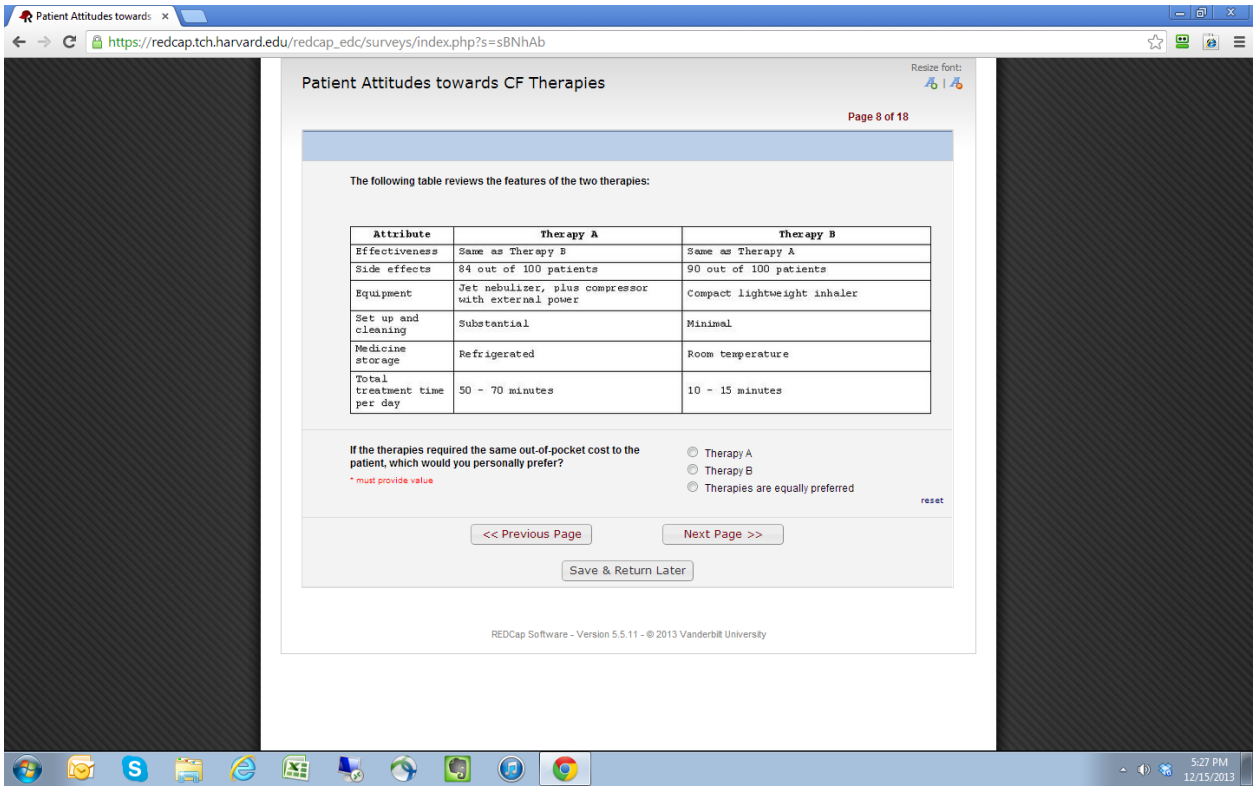
Efficacy and side effects



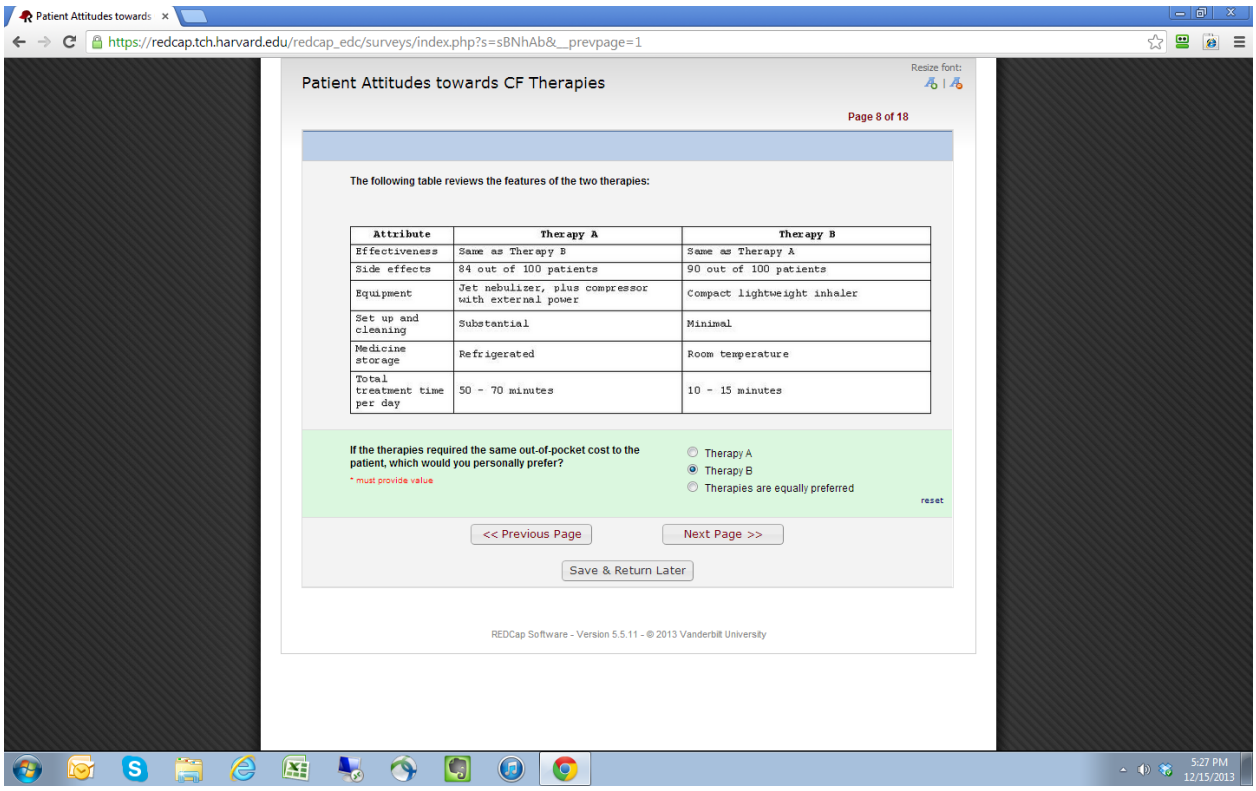
Therapy attributes relating to administration



