

**Bronchiolitis Obliterans Syndrome (BOS)**

# ***Voice of the patient***

Externally led patient-focused drug development meeting



Lung Transplant  
FOUNDATION

“

I guess it comes down to  
a simple choice, really:

**Get busy living or  
get busy dying.**

- The Shawshank Redemption

”

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# INTRODUCTION

**BOS is a serious, progressive, and often fatal complication of lung transplantation with significant morbidity and mortality.** The most common symptom is a progressive and unrelenting shortness of breath. **Quality of life is dramatically impacted due to the significant physical, emotional, and social impacts of the disease.** BOS is the leading cause of death in patients after they reach one year post-transplant and the majority of patients that survive 5 years post-transplant go on to develop BOS in one degree or another.

On June 22, 2022, the Lung Transplant Foundation (LTF) hosted an Externally-led Patient Focused Drug Development (EL-PFDD) virtual meeting on Bronchiolitis Obliterans Syndrome (BOS). The goals of the meeting were to inform the Food and Drug Administration (FDA) as well as other key stakeholders in the clinical development space about the unmet needs, quality of life impacts, and treatment preferences of patient communities impacted by BOS. This EL-PFDD meeting was a parallel effort to FDA's PFDD program, a systematic means of obtaining patient insights in respect to their condition and treatment options. The EL-PFDD shed light on:

1. The lived experiences of patients impacted by BOS, how BOS makes an already difficult transplant journey much harder, and what is most important to these individuals in terms of potential therapeutic benefits.
2. The need for improved diagnostic tools and methods, as well as optimal clinical trial design to capture and measure the potential therapeutic impact most important to patients, and to provide the necessary data to support rationale and acceptable trial designs.
3. Optimal ways to diagnose BOS and deliver potential therapeutic agents for BOS to targeted tissues and organs.

The purpose of this EL-PFDD was to systematically gather patient and caregiver perspectives and experiences on their condition, and needs or insights on available therapies to treat BOS, where treatments are inadequate or nonexistent for the lung transplant patient population.

The EL-PFDD meeting was modeled after the work of the U.S. Food and Drug Administration (FDA) Patient-Focused Drug Development (PFDD) initiative, and the subsequent report will be presented to the FDA to serve as patient experience data or related information for the Agency's consideration in the review of applications for new drugs to treat or prevent BOS. Prior to the meeting, a survey was conducted that was disseminated through a number of social media platforms and advocacy platforms. The insights gathered from the pre-meeting survey helped inform the live polling questions conducted during the EL-PFDD which helped shape the conversation. Post-meeting, several testimonies were received from those that were unable to attend or that preferred not to speak. This information is contained in the appendices to this report. Trends and themes are explored below and revisited in more detail in later sections of this report platforms and advocacy platforms.

# OVERVIEW OF BRONCHIOLITIS OBLITERANS SYNDROME (BOS)

Lung transplantation is an established treatment modality for patients with various end-stage lung diseases. Compared with 20 years ago, the median survival time after lung transplantation has increased from 4.7 to 6.7 years over the last decade. The International Society for Heart and Lung Transplantation Registry (ISHLT) reports a 1- and 5-year survival of 85% and 59%, respectively, for adult lung transplant recipients transplanted over the past decades. Long-term graft and patient outcomes still lag that of other solid organ transplantations. However, improvements in donor selection, organ preservation, perioperative management, immunosuppression, and therapeutic management of post-transplant infections have resulted in improved long-term survival and a decline in the number of patients with allograft rejection<sup>1,2,3</sup>. Nevertheless, allograft rejection continues to be a serious complication following lung transplantation, thereby leading to graft failure. Transplant rejection can be divided into three primary types: acute cellular rejection (ACR), antibody mediated rejection (AMR) and chronic lung allograft dysfunction (CLAD). CLAD is a life-threatening complication that limits the long-term survival of lung transplantation patients. It is the leading cause of post-transplant morbidity and mortality. ISHLT consensus statement defines CLAD as a persistent decline in pulmonary function, characterized by a decrease of at least 20% in forced expiratory volume in 1s (FEV1) for more than 3 months from post-transplant baseline, after excluding other reversible potential causes, such as infection<sup>4</sup>. CLAD patients can be classified in three groups: Restrictive Allograft Syndrome (RAS), Bronchiolitis Obliterans Syndrome (BOS), mixed BOS and RAS and undefined patients<sup>5</sup>.

Bronchiolitis obliterans syndrome (BOS) is the major form (phenotype) of CLAD (it represents 65 to 75% of patients)<sup>2</sup>: It is the leading cause of late mortality and morbidity in lung recipients, with 50% having developed it within 5 years of lung transplantation, with a median survival between 3 and 5 years after diagnosis<sup>1,2</sup> and cumulative incidence rates as high as 40% to 80% within the first five years. Phenotypes are not static, and patients can progress from the BOS to RAS phenotype, and more rarely from RAS to BOS. This is a major limitation to the long-term success of lung transplantation.<sup>4</sup>

BOS is characterized by a progressive obstructive ventilatory defect due to the development of obliterative bronchiolitis. In early stages, some patients don't have any symptoms, but with time, they detect a progressive worsening of breathing and limited functional activity and will develop breathlessness and chronic cough as BOS gets worse. BOS is not an infection, but fatigue and cough (with increased mucus production) may be also the earliest sign of an airway infection associated with BOS as an underlying condition<sup>5,6</sup>.

Microscopical (histopathological) features include progressive obliteration of small airways and inflammatory response (infiltration of lymphocytes) that results in a granulation tissue (scar) formation and eventual partial to complete obstruction of the small airways (bronchioles)<sup>4,5</sup>. This “scarring” leads to narrowing of the airways, limiting airflow with loss of lung function. Most patients who live beyond 5 years will develop some stage of BOS.

BOS diagnosis after lung transplant is challenging. While spirometry and computed tomography scans enable a specific CLAD diagnosis and remain the current gold diagnostic standard, they do not allow for a diagnosis before the onset of clinical symptoms. BOS is a diagnosis of exclusion and it comes after ruling out every other reversible cause of FEV1 decline. To date, no method has been demonstrated to verify CLAD with unequivocally ideal specificity and accuracy. Each noninvasive approach should be weighed with respect to disadvantages and advantages in terms of cost, specificity, sensitivity, and radiation exposure. Observation of clinical symptoms, spirometry, chest X-ray, and CT are currently the most used methods to detect CLAD. There is great clinical need for a minimally invasive biomarker of BOS<sup>7,8</sup>. The nonspecific symptomatology of BOS may contribute to diagnostic delays. Early diagnosis of CLAD may be more likely than GVHD-BOS, since pulmonary function is monitored more frequently in lung transplant recipients<sup>4</sup> (GVHD-BOS is the pathophysiology equivalent in the bone marrow transplant population).

Some risk factors have been associated with the development of chronic rejection -BOS- : primary graft dysfunction, acute cellular rejection, antibody mediated rejection, suboptimal immunosuppression, aspiration and gastro esophageal reflux disease (GERD), recurrent infections (viral, bacterial, fungal) and neutrophilia.

Current treatments available are limited and sadly ineffective. The best approach is prevention: avoiding or minimizing risk of lung injury<sup>9</sup>. Possible therapeutic approaches include a modification of the patient’s immunosuppressive regime, treatment with azithromycin or montelukast, or the initiation of extracorporeal photopheresis (ECP)<sup>10</sup>. The development of the condition leads to a very narrow set of therapeutic possibilities: extracorporeal photopheresis is an intensive treatment limited by insurance and logistical factors. The benefit is controversial. The role of antibiotics is still also unknown<sup>4</sup>.

Recent clinical trials include inhaled cyclosporine<sup>11</sup> (a trial that still enrolling patients), extracorporeal photopheresis<sup>12</sup> (Washington University is currently performing a multivariate analysis of its data collection) and use of JAK-1 inhibitors safety and efficacy in patients with graft-versus-host disease (not enrolling)<sup>13</sup>.

In the future perspective, there are some upcoming CTOT clinical trials: use of JAK inhibitors as prophylaxis with the determination of the development of CLAD and BOS in these patients.

In recent years, there has been little progress in the management of condition which means BOS remains a progressive, debilitating, and ultimately fatal disease. Any novel therapeutic approach for BOS management is driven by the understanding of the disease pathogenesis of obliterative bronchiolitis. Continued efforts in research to explain the alloimmune and non-immune mechanisms that contribute to the development of BOS pheno-types is the cue to tailor targeted therapies.

# MEETING OVERVIEW

The EL-PFDD meeting was intended to provide FDA and other key stakeholders the opportunity to hear directly from patients, caregivers, and care partners about their experiences living with the most daunting form of lung transplantation rejection: BOS. It was also designed to provide these same individuals with an opportunity to inform the clinical development process by sharing their preferences as well as the trade-offs they are or are not willing to make in exchange for expanded treatment options. The meeting agenda and the questions that guided the discussion are included in Appendices 1 and 2.

Leading up to the EL-PFDD itself, a pre-meeting survey was launched and shared with patients and caregivers impacted by BOS. The goal of this survey was to help shape and inform meeting materials and to generate additional discussion. **Though COVID made a fully in-person meeting impossible, the hybrid virtual and in-person format made the EL-PFDD accessible for a wider audience including those unable to or uncomfortable with travel.**

Amy Skiba, Executive Director of the Lung Transplant Foundation (LTF), hosted the meeting and Jonathan Reiss moderated the discussions. Jonathan is an active member of the board at the Lung Transplant Foundation and shared his personal connection to the Lung Transplant community. Sharing the stage with Amy was Martha Austrich. Martha is a former caretaker and advocate for the BOS community, as well as the wife of the late Jeff Goldstein, founder of the Lung Transplant Foundation. Martha gave an opening statement in which she shared some words about Jeff and his vision for this meeting. Martha reminded the audience of LTF's mission to advocate and agitate on behalf of lung transplant patients and their caregivers to build awareness and provide the support needed to address post-transplant diseases like BOS. Martha reminded the audience about how much effective therapy is needed in order to provide transplant recipients with a better quality of life and more time with their loved ones.

Following the opening statement, a previously recorded interview with Jeff Goldstein was shown to honor Jeff's legacy and pay tribute to the work he did for the lung transplant community and the foundation.

Opening remarks around the relevance of EL-PFDD meetings were illustrated by Dr. Ozlem Belen from the FDA in a pre-recorded video. Dr. Belen, is currently the Deputy Director in the FDA's Division of Rheumatology and Transplant Medicine (DRTM). The DRTM regulates Investigational New Drug Applications (INDs), New Drug Applications (NDAs), and Biologics Licensing Applications (BLAs) for prescription drugs and biologics intended for the prevention, treatment, or diagnosis of conditions that include solid organ transplant, such as lung transplantation. Dr. Belen stated that EL-PFDD meetings provide the FDA and other key drug development stakeholders unparalleled opportunities to broaden their understanding of the burden of a disease and provide patients and caregivers a direct avenue for engagement so that they can clearly articulate what matters most to them.

Unable to attend in real-time, Dr. John Reynolds, Medical Director of the Duke Lung Transplant Program, provided the audience with a clinical overview of BOS through a pre-recorded video. Dr. Reynolds reviewed the clinical presentation of BOS, diagnostic journey, available treatments and future avenues for research. His clinical overview provided helpful background and context for the discussions that followed.

Following Dr. Reynold's presentation, patients stepped into the spotlight. The next portion of the meeting explored symptoms and daily impacts of living with BOS. The second session focused on current treatment options, preferences for future treatment, and the tradeoffs patients impacted by BOS are willing to make. Each of the two topic-oriented sessions began with personal statements from preselected speakers comprised of patients and caregivers, followed by a moderated discussion. The moderated discussion began with a few discussion starters designed to inspire conversation. Those attending the webcast were able to participate in several ways. There were live polling questions using a web-based polling technology, a live call-in number where individuals that wanted to share their story could join the discussion, and finally the opportunity to share comments utilizing the meeting platform's chat function. Jonathan Reiss highlighted some of the written comments, reading them aloud during the meeting and answering several questions from the audience. He also used the webcast technology to capture and display responses of the live-polling questions, another means for generating conversation.

The meeting concluded with a summary provided by Amy Skiba and an emotional closing video, pre recorded by Jeff Goldstein, "I just couldn't understand why we would spend that kind of money, and time and put somebody and their family members through the lung transplant process not to have anything. Not to have any therapies to treat post-transplant rejection, particularly BOS... BOS patients, keep hoping".

In the 30 days that followed the meeting, members of the BOS community were encouraged to submit comments and written testimonies from LTF's website. These follow on materials are included in the appendix section of this Voice of the Patient report.

# REPORT OVERVIEW

This Voice of the Patient Report summarizes the perspectives shared by patients and caregivers at the EL-PFDD meeting, including patient testimonies (Appendix 3,4,5) as well as the polling questions (Appendix 6) posed during the meeting. The language used in this report to describe BOS signs, symptoms, treatment experiences, and views on participating in clinical trials, reflect those items expressed by patients and caregivers in attendance during the virtual EL-PFDD. There may be additional symptoms, impacts, treatments, or other aspects of the disease that are not captured in the report.

The purpose of this patient report is to support FDA's understanding of: 1) the unmet needs of patients and caregivers impacted by BOS; 2) quality of life impacts of the disease; and 3) patient preferences around clinical trials and treatment delivery.