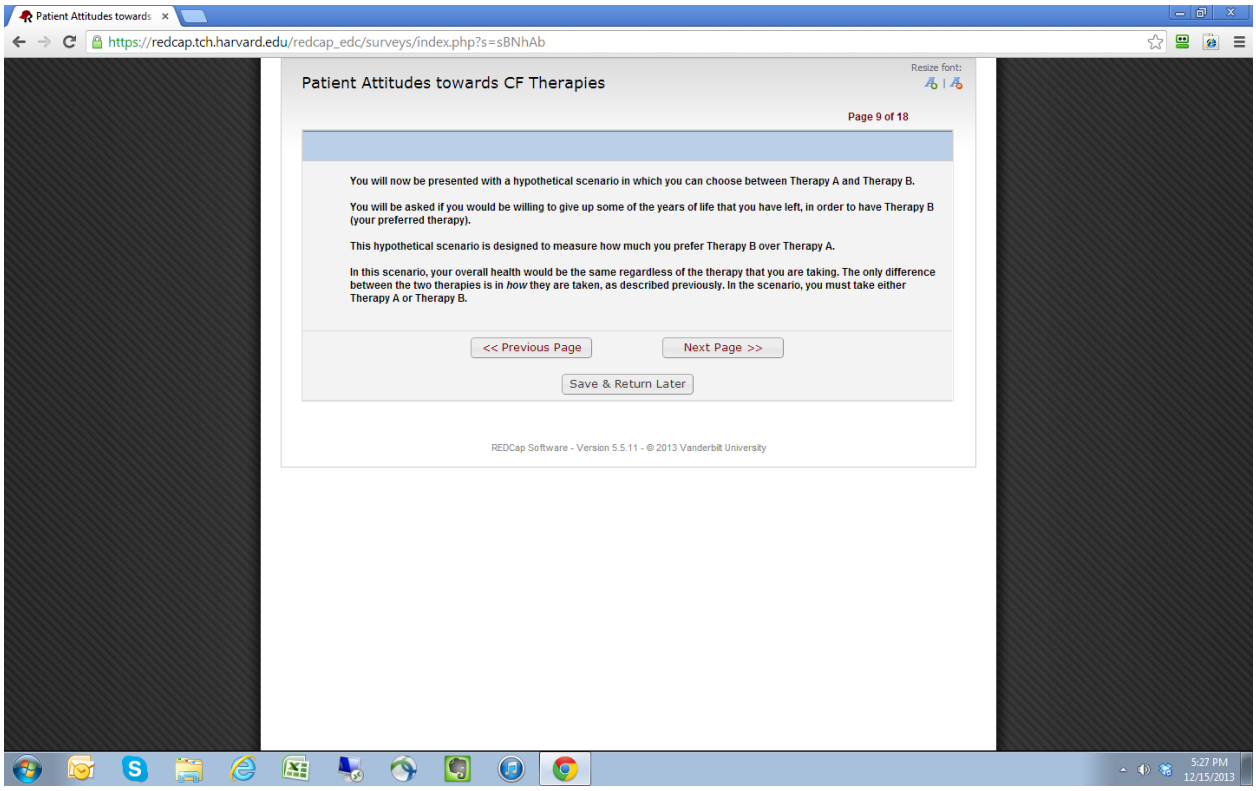
Visual description of therapies



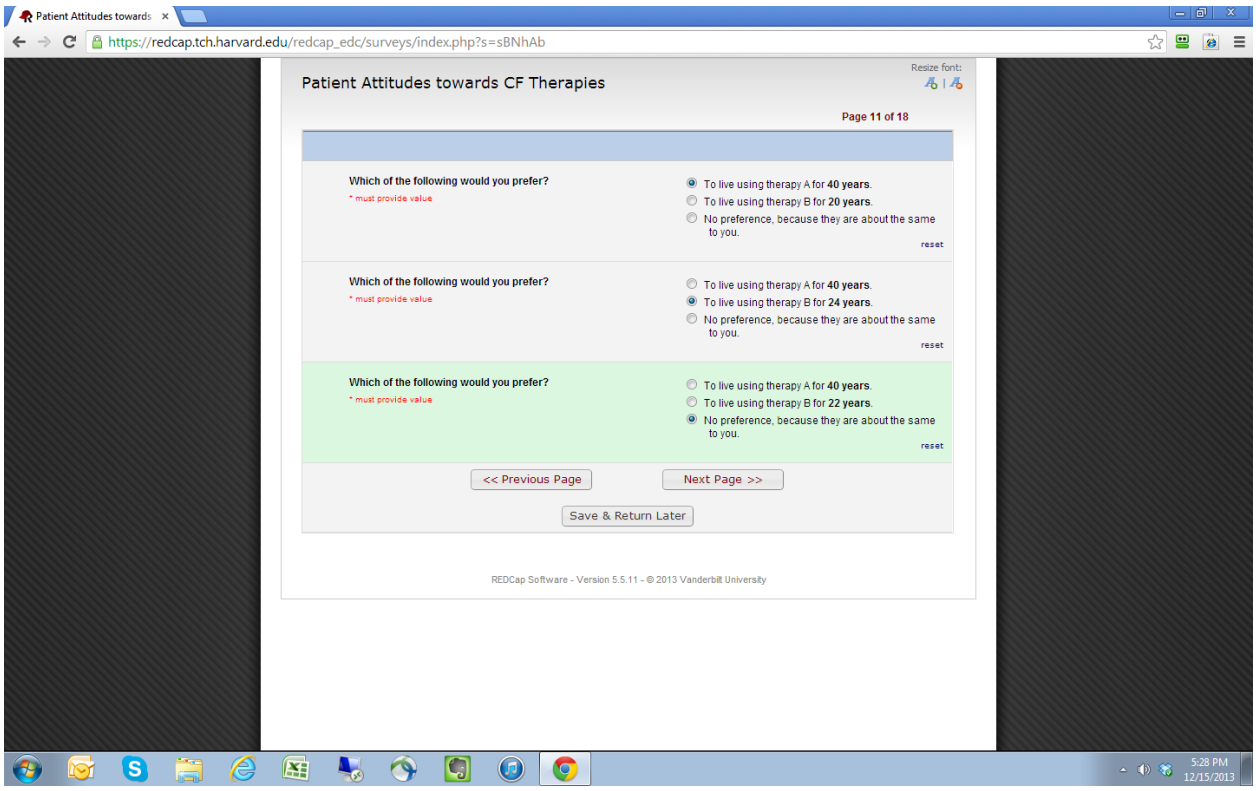
Summary of therapies



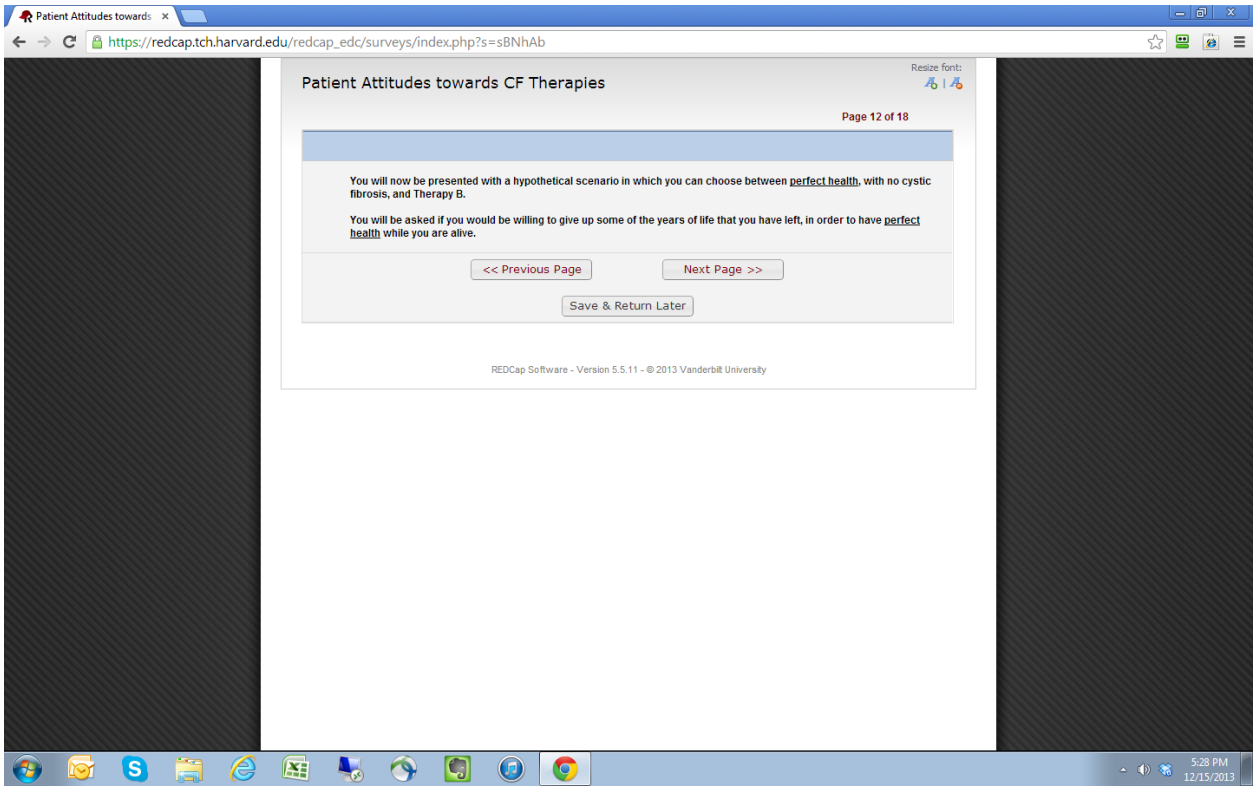
Elicitation of preference with equal cost



Introduction of TTO method



Hypothetical sequence of TTO responses



Introduction of TTO for perfect health

eAppendix Table 1. Characteristics of Patients Who Did Not Fully Participate in the Finalized Time Trade-off Survey Module (N = 25)

Characteristic	Mean ± SD	%	Min	Max
Age, years	27.9 ± 10.2		18	64
Female		72%		
Had spouse/partner or child		38%		
Annual family income >$50k		42%		
FEV_1	65.6 ± 24.5		22	102
CFQ-R Health Perceptions Score	67.1 ± 24.1		0	100
CFQ-R Treatment Burden Score	53.8 ± 20.5		22.2	100

FEV_1 indicates percent-predicted forced expiratory volume in 1 second; CFQ-R, Cystic Fibrosis Questionnaire-Revised.

Income was elicited in ranges in survey instrument, and dichotomized in table for expositional purposes; income was available for 19 of the 25 study participants.

Spousal/parental status was available for 26 participants, using administrative records.

Twenty-four patients participated in the study before the TTO module was finalized, 1 patient did not complete the TTO module, and 1 patient declined to participate in the study.