## PRE MEETING SURVEY

In order to choose topics of relevance for discussion during the meeting, the Lung Transplant Foundation (LTF) and its partners gathered information from the broader patient community, utilizing existing known data on patient and caregiver experience and a pre meeting survey that was made available prior to the meeting.

The survey was answered by 69 participants, 39% of whom are currently living with, or have experienced BOS; 29% of whom are at risk of developing BOS, and 20,3% of whom are caretakers.

For additional information, please visit the Lung Transplant Foundation's website: <https://lungtransplantfoundation.org/bos-pfdd/>

## REAL-TIME POLLING

355 individuals attended the live EL-PFDD and 83 individuals participated in live polling. 43% were patients concerned with developing BOS; 26% were patients living with BOS; 5% had previously experienced living with BOS; 29% were care-takers. 50% female-male. The vast majority, 94%, were from the US (across all regions) and the rest were from Europe.

Since the meeting, there have been an additional 2,622 viewers of the recording, a testament to the desire to better understand the unmet needs of this under served condition.

While the in-person and remote webcast attendees at this meeting represented a clinically and demographically diverse group, the extent to which this group reflected the BOS patient population at large is unknown, in part, due to the lack of quality epidemiology and natural history information available.



## KEY INSIGHTS

- Patients described how BOS has affected their quality of life and the frustration that comes along with it, from dealing with the newly acquired limitations that impact the performance of simple tasks like climbing the stairs to being forced to move to other climates in hopes of improving lung function.
- **Shortness of breath and fatigue were identified by patients as the most common, and most overwhelming physical manifestations of BOS.** These symptoms dramatically impact even the most routine physical activity, social interactions, family dynamics, and professional identities.
- **Patients and caregivers both expressed emotional distress** verbalized as anxiety and depression, and personal stories that illustrated the emotional burden that often accompanies life with an intractable illness like BOS.
- **Patients emphasized the different triggers of anxiety, not from the disease itself, but resulting from the economic strains of complex and costly medical expenses, and the fear of becoming a burden to caregivers and family members.**
- Caregivers expressed concern about the harrowing uncertainty and loved ones developing BOS, a constant concern for transplant recipients.
- Patients and caregivers described the unmet needs due to lack of an effective medical treatment that can accurately diagnose BOS at an early stage, and/or prevent/cure for it. Current treatment options are insufficient to guarantee physical improvement or a positive impact to quality and duration of life.
- **The need for educational materials geared towards treatment and early diagnosis is evident.** All patients that participated expressed interest in new studies and treatment options and expressed an openness to be contacted to learn more
- Patients impacted by BOS are all warriors, and each demonstrate a willingness to try experimental treatment options. These individuals are keenly aware that their survival and well-being will depend on their self-advocacy.

# Topic 1: Symptoms and Daily Impact of Living with BOS

*“Every lung transplant recipient wants to outrun rejection for as long as he or she can. I know that I am on borrowed time. My hope is that this pair of lungs will last longer; in the meantime, I’m living every day deliberately and with gratitude.”*

-Kim Cable,  
two-time lung transplant recipient

## PANELISTS

### **Sara Kominsky**

Cystic Fibrosis warrior and two-time bilateral lung transplant recipient. Ardent animal behaviorist and former professional equestrian. A mother of two daughters, author, and competitive athlete.

### **Denise DesRoberts**

Grandmother of two, former real estate agent who enjoys renovating properties and DIY tasks. Lifesaving bilateral lung transplant in 2017, diagnosed in 2019 with Stage 3 BOS.

### **Amanda Helderle**

Lover of nature as well as a hiker, independent in spirit. Bearer of the emotional and physical scars of losing a pair of lungs. Cystic Fibrosis warrior, two-time bilateral lung transplant patient. Previously diagnosed with BOS.

### **Jen Weber**

Former full-time practicing lawyer. Cellist. Cystic Fibrosis warrior, Two-time bilateral lung transplant recipient. A gold and bronze medalist athlete in the Transplant Games of America. Living with BOS, CF, diabetes, and pancreatic insufficiency.

### **Ruth Magnus**

Active grandmother. Social butterfly. Loving wife to Stan. Patient with idiopathic pulmonary fibrosis celebrating 14 years post-bilateral lung transplant. Diagnosed with BOS two years ago.

### **Stan Magnus**

Loving husband and primary caregiver of Ruth Magnus.

### **Martha Austrich.**

Passionate advocate for the lung transplant community. Wife of Jeff Goldstein, Founder of LTF.



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## Moderator: Jonathan Reiss

LTF Board member and advocate for the lung transplant community. Jonathan has a family member who is a 20-year post lung transplant recipient. Outside of his work in the Lung Transplant Community Jonathan is the Vice President of Internal Audit for Vimeo. In Jonathan's free time he enjoys swimming, exercising, traveling and enjoying a good bottle of wine!

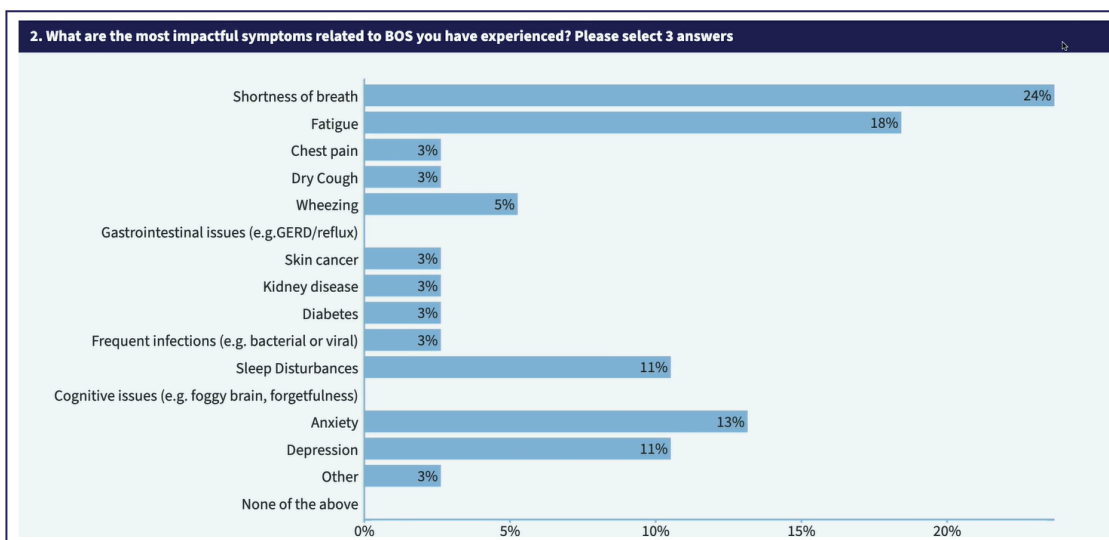
# SYMPTOMS AND DAILY IMPACTS OF BOS

Participants shared their personal experiences with lung transplant and subsequent BOS complications, whether physical, emotional, or social. There were a number of common themes related to quality of life impacts, emotional burdens, and forced adjustment to life with an intractable illness. These testimonies were followed by a moderated panel discussion (Appendix 3), as well as live polling questions around impact to their daily lives.

The most common symptoms experienced by patients living with BOS, are shortness of breath and fatigue. This came across through comments, polling responses from the meeting participants, as well as the moderated discussion.

Shortness of breath and fatigue are common, often overwhelming symptoms that dramatically impact patient lives leading to the inability to work, engage in favored physical activities, or socialize to the extent seen prior to BOS. Many patients also report emotional distress represented by anxiety and depression, illustrating the emotional burden of the disease.

GRAPH 1: MOST IMPACTFUL SYMPTOMS RELATED TO BOS EXPERIENCED BY PATIENTS



**BOS forces patients and caregivers to rearrange their lives**, whether it means moving into a home with fewer or no stairs, moving across the country to a location with more favorable weather, or being forced to give up careers and hobbies. These accommodations are one way of coping with the reality of newly-defined physical needs. Other common symptoms that were reported include pain and sleep disturbance.

## **FATIGUE AND SHORTNESS OF BREATH**

Most patients express their frustration around these physical limitations, which impact work, mobility, leisure, and social interactions. This metamorphosis limits almost every aspect of a person's life.

"I have to watch a lot of TV and it's just a kind of life I don't enjoy."

"Struggling to breath is exhausting, we had to seclude ourselves at home and limit our activities to just binge TV watching."

After a while the usual activities got limited. "Walking around the block he couldn't do it with his shortness of breath, and he was just tired a lot."

## **FATIGUE**

"A good day for me would be a bit of activity."

"It wasn't a matter of BOS limiting the activities I love, there really were NO MORE ACTIVITIES at the end stage BOS that I could do without distress."

"Unable to engage in meaningful activities with my loved ones."

## **SHORTNESS OF BREATH**

"With BOS there is no typical day. I could take the same medications every day, and some days experience extreme breathlessness no matter what."

"My struggling to breathe became an agonizing reminder that I was dying, inch by inch."

"I still don't think my brain has caught up with my breathing. I still THINK I can go do everything I used to (...) sometimes I think I'm being lazy, but I know I'm not and its just difficult to live with."

"Living in Florida in summertime is hard for people with chronic lung conditions as the high humidity makes it difficult to breath."

"When your loved one is struggling to breath, all you want to do is help."

"When you feel so lousy you can't breathe, you feel you are dying."

“My lungs retain carbon dioxide, and I can’t sleep without using a non-invasive ventilator to help alleviate crushing headaches. When I travel, I bring oxygen, my non-invasive ventilator, and enough medication to get through the week. This often makes my luggage look like a mini-hospital.”

## **CHEST PAIN**

“The never ending back and chest pain had the greatest impact in my existence. The suffering affected my ability to focus on even very mundane tasks.”

“The only real relief that I was able to experience was being sedated for procedure, sadly that became the highlight of most weeks.”

Worried about the pain worsening, if that was possible, “becoming unable to appreciate the beauty in everyday life and everyday small things because BOS was just tearing me apart.”

“BOS both destroyed my lung function and dismantled my once dynamic lifestyle – and then to work on my psyche – using pain, fatigue and anxiety as its minions.”

“I went from having an incredibly active lifestyle, to being trapped indoors within my own failing body.”

“The pain in my back and chest became so debilitating that it limited my activities to four very basic ones – sleeping, eating, rehab, and watching TV.”

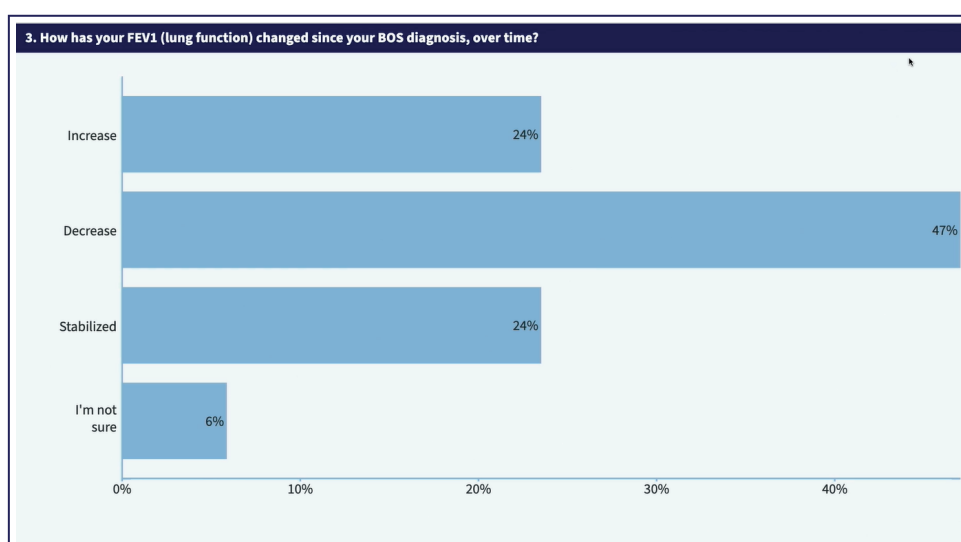


# BOS SYMPTOMS PROGRESSION

The experts consensus statement defines CLAD as a persistent decline in pulmonary function, characterized by a decrease of at least 20% in FEV1 for more than 3 months from post-transplant baseline. For some, shortness of breath may be the first and only symptom that presents for quite a long time.

Chart 3 shows how a large number (47%) of patients report experiencing a decrease in their FEV1 (lung function) since their diagnosis. Unexplained decline in lung function is also one of the key reasons many clinicians suspect BOS in the first place.

GRAPH 2 : LUNG FUNCTION OVERTIME



Lung function is affected by viruses that cause familiar infectious diseases such as the common cold, flu and warts. This is a common concern among patients and caretakers.

“Recently, I visited my beautiful grandchildren, a two year old and a two month old I was meeting for the first time. We hugged, talked, and played. Two days later, I was in the ER because I caught a virus from a 2 year old who wasn’t showing symptoms when Grammy came over to play. The doctors told me I had parainfluenza. When most people experience parainfluenza, it’s like a cold and they get over it quickly. I suffered for over a week with lungs full of mucus, a horrible cough, and headache. I spent a night in the hospital.”

Most patients consider decrease in lung function to be inevitable, “And now, despite absolute compliance and endless hard work, my regression continued to death’s door -- completely unchecked by the very best modern medicine had to offer.”

Some patients declared that their decrease in FEV1 has diminished or impaired their mental and/or intellectual function. This may be referred to in a multitude of ways including “foggy brain”, mood disorders or “forgetfulness” that can get worse as BOS progresses.

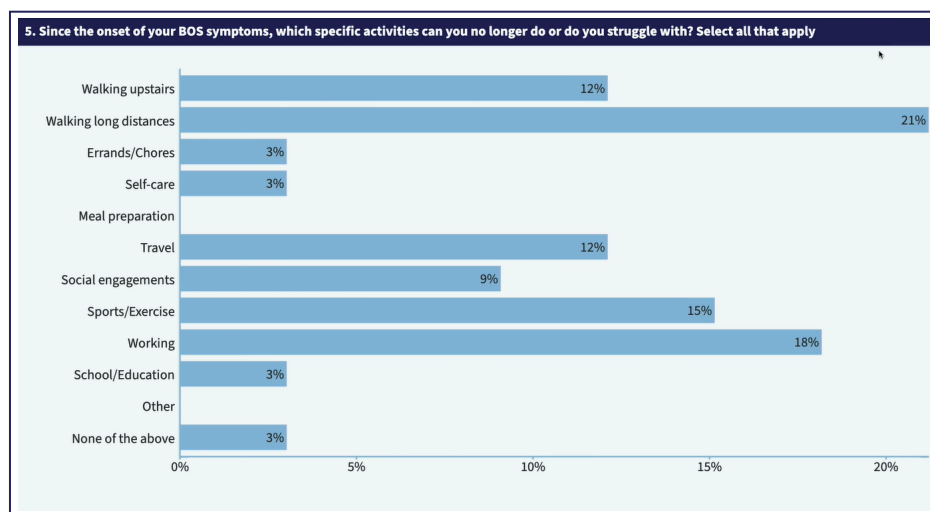
**“Mental fog limited simple pleasures like playing a board game.”**

Decrease in FEV1 was also noted in patient testimonies as a reason for increased social isolation, “I was unable to engage in meaningful activities with my loved ones, a lot of people not being able to understand the severity of my situation.”

## IMPACTS ON DAILY LIFE

BOS forces patients and caregivers to rearrange their lives to the point of moving their homes, limiting social interactions and leaving jobs to accommodate their new physical and emotional realities. When patients are asked about the impact the disease has on daily living, it becomes clear that **concerns about activities such as walking a long distance (21%) or climbing a set of stairs (12%)** are a common theme.

GRAPH 3 : ACTIVITIES LIMITED/NO LONGER ACHIEVABLE DUE TO BOS



As a patient from the audience shared: “One thing that changed significantly as my lung function dropped, was that I couldn’t climb stairs anymore. In my own home I had steps so I ended up selling my house to move to a single level.”

**One patient described the sensation as an “air hunger”, something she will never get back, and went on to recall “the delicious sensation of a long, slow, deep breath.”**

Others expressed how their new normal was limiting their activities, “The inability to do what we did before, (..) now I can’t even walk for half an hour.” Here’s a sampling of patient reported sentiments on the topics.

Here's a sampling of patient reported sentiments on the topics.

"Simple things like taking trash cans 40 feet to the road for trash day became a 2-part process. Prior to BOS, I used to get this chore done in about a minute. Both cans. Now, when it's humid, outdoor activities like this become difficult."

"One thing that changed significantly as my lung function dropped was that I couldn't climb stairs anymore."

"Walking 20 feet to the bathroom became an endeavor unto itself and supplemental oxygen did not help. Once so strong and vibrant, I now felt useless and a burden to my loved ones. Gone were the days of running along the Adirondack trails or galloping horses cross-country. A competitor all my life, this loss of athletic self-identity was heartbreaking on a very visceral level."

"Sometimes the way that BOS shows up in my life is more like minor inconveniences. For example, I make a high-pitched wheezing sound every single time I exhale. This makes it difficult to fall asleep at night because I both hear and feel the vibration coming from my body."

"I have learned to pick things up with my feet to avoid the stomach compression and lack of oxygen that comes with bending and twisting from the middle."

For many, activities of daily living now include in depth preparations that otherwise would be innate and automatic self-preserving behavior in people without BOS, like planning how many words to say in order not to run out of breath, "Whether talking casually to a friend or speaking at a formal event, I meticulously choose my words based on the length of my sentences. Then, I can plan a breathing break where a pause would naturally fall, instead of running out of air mid-sentence and having my final words come out silently."

"After my BOS diagnosis, I attempted to combine two of my passions, dog training and volunteering, by becoming a puppy raiser with Guide Dogs for the Blind (...) later I realized that BOS would prevent me from completing the yearlong commitment. At less than two months old, our puppy already weighed 25 pounds. I was unable to pick him up. I struggled to get up and down from the floor with him as much as was needed. And, as we were working on leash training, it became very clear that he could easily pull me over. With great sadness we had to drop out of the volunteer program. It absolutely broke my heart that I was not able to use my time and unique skill set to meaningfully give back to my community." My wife and I did ultimately adopt an older and smaller rescue dog, and he is a well-loved member of our family."

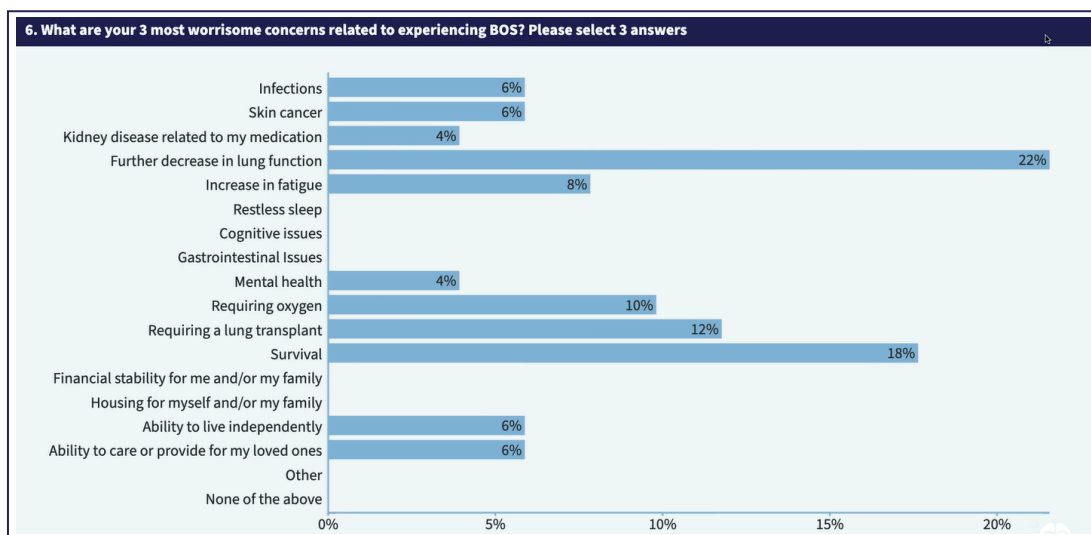
# EMOTIONAL DISTRESS

*"You can't deny the diagnosis, defy the verdict."*

-Norman Cousins

Despite improvements in survival rates, lung transplant recipients continue to experience the highest rates of morbidity and mortality of all solid organ recipients. **Nearly half of lung trans-plant recipients develop chronic rejection within 5 years post-transplant, and survival rates drop to 31% 10 years after transplant.** These odds are potential predictors of high prevalence of depression and anxiety disorders among lung transplant recipients during the first years of post-transplant, occurring in up to 30% of patients. On top of the complications of life post-transplant, comorbid conditions like BOS dramatically impact how patients and caregivers live their lives, altering daily routines, increasing financial pressures, and often leading to social isolation. In addition, lack of information about what to expect and where to turn for support may make the future hazy, thus increasing uncertainty.

GRAPH 4: MOST WORRISOME CONCERNS RELATED TO EXPERIENCING BOS



In one of the polls, patients shared their greatest concerns related to BOS. Uncertainty was at the top of the list. The uncertainty around expectations and disease impacts, financial uncertainty, uncertainty around further decrease in lung function and survival, and uncertainty around the emotional strain on loved ones.

As one patient with cystic fibrosis stated, **"What was different with BOS was the unpredictable nature of it.** With CF, I had largely understood the progressive nature and had a strict daily treatment regimen. With lung transplant and subsequent BOS, it was much more unpredictable and I had to get comfortable living with uncertainty."



Lung Transplant  
FOUNDATION

Mental health disorders, including anxiety and depression, were manifested by numerous patients and caretakers. (See Graph 2)

“While my body has healed, the emotional scars of losing a set of lungs very much remains. The emotional impacts of BOS cannot be underestimated, nor can the anxiety around potentially developing BOS a second time recognizing that most lung transplant recipients acquire BOS 5 years after transplant.”

BOS has a tremendous physical and emotional impact on patients as well as caregivers and care partners. As one patient put it, “it was an entire way of life taken away from me.”

Feelings of dread, apprehension, and impending disaster are frequent and progressive for many, and the sense of self is often questioned as a result of the emotional stress placed upon these individuals “As my BOS progressed, I feared losing my athletic, adventurous personality, essentially everything that made up me as a person.”

**This sense of self is not only questioned short term, it also affects how patients see their future self and their sense of being,** “At other times, the impact of BOS is much more profound. A terminal illness shortens the timeline for accomplishing your life’s legacy, while simultaneously making it nearly impossible to carry out many of the actions you want that legacy to include...being part of something larger than myself.”

For caregivers, seeing their loved ones unexpectedly diminish presented a heavy emotional burden, “It’s very difficult for me as her caretaker, husband, lover to see how she has deteriorated in a way, that she can’t do what we as a couple love to do... we loved to travel, we had to cut that back. we entertained a lot and we’ve cut that as well.”

## DEPRESSION

The physical strains of BOS have another consequence identified by numerous patients, “the inability to do what we used to do before, it is so frustrating and quite depressing.”

“I was angry and extremely upset about having caregivers again after so much time on my own.”

“The first year of treatments was really difficult, (..) burdensome (..) depressing, hard to see hope when I just kept seeing declines.”

## ANXIETY

**Persistent and disabling anxiety is a major and often incapacitating issue experienced by many patients with BOS.** There were three main triggers to this anxiety among patients and caregivers: the natural uncertainty of the condition, the responsibility of becoming a burden to caregivers and family members, and the economic strain brought up by the management of BOS.

## ANXIETY TRIGGERED BY UNCERTAIN CHARACTER OF THE CONDITION

Psychiatric disorders, like anxiety, should be considered important potential side effects of organ transplantation.

Signs and symptoms of BOS may initially present as nonspecific. This clinical feature may contribute to diagnostic delays because diagnosis is only made after excluding other reversible causes such as infection. “The worst day for me was just being stuck in the hospital while doctors try to figure out what was wrong with me.”

When BOS develops, the course of the disease isn’t necessarily easy to predict over time, triggering feelings of anxiety. “Never knowing when feeling poorly was just a bad day or a temporary setback, rather than a warning sign of something worse ahead, was probably the most challenging part of learning to live with BOS/chronic lung rejection.”

“I worried about the pain worsening, if that was possible, and becoming unable to appreciate the beauty in everyday life and everyday small things because BOS was tearing me apart.”

“Those of us who don’t have BOS yet, live in fear of it. Anxiety for sure.”

“That’s probably one of the things that affected me greatly after my diagnosis and still does to this day is anxiety. I never had that before BOS.”

“BOS has an impact on all of us on the lung transplant journey: pre- and post-transplant, patients and caregivers. It looms as a possibility in our future even if we have not yet experienced it.”

When asked what they feared the most, a patient replied “Honestly, death.”

**Uncertainty puts a substantial strain on patients and caregivers, often changing the dynamics of their lives together.** “I was so scared of being alone that my dad had to move out of my parents’ bedroom so my mom and I could sleep together. I needed her close to help calm me when I woke up in a complete panic, too weak to retrieve my anti-anxiety drugs. Several times, my mom had to call the ambulance because the anxiety made me feel like I was dying”

“There were no discussions of next steps or what changes I needed to make to my life. I left the doctors office thinking I was being sent home to die, like many patients, I did not know what was to come or when.”

**The lack of patient and caregiver educational resources was another common theme that contributed to feelings of uncertainty.** Numerous individuals mentioned that better, more accessible educational materials could help ease the anxiety they experienced. “I thought I was sent home to die, and for the first few months not understanding BOS, I was afraid, how long was this going to take.

Then when I did all this research and found out that people were actually living with BOS, I started to feel a little less anxious, slowly overtime.” One caregiver noted, “when your loved one is struggling to breathe, all you want to do is help, but without clear concise patient information, the situation becomes even more challenging.”

At the end of the day, the forbearance of overthinking is of no use. As a caretaker said, “Nobody can prepare us for the unknown, we take it day by day, it is what it is.”

## **THE ANXIETY OF BECOMING A BURDEN TO FAMILY AND CARETAKERS**

“I dreaded to become a burden to my family”

**“It hurt my heart that they (my family) had to suffer along with me”.**

“Demoralizing, hurt my heart to see the extra burden fall in my husband”  
“Feeling like I’m a burden to my family is a huge thing. They say I’m not but it’s hard not to feel that way.”

“I agree with your assessment of how hard it is to watch your wife/daughter etc. go through this. I am the mother of Jenifer, and watching her deal with this from afar has been challenging.”

## **ANXIETY DUE TO THE ECONOMIC STRAIN OF COMPLEX AND COSTLY MEDICAL EXPENSES**

Several patients stated that photopheresis, a form of apheresis and photodynamic therapy used to treat medical conditions such as lung transplant rejection, heart transplant rejection and chronic graft versus host disease (GVHD), is often recommended for off label use. Due to the off label nature of the therapy, insurance companies do not typically cover the treatment

“My insurance denied coverage saying that photopheresis is not an approved treatment for BOS. Without this treatment, I’m quite sure that I wouldn’t be here today. Though my lung function is less than 50% of what it once was, at least I am alive.”

“Photopheresis has stabilized me but is really very expensive!”

“Medicare doesn’t cover photopheresis as a treatment option for my condition and insurers often decline to pay for the therapy as it’s being used for an off-label purpose.”

## Topic 2: Managing BOS

*“Even if I am dying,  
until I actually die,  
I am still living”*

-Paul Kalanathi

**MODERATED BY**  
**Jonathan Reiss**

### **PANELISTS**

#### **John Rost**

Loving caregiver for his wife, grandfather, kettlebell enthusiast. Blogger in pursuit of helping others with lung transplants and living with BOS. John is a patient diagnosed with idiopathic pulmonary fibrosis. Bilateral lung transplant recipient.

#### **Carmel Aronson**

Altruist, advocate for organ donation, dog lover. On her personal quest to achieve life legacy. Previously diagnosed with Idiopathic Pulmonary Arterial Hypertension (IPAH) and Interstitial Lung Disease. Bilateral lung transplant patient, currently diagnosed with BOS.

#### **Carrie Gobble**

Survivor and fighter of many battles. Passionate about friends, family and animals. Double lung transplant recipient due to Cystic fibrosis (CF). Has lived through BOS twice.

#### **Gary Gobble**

Loving husband and primary caregiver of Carrie, patient impacted by Cystic fibrosis. Recipient of a lung transplant.

#### **Cara Favuzza**

22 year old, college graduate and valedictorian in pursuit of an accelerated nursing degree. Diagnosed with BOS at age 10 after a case of mycoplasma pneumonia, hasn't required lung transplant.

#### **Amanda Helderle**

Lover of nature as well as an avid hiker, independent in spirit. Bearer of the emotional and physical scars of losing a pair of lungs. Cystic Fibrosis warrior, two-time bilateral lung transplant recipient. Previously diagnosed with BOS.

#### **Jen Weber**

Former lawyer. Cellist. Cystic Fibrosis warrior, two time bilateral lung transplant recipient. Living with BOS, CF, diabetes, and pancreatic insufficiency.

## MANAGING BOS

**The journey to get a lung transplant is long and hard.** The transplant journey is a long and arduous one. In many respects, the adventure does not end when surgery is complete”. Risk of complications is high. Some are related from the operation itself. Others are a result the consequence of treatment with anti-rejection medications. **Some complications** common in the BOS community include: **reimplantation response, acute rejection (during the first 3 months after surgery), post-transplantation lymphoproliferative disorders (Non-Hodgkin Lymphoma), infections, kidney disease, diabetes, cancer, high blood pressure and chronic rejection (Bronchiolitis Obliterans Syndrome -BOS-).**

BOS is defined as a form of chronic lung allograft dysfunction (CLAD) or chronic rejection that affects a majority of lung transplant recipients and is the principal factor limiting long-term transplant survival<sup>1</sup>. BOS is characterized by progressive airflow obstruction unexplained by acute rejection, infection, or other coexisting condition. This is the scientific definition, but in order to immerse in the world of patients, a better illustration of what BOS means to them is needed.

“Most of you have probably had an experience where you suddenly, temporarily, struggled to breathe. Maybe you swallowed wrong, and in the moment before you began to cough you could feel the panic rising in your body. All of your other senses dimmed. There was no sound, light, or smell. Just the desperate need to breathe. Living with BOS feels like being frozen in a version of that panic moment, forever.”

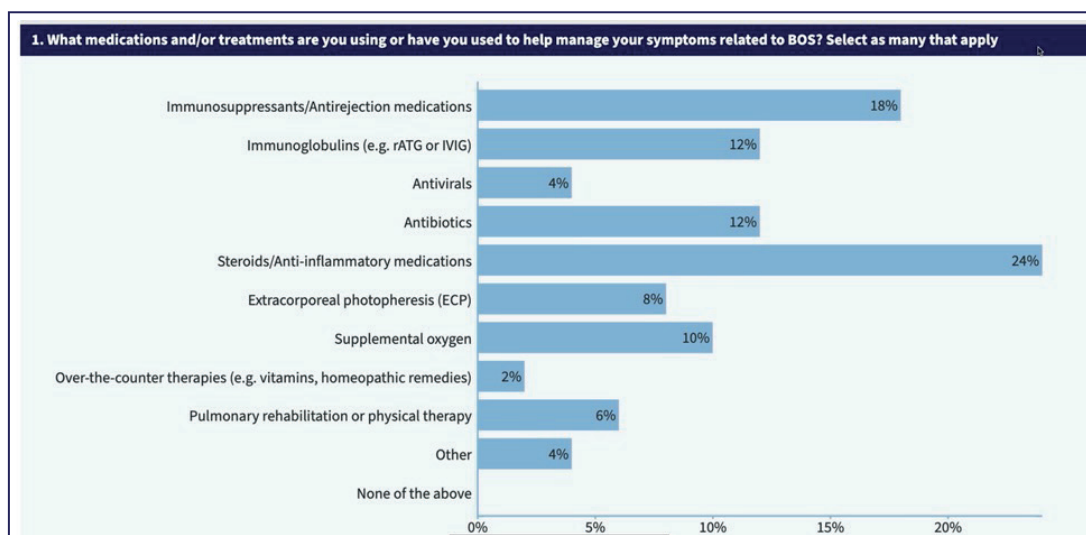
## CURRENT TREATMENTS

The first successful lung transplant was performed in 1983. Despite the remarkable progress that has been achieved since then, median survival rates remain the lowest of the solid organ transplants. There is still a long way to go in order to lengthen and improve the quality of life post-lung transplant. The main challenge impairing long-term survival after lung transplantation is chronic rejection, BOS. Advances in accurate and prompt diagnosis and improved forms of treatment of chronic rejection are critical to further improve patient outcomes. Normally, doctors develop a document with modern medical guidelines based on an examination of current scientific evidence with the aim of guiding decisions and criteria regarding diagnosis, management, and treatment in specific areas of care. Unfortunately, these revise to guidelines do not exist for BOS.

When asked about the treatments and or medications they are currently using or have used, patients report that the most common treatment options are steroids or anti-inflammatory medications, immuno suppressants or **anti rejection** medications, and Immunoglobulins like IVIG. Their current medications, 44% rated their current medications as performing poorly in their ability to manage their symptoms and 19% responded very poorly.

As a patient said, “(Treatments) are not as effective as I would like them to be and so knowing that you are putting significant time, energy and money into something that just doesn’t work is kind of a weird thing to do..., you walk into the hospital, you are plugged into this machine and you are like, okay, i’m giving you a go, but you just don’t know how the next month’s gonna be, it’s just the constant gamble.”

GRAPH 5: MEDICATIONS AND/OR TREATMENTS USED TO MANAGE SYMPTOMS RELATED TO BOS



**The biggest drawback of current treatments is how they affect the daily lives of patients and caregivers.** The treatments' success will depend on the timing of a diagnosis, on careful management of immunosuppressive regimens to reduce the rate of rejection, while monitoring recipients for infections and other complications related to side effects.

Some patients still feel lost, not only because of their own lack of understanding on how to manage their BOS, but also due to the lack of answers received from their healthcare professionals. "I was diagnosed at 14 when I was about to go to high school it took almost a year to get a diagnosis, doctors didn't really know if they could help me, how to treat it, the different medications, and how the side effects made my body sicker."

**There is no standard of care when you receive a BOS diagnosis.** Each of the 80 centers in the US handles things differently based on their own clinical expertise. This also includes a lack of standardization for what medications apply to the specific needs of the patient: which should go first, the order these medications are tried, or what pre-existing conditions may affect a given treatment. This lack of a standardized guideline creates market access challenges as well for healthcare professionals and is an opportunity for patients to feel more reassured, "You put your body through a lot, we get transplants, you know, and to hope that it's going to be better. And you think, when we do photopheresis and you take pills that have horrible side effects, and then they tell you "we don't know", it's kind of a weird process to go through.. I think that is the hardest part."

**Some patients report that the lack of an approved treatment makes them more willing to pursue treatment by trial and error,** "if this medication helps a transplant patient, it might help a more extreme condition (lung transplantation), more dose or frequency and see how it goes."

"Those of us who have had a lung transplant, and survived a lung transplant, we are used to our bodies going through quite a bit, much much more than the average person, which is not

to say we should have to continue experiencing it, but if it comes down to it, we already shown that we are willing to go thru quite a bit. But, where is it that it gets easier for us, where is it that this completely unnecessary stress could be taken away so that we could then use the energy we have to play with our dogs, or pursue our passions, or to do the things that are able to bring us joy.”

Patients report that, while current therapies are hard on patients with BOS, they are even harder for those that have multiple conditions.

“The purpose of my current treatment is to try to extend my life, but it does not address what my life has become living with BOS.”

“For me, I suffer from anemia so I have to get blood transfusions which have their own host of problems, so that’s part of the process of problems people don’t realize- think about.”

## **STEROIDS/ ANTI-INFLAMMATORY MEDICATIONS**

BOS may be treated with additional immunosuppressant medicine. Prednisone has a non-specific anti-inflammatory effect that inhibits the granulocyte function, thus limiting damage to an organ in which the rejection process has already begun.

“At first, I was treated with prednisone.”

“I spent 3 years on steroids post-diagnosis. Every time my care team would stop the steroids, my lung function suffered. Steroids are not without their own side effects. Middle school is difficult enough and the anxiety caused by steroid-induced swelling and weight gain only made my experience more challenging.”

Corticosteroids are known to have a number of side effects impacting quality of life. One patient describes “A steroid with horrible side effects like irritability, sleep deprivation, and weight gain. Not a fun option for patients to have to endure.”

## **IMMUNOSUPPRESSIVE THERAPIES**

While the body's immune system protects you from infection, immune cells recognize the transplanted lung as different from the rest of the body and attempt to destroy it. When a new organ is transplanted, the body's immune system treats it as a threat and produces antibodies against it. This is why immunosuppressive therapies are crucial to the lung transplant community.

“My daily treatment regimen for BOS includes twice-a-day anti-rejection medication and various meds to combat immune suppression, (which is in excess of 20 pills), two inhalers, along with using supplemental oxygen.” This patient points out how despite the need of immunosuppressive medications, medications needed to boost or help your immune system are needed as well.

Each patient living with BOS deals with a unique condition in itself, “My team tried a variety of conventional treatments: high dose steroids, modifications to my anti-rejection drug program, five days of anti-thymocyte globulin treatment, and a three-month course of immunotherapy.”

During the panel, most patients expressed how immunosuppression made them more vulnerable to different viruses:

“Unfortunately I caught some kind of virus, which ended up making my lung function even worse. I think I lost a total of almost 60% of my lung function while fighting BOS and the virus I caught due to the increased immunosuppression.”

“When most people experience parainfluenza, it's like a cold and they get over it quickly. I suffered for over a week with lungs full of mucus, a horrible cough, and headache. I spent a night in the hospital.”

Statins and Azithromycin, although not considered immunosuppressive therapy, can be used as adjunctive therapy in specific cases, to improve long term outcomes against chronic rejection. Azithromycin is a macrolide antibiotic with anti-inflammatory, immunomodulatory<sup>7</sup>, and pleiotropic effects. In addition to its antibacterial activity, it has been used successfully as a part of maintenance therapy in lung transplant patients with chronic rejection, providing stabilization or improvement in lung function. Azithromycin is well tolerated, and some programs initiate azithromycin soon after transplant, even in the absence of such indicator.

“I was enjoying that 5-liter FEV-1 for about 4 months before it started to drop. In another 4 months, I was back down to 3 liters. This decrease in lung function triggered conversations about chronic rejection and I started taking Azithromycin for BOS in December of 2016.”

“Then, they added Azithromycin to give my immune system a boost before revisiting the acid reflux problem to tighten my esophagus and, hopefully, reduce the amount of acid passing through my airways while asleep.”

## **EXTRACORPOREAL PHOTOPHERESIS (ECP)**

Extracorporeal Photopheresis (ECP) is an increasingly used therapy to address CLAD (chronic rejection) following lung transplantation, which has been shown to result in preservation of lung function with low side effect profile. It is a treatment option strongly recommended by the American Society of Apheresis, and was mentioned by several patients as part of their current treatments.

As one caregiver in the audience shared, “We just walked in the door from Photopheresis - this treatment has saved and prolonged my husband's life.”

“My number one current treatment is ECP.”

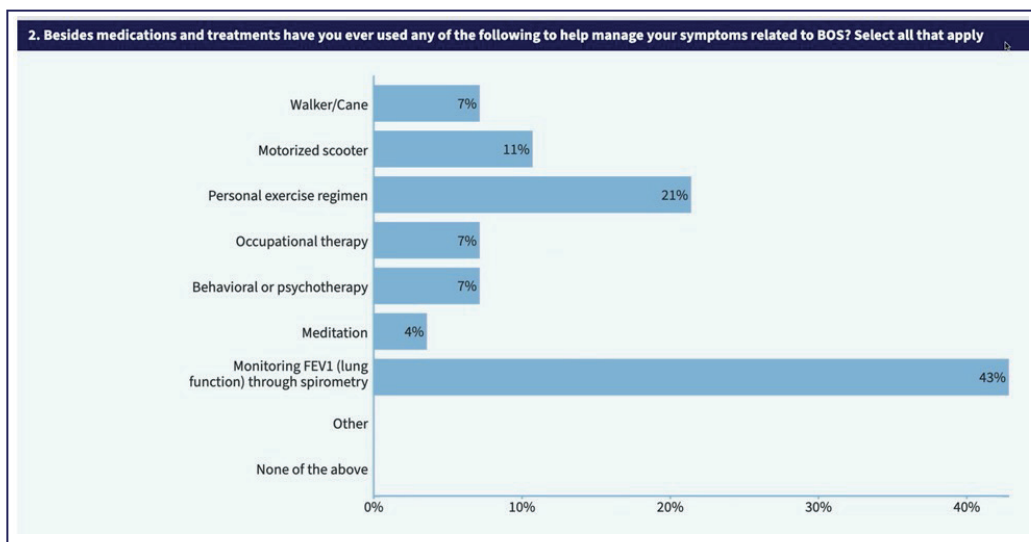
“I am one of the fortunate ones, that is I am excelling with the current treatment (photopheresis)”, this patient narrated her story on how, she has been one of the lucky ones that because of photopheresis, has a stable lung function, but it took her four years to get this way. In the meantime, the process of the treatment is hard.

Despite being a treatment that most patients pursue at a specific moment in their journey, this treatment is being used off label, and comes with certain drawbacks: “Photopheresis has stabilized me, but it is really expensive and I have had port infections and possibly blood clots because of it.”

“When I lost 20% lung function that meant I qualified for treatment with photopheresis. Photopheresis requires a catheter or some sort of access. Practically speaking, you’re isolated in a treatment room and pretty much stuck there. You can’t even go to the bathroom for up to 5 hours depending on what the photopheresis machine tells you you need that particular day.”

“...and its big drawback (Photopheresis) is the fatigue following the procedure, the time and effort to get to the procedure, (the procedure itself) where you are locked in several hours to the machine. I don’t have a port, so it’s a dual IV for me.. I had a pulmonary embolism caused by the procedure, mineral issues caused by the procedure, fatigue caused by the procedure, my heart in different arrhythmia that’s likely caused by the procedure, like I said, they list all the side effects I have in the commercial, - I helped find most of them -, but just in the day to day life, it’s just the fatigue after the procedure, and the mental fatigue .”

GRAPH 6: OTHER NON MEDICAL RESOURCES USED BY PATIENTS TO MANAGE BOS RELATED SYMPTOMS



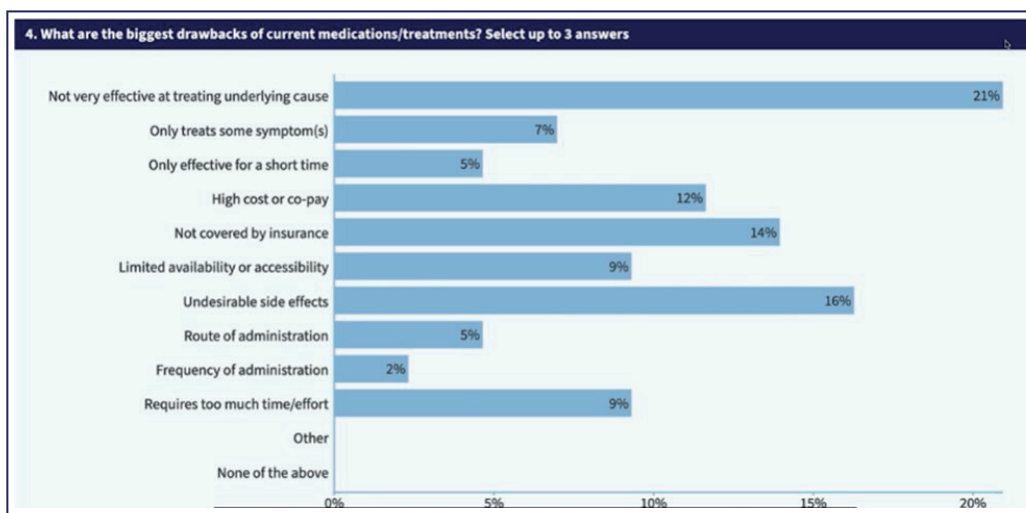
Besides medications, most patients participating in the poll highlighted the use of monitoring lung function through spirometry. In a previous poll, it was found that 30% measured their FEV1 daily, and 40% once per week.

In addition to the use of spirometry to monitor lung function, several touched on the importance of a personal exercise regime as noted in chapter 1.

**“I use exercises to keep my energy and strength up, and pulmonary rehab,.. they help me consciously keep panic at bay.”**

The biggest drawbacks or downsides of current treatments is how they affect the daily lives of patients and caregivers. The treatments’ success will depend on the timing of a diagnosis, on careful management of immunosuppressive regimens to reduce the rate of rejection, while monitoring recipients for infections and other complications related to side effects.

GRAPH 7: BIGGEST DRAWBACKS OF CURRENT MEDICATIONS/TREATMENTS FOR BOS



Some patients still feel lost, not only because of their own lack of understanding on how to manage their BOS, but also due to lack of answers from their healthcare professionals, “I was diagnosed at 14 when I was about to go to high school it took almost a year to get a diagnosis, doctors didn’t really know if they could help me, how to treat it , the different medications, and how the side effects made my body sicker.”

“Those of us who have had a lung transplant, and survived a lung transplant, we are used to our bodies going through quite a bit, much much more than the average person, which is not to say we should have to continue experiencing it, but if it comes down to it, we already shown that we are willing to go thru quite a bit. But, where is it that it gets easier for us, where is it that this completely unnecessary stress could be taken away so that we could then use the energy we have to play with our dogs, or pursue our passions or to do the things that are able to bring us joy.”

One downside from current treatments and medications, is that they are hard enough on patients, and even harder on the ones that have other conditions, “For me, I suffer from anemia so I have to get blood transfusions which have their own host of problems, so that’s part of the process of problems people don’t realize, think about.”

# PATIENT JOURNEY

*“Living with BOS means that my survival is directly linked to my willingness to continuously educate myself about my condition.”*

## Lung transplant patient

Patient expectations about management of their health have changed over the years. More choices, more services, and the availability of more information has empowered patients to make better informed decisions about their health journey.

This is exceptionally true for patients post-lung transplant, where the concept of self-advocacy has surfaced not only in public debates, but has been key in shaping patients' health care attitudes and behaviors in navigating what's best for their health. For many lung transplant patients, self advocacy is a necessary part of the patient journey. For this particular document, it is key to highlight the role of patient education in the journey ahead.

### SELF ADVOCACY - A LEARNING CURVE

“Living with BOS means that a percentage of my available brain space and life energy must always be spent on self-advocacy. Twice so far, new medications have been added to my treatment regimen based on research that I have personally brought to my care team...but only after I was able to convince my insurance provider to cover them.”

“It's a continuous battle, it takes personal effort and dedication, making sure you are paying attention in being that self-advocate, so if you are not going to do that, you can find yourself in a bad situation pretty quickly. That's the challenge.”

“Finding hidden documents on my own, spending days on the phone, (...) and this is what I'm doing while I'm also struggling to breathe. This is what I'm doing while it's also difficult for me to have the energy to feed myself or make it to the bathroom. This is how we are using our time and energy. Contacting our insurance companies.”

“I focused on my own care. On top of having to suction mucus from my lungs 3x-4x/daily, I was able to convince the hospital to let me serve as the test case for use of a portable ventilator. I learned to talk through an electrolarynx. I learned to become attuned to how my body was feeling so I could catch issues before they spiraled out of control.”

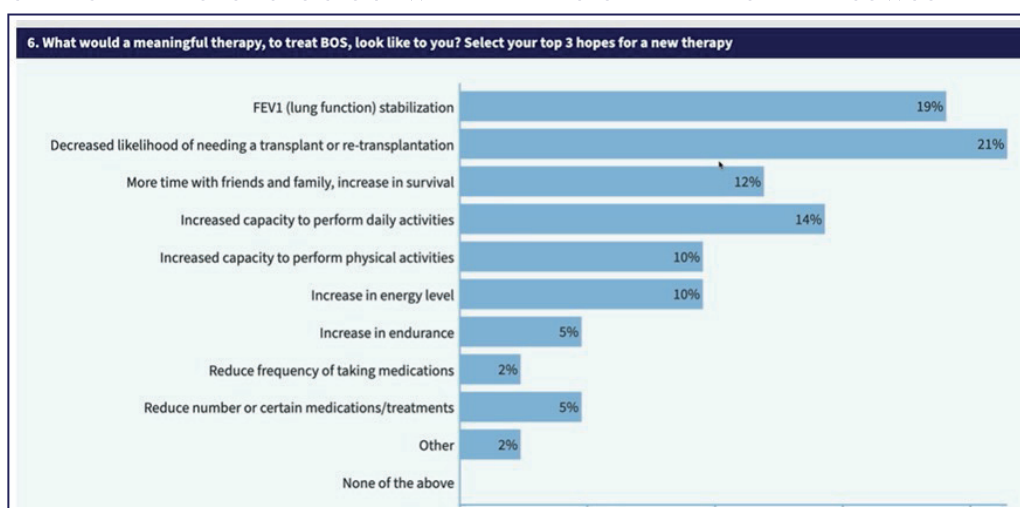
One patient reminded the panel that accessing information is key, and not everyone knows exactly how to navigate the complex information ecosystem. He asked, “How can we find out what clinical trials are going on and how we can possibly participate in those? I realize right now those are limited.” There is still much to be done in educating and helping patients and caretakers in their journey. Learning to access clinical trials should be a simple step in their journey, but it's not. As it was pointed out by other patients “it's hard to find where those are being done, if there are any”

A primary caregiver to a patient living with BOS wrote “(it is important) for caregivers to have access to educational information regarding BOS and the therapies available and research that is being done. So much to be learned.”

## PREFERENCES FOR FUTURE TREATMENTS

While the stories of patients impacted by BOS are as different as their underlying forms of lung disease, all are connected in their deficit of lung function, and their willingness to support research aimed at finding a cure. Patients were asked a number of questions around treatment preferences (i.e. frequency, location, and delivery mechanism) as well as outcomes of interest.

GRAPH 8: PATIENT'S TOP CHOICES ON WHAT A MEANINGFUL THERAPY TO TREAT BOS WOULD BE LIKE



As shown in Graph 8, patients are looking not only to feel better, but to actually get better. Concretely, this means stabilization of their lung function, increased survival and the ability to live a decent, dignified life.

“Looking to the future, we need more effective and less invasive treatments to preferably prevent, and if not prevent, treat all chronic rejections. Treatments that can be started earlier by identifying chronic rejection in very early stages will allow future patients to maintain higher lung function and quality of life for much longer.”

## DIAGNOSIS

**BOS is typically a diagnosis of exclusion** which often means delay a in treatment that might reduce the deterioration of lung function.

“My first experience with BOS was back in 2011-2012 when my lung function decreased by 10%. When you experience that kind of reduction in lung function, your care team wants to uncover the root cause. Eventually, I was diagnosed with chronic rejection, a diagnosis of exclusion.” This is the first step of a patient's journey in managing BOS, having to endure the process of a long, and often irreversible damaging, diagnosis of exclusion”

“It’s a diagnosis by exclusion, which means that a lot of time passes while our lungs function is dropping dramatically before we can conclusively say, this is BOS. Then some of our insurances have rules that say you have to have shown that you did not progress on every other treatment before you can start something like Photopheresis. That’s additional time wasted, time during which our lung function is dropping and we may never get it back. So absolutely one of the areas that needs to improve is early detection, coupled with starting treatment immediately.”

Patients and caregivers spoke of the need for a faster means of diagnosis “I was diagnosed at 14 when I was about to go to high school it took almost a year to get a diagnose, doctors didn’t really know if they could help me, how to treat it , the different medications, and how the side effects made my body sicker”

“We need more effective and less invasive treatments to preferably prevent, and if not prevent, treat all chronic rejections.”

“Treatments that can be started earlier by identifying chronic rejection in very early stages will allow future patients to maintain higher lung function and quality of life for much longer.”

“I think the focus needs to be in prevention or treatment specific to stopping BOS from progressing.”

## STABILIZATION

Stabilization means a halt to deteriorating lung function.

**“What we would love to see is stabilization.** What could we do to stop the drop in lung function, and this would just buy us more time so that additional research can happen, so we can figure out if we want to get more realistic or not, instead of having to do all these very big decisions in the ICU, in absolute panic state.”

“I lived in the era of CF research, I saw the progression made, (...)and that’s what I hope (for BOS) that through these efforts that they will come up with something that is accessible, affordable and that can hopefully halt this progression that seems so unpredictable.”

“Despite my willingness and my own self advocacy, the sad truth is that there are no treatments available to me beyond what I am already on. There are no medications on the market that have been shown to halt the progression of my disease.

## **PATIENT FRIENDLY TREATMENTS**

**When developing a new therapy for BOS, it is critically important to take patient preferences to heart.** This manifested in respect to preferred route of administration, acceptable treatment delivery timelines, and acceptable side effects, “The biggest things I want you to consider are treatment coverage; treatment frequency; availability; patient comfort; and treatment duration. Taking these factors into consideration at the beginning of clinical development and asking patients for their input would lead to the creation of more patient-friendly treatment options and less burdensome clinical trials.”

“I’ve been asked about what the ideal treatment would look like. To me the ideal treatment would be similar to Azithromycin, a small pill or inhaler that is easy to take, has minimal side effects, and makes a noticeable improvement in lung function.”

“(Treatment) takes time, energy, and money, all of which are in short supply. For these reasons, I’d urge you to carefully consider both frequency of treatment as well as treatment setting. How many facilities will be able to administer your new therapy?”

“I challenge you to think outside the box and consider not only treatment itself but pre and post-treatment as well. Consider portability. Is the treatment being developed something I can take with me when I travel to visit family? Will it limit how I’m able to live my life even more than BOS already does? If a treatment is designed for home use, what are the storage requirements? How about the shelf life? If something has to stay refrigerated, that’s a life-limiting factor.”

“We had lung transplants so we can live our lives as fully as we are able and spend more time outside the hospital. If a new treatment can be developed that focuses on quality of life and can blend into the background of our day to day, that would be amazing.”

“Patients that need treatment for chronic rejection don’t have many options. I know patients who choose to forego treatment because, for them, untreated chronic rejection is more appealing than all that treatment entails.”

“I’ve often felt like a fish in a fish tank because I’m typically tethered to a treatment room, alone, behind a curtain, with the occasional nurse popping in to check on me. This is lonely and awkward.”

“Despite my numbers remaining relatively stable on IVIG, I have a number of unmet needs that I’m hopeful future clinical development programs will address. A more patient-friendly treatment for BOS would mean less time in treatment and more time to focus on the things that matter most to me like family and my nursing program.”

“Let's talk about what I'd hope for in a new, more patient-friendly treatment for BOS. Whether treatment is delivered through IV, inhaled, or delivered some other way, I'd love to see less time intensive mechanisms of delivery as well as fewer treatments required or, alternatively, longer acting treatments”

## **RECOVERY FROM LUNG DAMAGE**

“I don't want 40% to be good. That's not what it should be. While I'm celebrating the fact that I'm not at 9%, I don't want to be happy at 40% lung function”

“There are no medications that can reverse the lung damage that has already occurred. My only hope for recovery is for new pharmaceuticals to be researched, developed, and brought to market.”

“Discovering treatments for BOS is vital for lung transplant patients. Shortly after life saving and extending lung transplant surgery, I started to quietly worry about BOS. At 6 plus years out from transplant, I'm more apprehensive. I'm so grateful to have been given the gift of more years. Doesn't it make sense to put much more effort into finding a cure for BOS?”

“25 years with a lung transplant and been in chronic rejection since 2008, I would love to see new medications out there not only for prevention for BOS, but also treatments that repair the damage done from BOS, something like an inhaler or even an infusion”



# TRADEOFFS PATIENTS ARE WILLING TO MAKE

Lung transplant recipients are survivors and their lives often reflect this commitment. They are willing to try experimental treatment options and are acutely aware that their survival and well being depends on their own advocacy and discovery. They are, as one patient said, “all in”.

“I know patients that have had to travel 8+ hours and find a place to stay for their course of treatment. This takes time, energy, and money, all of which are in short supply.”

“Honestly I think I would have been all in, I would have started whatever they told me to do.”

“I had a lung transplant, I've had two, I think I wouldn't mind, it could be relatively invasive if they told me this is going to save your lungs.”

“I don't think I can accept that BOS is inevitable,... (i know) we are going to lose lung function, but what I don't accept is that we don't have anything that they can say with certainty that this is going to help us.”

“A less time intensive, pill formulation would be ideal but I'm willing to try just about anything so long as I don't have to come off my current meds.”

Caregivers are also willing to make sacrifices for their loved ones, “We were very disappointed in the lack of BOS treatment options at our original transplant hospital. We relocated to another state in order to have treatment for BOS.”

Transplant recipients and caregivers are willing to not only endure logistical barriers, time management constraints, seemingly insurmountable treatment costs, and monumental physical and mental burdens placed on them by less than ideal treatment options. They are willing to study, learn, and even fight to be considered to participate in a clinical trial (with unknown results).

“Twice so far, new medications have been added to my treatment regimen based on research that I have personally brought to my care team.”

“I was able to convince the hospital to let me serve as the test case”

“Towards the end of 2019, our hospital began participating in a Medicare-sponsored ECP clinical trial and I was the second patient to start the treatment. After one year, my FEV-1 had increased to 2.1 liters, higher than it had been for the two previous years. **This meant hope, not just for me and my family, but for all lung transplant recipients and even candidates who read about and study post-transplant issues and mortality.**”

# CONCLUSION

*“The delicious sensation of a long, slow, deep breath.”*

- Lung Transplant Patient

For a certain subset of patients with end stage lung disease, lung transplantation can make the difference between life or death. It is their only hope. But lung transplants are not carried out frequently: the demand for lung transplants is far greater than the available supply of donated lungs. This means a transplant will only be carried out if it's thought there's a relatively good chance of it being successful.

For patients with end state lung disease, lung transplantation can be the difference between life and death. Long-term survival post-transplant may be improved by better anticipation of developing diseases after transplantation, gained by experience and active patient, healthcare professional and caregiver involvement. Lung transplant patients still have a shorter life expectancy than normal, especially caused by side effects of immunosuppression and our current treatment's inability to stop chronic deterioration of the graft, manifested mainly as chronic rejection.

Over the last 20 years, median lung transplantation survival rates have increased from 4.7 to 6.7 years, although this still varies across indications. Survival is hampered by the high prevalence of complications, especially the development of chronic rejection (70% of patients develop BOS). Despite all the efforts, the percentage of patients who develop chronic rejection remains largely unchanged at 50%, 5 years after surgery.

An effective medical treatment for BOS is one of the greatest unmet needs in lung transplantation. Different options available are used to prevent or attenuate the progression of BOS, but they are limited, difficult and/or experimental.

Clinical guidelines recommend lung function monitoring to aid early identification of BOS, but lung function is only a tool to evaluate the impact of treatments received. In addition to spirometry, measurements of static lung volumes and lung capacities are used to classify patients. Immunomodulation mediated via Extracorporeal Photopheresis (ECP) is an increasingly used therapy to address chronic rejection following lung transplantation. But availability, financial, and logistical difficulties prevent many patients from accessing the treatment.

ECP is not an approved treatment for BOS and insurance reimbursement is a major challenge. As a result, treatment is frequently interrupted.

Because of the rarity of disease, associated morbidity, and reluctance of investigators to randomize patients to placebo, new clinical studies are scarce.

Now that the unmet needs and quality of life impacts of BOS are better understood, it is time to break the gridlock in the development of new diagnostics and treatments to prevent and manage BOS, and give these patients the chance for improved quality of life and the opportunity to take a deep, long, slow breath.

# GLOSSARY

## COMMON MEDICAL TERMS

### -Symptoms:

This is what a patient feels. They present themselves as physical or mental features that may indicate a condition of disease, and can be described as perceptions and sensations. Chronic: in medical terms chronicity is defined by how long a condition has lasted. A chronic disease is a condition that has lasted more than three months.

### Acute:

In medical terms an acute condition is abrupt reduction in the abrupt reduction in the function of an organ or system due to disease.

### Cystic fibrosis (CF):

A chronic, inherited disease that affects lungs and digestive system. It causes thick, sticky mucus to build up in the lungs and other organs. The sticky mucus obstructs airways, which can result in troubled breathing. It also tends to cause repeated lung infections that may eventually damage the lung. When CF patients develop severe lung disease, they might be a candidate for receiving a lung transplant.

### Idiopathic pulmonary fibrosis (IPF):

A disease that causes scarring (fibrosis) of the lungs. The word "idiopathic" means it has no known cause. Scarring causes stiffness in the lungs and makes it difficult to breathe. Lung damage from IPF is irreversible and it gets worse over time. People with IPF may be recommended for lung transplant.

### Allograft:

Tissues, cells, or organs transplanted between two individuals from the same species.

### Quality of life:

The perceived quality of an individual's daily life, that is, an assessment of their well-being or lack thereof. This includes all emotional, social and physical aspects of the individual's life. Health is a major issue in quality of life.

### Health related Quality of Life -HRQoL-:

An assessment of how the individual's well-being may be affected over time by a disease, disability or disorder. A concept reflecting concern with the modification and enhancement of life attributes, it acknowledges that subjects put their actual situation in relation to their personal expectation.

# SYMPTOMS

## -Cough:

We've all had a cough! Cough is a sudden, audible expulsion of air from the airway (trachea, bronchi, and/or lungs) of irritants and secretions, or to prevent aspiration of foreign materials into the lungs.

## -Shortness of breath:

Usually, people are not aware of their own breathing. But people with BOS are constantly aware of it. Difficult or labored breathing is referred to as “dyspnea” by physicians. BOS patients detect a progressive worsening of breathing and limited functional activity that will develop dyspnea in every case.

## -Pain:

Pain is an unpleasant sensation induced by unpleasant stimuli which are detected by the body. Pain is a good ally but it can become a powerful enemy. In chronic disease, pain may persist after the initial injury has healed. Its localization, character, and timing are vague. BOS patients frequently refer to chest pain during early stage disease. Pain progresses as BOS becomes more severe.

## -Sleep disturbances:

Patients with chronic lung disease may experience abnormal sleep patterns which affect the length, timing, and/or rigidity of the sleep-wake cycle. Patients may notice impairment of the ability to initiate or maintain sleep (insomnia) or sleepiness during normal waking hours that may impair mental functioning.

## -Cognitive issues:

Many patients refer to diminished or impaired mental and/or intellectual function associated with BOS. This may be identified as “foggy brain”, mood disorders (sadness or irritability) or “forgetfulness”. It can be a consequence of low oxygen levels in the blood combined with reduced blood flow (hypoxia) and the subsequent reduction in brain oxygen supply . .

## -Anxiety:

Feelings or emotions of dread, apprehension, and impending disaster are frequent in patients with BOS. Sometimes they may become disabling, transforming into anxiety disorders. In BOS patients, anxiety is often triggered by the shortness of breath.

## -Gastrointestinal Issues :

Impaired digestion (especially after eating), impaired appetite, sensation of discomfort, distress, or agony in the abdominal region are common in BOS patients. It is a frequent finding of gastroesophageal reflux disease (GERD). Some of them must deal additionally with other serious digestive issues associated with their original condition (eg. Cystic Fibrosis).

## -Chronic Kidney Disease:

Kidney damage is a common long-term complication in lung transplant patients: 25% of patients will develop some degree of kidney disease a year after the transplant. After 5 years, 10% of lung transplant recipients will experience kidney failure.

# SIGNS

B-ronchiolitis obliterans syndrome (BOS):

BOS is the name given to the inflammation of the bronchioles (very small airways branching) leading to an obstructive (obliterans) lung disease. Bronchioles with BOS are characterized by scar with mucus inside that impedes airflow. Symptoms include mainly dry cough and shortness of breath (called dyspnea in medical terms).

-Decrease in lung function:

Lung function is measured by the volume of air that is exhaled by a maximal expiration following a maximal inspiration. Forced Expiratory Volume 1 (FEV1) is the measure of the maximum amount of air that can be expelled in one second. Experts' consensus statement defines chronic rejection as a persistent decline in pulmonary function, characterized by a decrease of at least 20% in FEV1 for more than 3 months from post-transplant baseline.

-CT scan:

CT scans are sometimes referred to as CAT scans or computed tomography scans. It is an X-ray image and uses computer algorithms to reconstruct the image for an accurate diagnosis.

-Wheezing:

Doctors or patients may note noises, both normal and abnormal, by listening to any part of the respiratory tract. Wheezing is an abnormal respiratory sound often detected by a stethoscope. It is a high-pitched whistling sound that corresponds to the passage of air through obstructed airways.

-Depression:

Depression is a common mood disorder which may cause impairment to the way patients think, handle daily activities, or feel. Most frequently it is a state of low mood and aversion to activity. The experience of depression affects a person's thoughts, behavior, motivation, and feelings.

-Anxiety disorder:

Anxiety disorder is another frequently occurring mental health disturbance experienced by many patients with BOS. Anxiety becomes a "disorder" when feelings of dread, worry, or fear impact and impair daily living.

-Gastroesophageal reflux disease (GERD):

Is a digestive condition where stomach acid or bile irritate the lining of the tube located between the mouth and the stomach. GERD is commonly found in patients with chronic lung disease. By proximity, refluxed gastric liquid or duodenal contents may go to the airway, and causes severe lung damage.

-Frequent infections:

Invasion of the patient by microorganisms (bacteria or viruses) or their toxins and by parasites that can cause diseases is common in patients with BOS. Efforts to prevent and control the spread of respiratory infections, persistent infections are a major concern in this group of patients.

-Respiratory tract infection:

Invasion of the patient respiratory system by microorganisms, usually leading to diseases is a frequent finding in BOS patients. Paradoxically it is also the principal confounding diagnosis in early stages of BOS.

-Tumors or cancer of the skin:

Transplant recipients are often on strong immuno-suppressive therapies, a deliberate prevention or diminution of the host's immune response. After organ transplantation, patients are prone to have many cutaneous adverse events, both infections and neoplasms. The leading malignancy is skin cancer.

-Hypogammaglobulinemia

An immunologic deficiency state characterized by an extremely low level of gamma-globulin in the blood.

-Acute rejection

Rejection is a response of the host's immune system. Most people experience acute rejection, during the first 3 months after the transplant. Patient's immune system produces antibodies against the new organ, which can stop it working properly. There is an association between frequency and severity of acute rejection episodes and subsequent development of BOS,

## TREATMENT

-Immunosuppression Therapy:

Deliberate prevention or diminution of the immune response. It may be nonspecific as in the administration of immunosuppressive agents (drugs or radiation) or may be specific as in desensitization or the simultaneous administration of antigen and immunosuppressive drugs.

-Steroids (glucocorticoids)

A group of very useful compounds closely related biochemically Glucocorticoids are used in transplantation for their anti-inflammatory effect.

-Prednisone

Is a synthetic anti-inflammatory glucocorticoid used to suppress the immune system and decrease inflammation in conditions such as asthma, COPD, and rheumatologic diseases. Prednisone possesses pronounced anti-inflammatory activity. It causes an alteration of the immune system or of an immune response by agents that activate or suppress its function, according to the dose and time of use.

#### -Photopheresis

A blood-filtering treatment in which blood is exposed (in an extracorporeal flow system) to photoactivated medications and ultraviolet light -a procedure known as a PUVA THERAPY-. Photopheresis is at present a standard therapy for some diseases; it shows promise in the treatment of autoimmune diseases and BOS.

#### -Patient Education:

The teaching or training of patients concerning their own health needs. It is usually made of works consisting of informative material used to explain a procedure or a condition or the contents of a specific article in a biomedical journal and written in non-technical language for the patient or caregivers.

#### Patient Advocacy

This term refers to the promotion and protection of the rights of patients, frequently through a legal process, but also by education, adherence and cooperation of the patient, caregivers and medical staff.

#### -Market Access

Market access is the ability to obtain health services and medications in the correct timing and opportunity. Health market access is normally subject to conditions or requirements linked to the patient's needs, treatment or medication that will help them manage a specific condition, at an appropriate price.

#### -Clinical trials

A type of research that studies new tests and treatments and evaluates their effects on human health outcomes. They usually focus on pre-planned studies of the safety, efficacy, or optimum dosage schedule (if appropriate) of one or more diagnostic, therapeutic prophylactic drugs, devices, or techniques selected according to predetermined criteria of eligibility and observed for predefined evidence of favorable and unfavorable effects. Clinical trials are carefully designed, reviewed and completed, and need to be approved before they can start. People of all ages can take part in clinical trials, including children.

There are 4 phases of biomedical clinical trials:

- Phase I studies usually test new drugs for the first time in a small group of people to evaluate a safe dosage range and identify side effects.
- Phase II studies test treatments that have been found to be safe in phase I but now need a larger group of human subjects to monitor for any adverse effects.
- Phase III studies are conducted on larger populations and in different regions and countries, and are often the step right before a new treatment is approved.
- Phase IV studies take place after country's board of health approval and there is a need for further testing in a wide population over a longer timeframe.

# APPENDIX

## APPENDIX 1: MEETING AGENDA

|          |                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 10:00 AM | <b>Welcome Remarks</b><br>Amy Skiba, Lung Transplant Foundation<br>Jonathan Reiss, Lung Transplant Foundation<br>Martha Austrich, caregiver and advocate                                                                                                                                                                                                                                         |
| 10:13 AM | <i>Jeff Goldstein, Lung Transplant Foundation, posthumously via recording</i>                                                                                                                                                                                                                                                                                                                    |
| 10:15 AM | <b>Opening Remarks – PFDD Overview</b><br>Dr. Ozlem Belen, Deputy Director, Division of Rheumatology and Transplant Medicine, Office of New Drugs, FDA                                                                                                                                                                                                                                           |
| 10:20 AM | <b>Clinical Overview of Bronchiolitis Obliterans Syndrome</b><br>John M. Reynolds, MD, Associate Professor, Duke University School of Medicine, Medical Director, Medical Director, Duke Lung Transplant Program, Pulmonologist and Transplant Pulmonologist                                                                                                                                     |
| 10:40 AM | <b>Overview of Meeting, Discussion Format, Demographic Polling Questions</b><br>Amy Skiba, Lung Transplant Foundation                                                                                                                                                                                                                                                                            |
| 10:50 AM | <b>Topic 1: Living with BOS – Symptoms and Daily Impact</b><br>Jonathan Reiss, Moderator<br><br>Sara Kominsky, patient<br>Ruth and Stan Magnus, patient and caregiver<br><b>Denise Desroberts</b> , patient<br>Amanda Helderle, patient<br>Jen Weber, patient<br>Martha Austrich, caregiver<br><br>Session 1: Polling Questions and Facilitated Audience Discussion<br>Jonathan Reiss, Moderator |
| 11:15 AM | <b>Break</b>                                                                                                                                                                                                                                                                                                                                                                                     |
| 12:15 PM | <b>Topic 2: Current Treatments for Patients and Future Therapies</b><br>Tim Berger, Moderator<br><br>John Rost, patient<br>Carrie Gobble, patient<br>Gary Gobble, patient and caregiver<br>Carmel Aronson, patient<br>Jen Weber, patient<br>Amanda Helderle, patient<br>Cara Favuzza, patient                                                                                                    |
| 12:30 PM | <b>Session 2: Polling Questions and Facilitated Audience Discussion</b><br>Jonathan Reiss, Moderator                                                                                                                                                                                                                                                                                             |
| 12:55 PM | <b>Closing Remarks</b><br>Amy Skiba, Lung Transplant Foundation                                                                                                                                                                                                                                                                                                                                  |
| 1:55 PM  | <i>Jeff Goldstein, Lung Transplant Foundation, posthumously via recording</i>                                                                                                                                                                                                                                                                                                                    |
| 2:05 PM  | <b>Next Steps and Meeting Wrap Up</b><br>Amy Skiba, Lung Transplant Foundation                                                                                                                                                                                                                                                                                                                   |
| 2:15 PM  | <b>Adjourn</b>                                                                                                                                                                                                                                                                                                                                                                                   |

## **Appendix 2**

### **Questions For Guided Discussions**

#### **Topic 1 – Symptoms and Daily Impact of Living with BOS**

1. Of all the impacts of BOS, which symptom has the most significant impact on your life?
2. What are your best and worst days like living with BOS?
3. How have your BOS symptoms changed over time? How has your ability to cope changed over time?
4. Are there any activities that are important to you that you can no longer do as a result of having BOS?
5. What do you fear the most as your BOS progresses? What worries you about your health living with BOS?

#### **Topic 2 – Perspective on Current Therapies and Future Approaches to Treatments for BOS**

1. How are you currently managing your symptoms?
2. How well are your current medications/treatments managing your symptoms related to BOS?
3. What are the biggest downsides to your current treatments for BOS and how do they affect your daily life?
4. Short of a cure or a reversal of your impaired lung function, what would an ideal treatment look like for you?

## Appendix 3

### Written statements from the panelists

#### CARMEL ARONSON

Hello, my name is Carmel. When I was 33 years old, I received a bilateral lung transplant. But my story doesn't end there. Just a few years after my transplant, I developed BOS. For the second time in my thirties, I was told that I probably had about two years to live. Despite being caught immediately and treated aggressively, my lung function has fallen to only 28%.

Most of you have probably had an experience where you suddenly and temporarily struggled to breathe. Maybe you swallowed wrong, and in the moment before you began to cough you could feel the panic rising in your body. All of your other senses dimmed. There was no sound, light, or smell. Just the desperate need for breath. Living with BOS feels like being frozen in a low-key version of that panic moment, forever. Although I can often control the severity of my breathlessness by limiting my physical movements, it is always an internal factor that I am negotiating with.

Many people with lung disease talk about experiencing "shortness of breath," but that phrase has never been relatable to me. I'm not breathing "shortly." I'm breathing extra. Because so much of my lung area doesn't function, when I need to increase the available oxygen in my body my only option is to breath shallowly and faster. With my rapid breathing, I don't ever get the delicious sensation of a long, slow, deep breath. Instead, it feels like there is a maximum amount of expansion my chest cavity is capable of, and if I try to expand beyond that limit it will snap back like a rubber band pushed beyond its stretch capacity. The only way I've found to overcome the sensation of "air hunger" is to hold my breath, which is the exact opposite of my survival instinct. While I wait in this breathless space, I use sheer force of will to keep panic at bay.

Sometimes the way that BOS shows up in my life is more like minor inconveniences. For example, I make a high-pitched wheezing sound every single time I exhale. This makes it difficult to fall asleep at night because I both hear and feel the vibration coming from my body. When I wake up in the morning, I have the deep imprint of oxygen tubing across both cheeks, which can last for quite a while. If I have a morning event, like filming this video, I may need to wake up several hours early just to give my face a chance to regain its shape. Whethertalking casually to a friend or speaking at a formal event, I meticulously choose my words based on the length of my sentences.



Then, I can plan a breathing break where a pause would naturally fall, instead of running out of air mid-sentence and having my final words come out silently. I have also learned to pick things up with my feet to avoid the stomach compression and lack of oxygen that comes with bending and twisting from the middle. At other times, the impact of BOS is much more profound. A terminal illness shortens the timeline for accomplishing your life's legacy, while simultaneously making it nearly impossible to carry out many of the actions you want that legacy to include. After my BOS diagnosis, I attempted to combine two of my passions, dog training and volunteering, by becoming a puppy raiser with Guide Dogs for the Blind. My wife and I spent about six months getting trained to raise and train a puppy under the strict protocols that they require. All that hard work paid off, and we were the first in our training cohort to be assigned our very own puppy. Almost immediately, I realized that BOS would prevent me from completing the yearlong commitment. At less than two months old, our puppy already weighed 25 pounds. I was unable to pick him up. I struggled to get up and down from the floor with him as much as was needed. And, as we were working on leash training, it became very clear that he could easily pull me over. With great sadness we had to drop out of the volunteer program. It absolutely broke my heart that I was not able to use my time and unique skill set to meaningfully give back to my community. My wife and I did ultimately adopt an older and smaller rescue dog, and he is a well-loved member of our family. But it's not the same as being part of something larger than myself.

Living with BOS means that a percentage of my available brain space and life energy must always be spent on self-advocacy. It means that my survival is directly linked to my willingness to continuously educate myself about my condition. Twice so far, new medications have been added to my treatment regimen based on research that I have personally brought to my care team...but only after I was able to convince my insurance provider to cover them. Despite my willingness and my own self advocacy, the sad truth is that there are no treatments available to me beyond what I am already on. There are no medications on the market that have been shown to halt the progression of my disease. And there are no medications that can reverse the lung damage that has already occurred. My only hope for recovery is for new pharmaceuticals to be researched, developed, and brought to market. That is why I am sharing my story today. Thank you for listening.

## DENISE DESROBERTS

Hello! My name is Denise DesRoberts and I'm joining you today from sunny, temperate Connecticut though my home is in hot, humid, and equally sunny Florida. I'll get to that later. Before I do, I'd like to share a bit about my life with BOS.

In 2017, I had a life saving bilateral lung transplant. Post-transplantation, life was steadily improving. I was getting back to normal after experiencing end stage lung disease.

Two years after receiving the gift of life, things took a turn when I began to experience a dramatic decline. I learned that I was now experiencing Stage 3 BOS or chronic rejection. My doctor recommended I begin photopheresis right away. I started treatment just a few days later.

For 6 months, I drove nearly 2 hours each way for treatment twice a week. Then, once a week. I actually saw some improvement. Yay! But then I got the bill, \$192,000. My insurance denied coverage saying that photopheresis is not an approved treatment for BOS. Without this treatment, I'm quite sure that I wouldn't be here today. Though my lung function is less than 50% of what it once was, at least I am alive. Living in Florida in the summertime is hard for people with chronic lung conditions as the high humidity makes it difficult to breathe. Simple things like taking trash cans 40 feet to the road for trash day become a 2 part process. Prior to BOS, I used to get this chore done in about a minute. Both cans. Now, when it's humid, outdoor activities like this become difficult. Now, the process involves setting a chair outside my door. Then, I move the first can, sit to catch my breath, then tackle the second trash can. Sometimes, a neighbor will help me. I adjust. As I alluded to at the start, because the humidity is so high during summers in Florida, I have taken to spending summers in Connecticut. I'm here now. I have family here. Between my compromised immune system and COVID, I have to be extra careful. Recently, I visited my beautiful grandchildren, a two year old and a two month old I was meeting for the first time. We hugged, talked, played. Two days later, I was in the ER because I caught a virus from the 2 year old who wasn't showing symptoms when grammy came over to play. The doctors told me I had parainfluenza. When most people experience parainfluenza, it's like a cold and they get over it quickly. I suffered for over a week with lungs full of mucus, a horrible cough, and headache. I spent a night in the hospital. Before I got sick, I had an active career in real estate. I enjoyed renovating properties with my own two hands and was looking forward to renovating an apartment here in Connecticut that I own. I wanted to do most of the work myself, just as I used to do. Painting the bathroom took me over a week as I had to stop and rest about every 15 minutes. But I got it done. I had planned on putting down a laminate floor. I learned the hard way that I can't do that anymore. I will be hiring out the rest of the work. BOS has forced me to adjust my way of getting things done. One of the things I especially enjoy about my time in Connecticut is going for a long walk on the beautiful trails. Now, I just need to make sure there are benches or even fallen trees to rest at as needed. I make sure to walk with others and they just stand there and patiently wait for me while I rest. I hate making people wait but I adjust.

## CARA FAVUZZA

As you've heard today, the stories of patients impacted by BOS are as different as their underlying forms of lung disease. Me? I'm a 22 year old, recent college graduate and valedictorian living in Boston with my parents. After a short break from school, I'll be going back to pursue my accelerated nursing degree.

In 2010, I was diagnosed with BOS at age 10 after a case of mycoplasma pneumonia. Initially, the doctors thought I was experiencing an allergic reaction to augmentin. Once the pneumonia cleared and I was taken off augmentin, my strange symptoms remained. I struggled to walk up stairs without experiencing shortness of breath. I couldn't climb into my bunk bed. The mysterious symptoms puzzled my pediatrician and the allergy testing performed to dig deeper into my condition showed nothing. Eventually, the results of pulmonary function tests made it clear that a referral to a pulmonologist would be needed. The pulmonologist ultimately diagnosed me with BOS.

My experience with BOS hasn't been easy. Though I haven't required a lung transplant, I suffer from shortness of breath when talking or eating. This makes me exceedingly anxious. Can other people hear that I'm struggling to breathe? On top of that, I spent 3 years on steroids post-diagnosis. Every time my care team would stop the steroids, my lung function suffered. Steroids are not without their own side effects. Middle school is difficult enough and the anxiety caused by steroid-induced swelling and weight gain only made my experience more challenging.

After the steroids, we moved on to IVIg, a treatment I've been on for 3 years now. We say that I'm pretty high functioning at 42% FEV. My numbers are good for having a lung disease but I don't want 40% to be good. That's not what it should be. While I'm celebrating the fact that I'm not at 9%, I don't want to be happy at 40% lung function.

Despite my numbers remaining relatively stable on IVIg, I have a number of unmet needs that I'm hopeful future clinical development programs will address.

Let's start with the unmet need for support. Even though I was diagnosed over a decade ago, I only know 2 other patients with BOS and neither are local to me or each other. We stay in touch via text but a more formal means for patients to connect, learn from each other, and provide support would be very much welcome.

Additionally, I want to be confident that I won't struggle with shortness of breath while eating or talking and the anxiety these disease manifestations cause. My current therapy requires 2 days of treatment, 4.5 hours each day, every 4 weeks. That's 10 hours per month. A less time intensive, pill formulation would be ideal but I'm willing to try just about anything so long as I don't have to come off my current meds. A more patient-friendly treatment for BOS would mean less time in treatment and more time to focus on the things that matter most to me like family and my nursing program. I am a 22 year old woman, with a lot that I want to accomplish and do, and I am hopeful that new therapies on the horizon will help ensure that I have the lung function to do so.

## CARRIE GOBLE

Hi! My name is Carrie Gobble. I am a double lung transplant recipient originally transplanted due to Cystic fibrosis (CF). I'm here to share my experiences with chronic rejection or BOS having been through it twice now. I would also like to share my hope and thoughts for consideration for future treatments for BOS.

Back in 2004, I received my new lungs and was diagnosed with acute rejection 5 times within the first 18 month. I've been told by doctors that patients who experience acute rejection are more prone to chronic rejection. I'm also told that survival rates decrease and complications increase when patients experience additional health issues like contracting viruses, acid reflux, and, in my case, hypogammaglobulinemia. This means I'm unable to fight off common colds and viruses which limited potential treatment for dealing with my chronic rejection.

My first experience with BOS was back in 2011-2012 when my lung function decreased by 10%. When you experience that kind of reduction in lung function, your care team wants to uncover the root cause. Eventually, I was diagnosed with chronic rejection, a diagnosis of exclusion.

At first, I was treated with prednisone, a steroid with horrible side effects like irritability, sleep deprivation, and weight gain. Not a fun option for patients to have to endure. Then, they added Azithromycin to give my immune system a boost before revisiting the acid reflux problem to tighten my esophagus and, hopefully, reduce the amount of acid passing through my airways while asleep. Most other treatment options for chronic rejection involve admission to the hospital which presents its own host of problems—limited access to visitors, loneliness, etc. When you go home, you have to be very careful because your immune system is greatly suppressed. Suffice to say, these options aren't great and don't work particularly well.

My second experience with chronic rejection began in 2017 when I lost 20% lung function which meant I qualified for treatment with photophoresis. Photophoresis requires a catheter or some sort of access. Practically speaking, you're isolated in a treatment room and pretty much stuck there. You can't even go to the bathroom for up to 5 hours depending on what the photophoresis machine tells you you need that particular day. There are few treatment centers and insurance coverage is a mess. Medicare doesn't cover photophoresis as a treatment option for my condition and insurers often decline to pay for the therapy as it's being used for an off label purpose.

Now that I've covered current treatment options and unmet needs, let's talk about what I'd hope for in a new, more patient-friendly treatment for BOS. Whether treatment is delivered through IV, inhaled, or delivered some other way, I'd love to see less time intensive mechanisms of delivery as well as fewer treatments required or, alternatively, longer acting treatments. For example, when you start photophoresis, you begin with 1 treatment per week for 5 weeks and always 2 treatments within a 7 day period. Then, treatment spreads out to every other week. After 3 months, you move to once a month. As I mentioned earlier, treatment centers are few and far between. I know patients that have had to travel 8+ hours and find a place to stay for their course of treatment. This takes time, energy, and money, all of which are in short supply.

For these reasons, I'd urge you to carefully consider both frequency of treatment as well as treatment setting. How many facilities will be able to administer your new therapy? I've often felt like a fish in a fish tank because I'm typically tethered to a treatment room, alone, behind a curtain, with the occasional nurse popping in to check on me. This is lonely and awkward.

The other thing I want to talk about is pre-treatment. What prerequisite medications are necessary in order to take the treatment? I challenge you to think outside the box and consider not only treatment itself but pre and post-treatment as well. Consider portability. Is the treatment being developed something I can take with me when I travel to visit family? Will it limit how I'm able to live my life even more than BOS already does? We had lung transplants so we can live our lives as fully as we are able and spend more time outside the hospital. If a new treatment can be developed that focuses on quality of life and can blend into the background of our day to day, that would be amazing.

There are, of course, other logistical concerns. If a treatment is designed for home use, what are the storage requirements? How about the shelf life? If something has to stay refrigerated, that's a life-limiting factor.

The biggest things I want you to consider are treatment coverage; treatment frequency; availability; patient comfort; and treatment duration. Taking these factors into consideration at the beginning of clinical development and asking patients for their input would lead to the creation of more patient-friendly treatment options and less burdensome clinical trials.

Patients that need treatment for chronic rejection don't have many options. A common alternative to what I outlined above is no treatment at all. I know patients who choose to forego treatment because, for them, untreated chronic rejection is more appealing than all that treatment entails.

Thank you for your time and I appreciate your consideration.

## AMANDA HELDERLE

My name is Amanda. Over the years, I've had 2 lung transplants, the first a result of my Cystic fibrosis and the second caused by BOS. I'm here to share my story so you can better understand the impact of BOS, a truly devastating disease. Before we talk about that, I want to tell you a bit about me.

When I was younger, I used to live in Los Angeles, and, when I did, I got really into hiking. In fact, hiking quickly became my favorite activity. Spending time being active in nature was invigorating to my soul, especially in such a beautiful place. Arguably my favorite part of hiking was exploring new trails with my dog, Sosa, and we became intimately familiar with all the hiking areas within 20 miles of our house. After all our wonderful experiences hiking together in Southern California, we decided to move back to my hometown, St. Louis, to be closer to my brother's growing family as well as my aging parents.

Once I got back to Missouri, I continued to hike every single weekend.

On a nondescript Spring day in 2007, I was hiking as usual when I suddenly could not go any further. I was on an elevated trail I frequented and was more than a little surprised. I came to a complete stop, unable to catch my breath. It felt like my respiratory system had shut down completely and I still had to get back to my car. I was terrified. Fortunately, I was able to see my new transplant team rather quickly.

We learned that my lung function had dropped 30% from earlier in the year. All signs pointed to infection or rejection. As my lung function dropped further and the treatments for infection didn't work, my stress and anxiety grew. While the lack of oxygen and the thoughts of losing my new lungs increased, so did these new feelings of anxiety and dread. Prior to this, I had never suffered from anxiety before in my life. It felt like I was slowly dying, and I suppose, in essence, I was, as I got closer to end stage BOS. That's how I lost my first set of lungs, 3.5 years post-transplant. My only option was to be relisted for a second transplant which I did in the Summer of 2007. The anxiety and sense of doom and gloom hung over me like a black cloud. My anxiety and inability to take care of myself got so bad I had to move back in with my parents at the age of 31. I hadn't lived at home since I was 18 years old and this was especially difficult for me as I'm fiercely independent.

Though my parents were wonderful and thrilled to spend more time with me, I was angry and extremely upset about having caregivers again after so much time on my own.

I was so scared of being alone that my dad had to move out of my parents' bedroom so my mom and I could sleep together. I needed her close to help calm me when I woke up in a complete panic, too weak to retrieve my anti-anxiety drugs. Several times, my mom had to call the ambulance because the anxiety made me feel like I was dying. I did not believe the emergency workers when they told me I was experiencing an anxiety attack.. They tried teaching me to breathe deeply to calm myself. It wasn't their fault, of course, but, taking a deep breath is impossible when you have BOS. I could never calm myself and every 911 call eventually led to an ambulance ride and a 5-7 day hospital stay.

During my stays, I spent most of my time sleeping and doing breathing treatments, connected to machines that made it impossible to rest. Even eating became uncomfortable. My chronic rejection treatments weren't working. The bottom line was that my transplant doctors were trying to keep me alive until viable lungs became available. This was my life for much of 2007 and the start of 2008.

Finally, the call came for a new set of lungs on February 14, 2008, and not a moment too soon. My lung function had dropped to 18% and my situation was precarious. Though my second transplant was a success, surgery took an exceptionally long time and was made quite difficult because my body was full of scar tissue from my previous transplant.

I was fortunate that physical recovery from my second transplant was relatively swift. While my body has healed, the emotional scars of losing a set of lungs very much remain. The emotional impacts of BOS cannot be underestimated, nor can the anxiety around potentially developing BOS a second time recognizing that most lung transplant recipients acquire BOS 5 years after transplant.

## SARA KOMINSKY

When I was born with Cystic fibrosis (CF) in 1971, life expectancy was 12 years. I was 46 when a life-saving, double lung transplant became imperative. After experiencing complications post-transplant, I fought tenaciously to regain my vitality. At long last, I was able to re-engage in the activities I loved – spending quality time with my husband and two teenage daughters, volunteering, riding horses, hiking, swimming, and playing tennis. 20 months post-transplant, my health took a turn for the worse. I developed a dry cough and chest pain, was inexplicably tired, and my home spirometry numbers started plummeting.

After alternative etiologies were ruled out, it was eventually determined that I had early-onset, fast-moving BOS. My team tried a variety of conventional treatments: high dose steroids, modifications to my anti-rejection drug program, five days of anti-thymocyte globulin treatment, and a three-month course of immunotherapy. These treatments were as expensive and time-consuming as the outcomes were uncertain. They also placed a considerable amount of physical and emotional stress on my body while also testing the fortitude of my support system. But ultimately, nothing slowed the progression -- never mind halting or reversing it.

BOS both destroyed my lung function and dismantled my once dynamic lifestyle -- and then went to work on my psyche -- using pain, fatigue, and anxiety as its minions.

As BOS progressed, the pain in my back and chest became so debilitating that it limited my activities to four very basic ones – sleeping, eating, rehab, and watching TV. Sanctioned methods of control -- such as Tylenol, heating pads, or massage -- had little-or-no effect against such a potent adversary. My struggling to breathe became an agonizing reminder that I was dying, inch by inch.

On top of the pain, seemingly insurmountable exhaustion was also pervasive. Walking 20 feet to the bathroom became an endeavor unto itself and supplemental oxygen did not help. Once so strong and vibrant, I now felt useless and a burden to my loved ones. Gone were the days of running along the Adirondack trails or galloping horses cross-country. A competitor all my life, this loss of athletic self-identity was heartbreaking on a very visceral level.

Then, there was the depression, continually trying to overwhelm my natural optimism. Days that were not marked by fear and anguish about my uncertain future and that of my children -- were few and far between. I found myself in a constant state of high alert, always waiting for the next shoes to drop, trapped in a continual state of unrest.

A well-seasoned CF warrior, I had already defied the odds for nearly five decades -- was this how my narrative ended, barely two years post-transplant? It certainly wasn't what I had envisioned – and I was frustrated and angry. I had followed my Transplant Center's instructions to the letter and still developed BOS. And now, despite absolute compliance and endless hard work, my regression continued to death's door -- completely unchecked by the very best modern medicine had to offer.

Only a small percentage of lung transplant recipients qualify for a redo, and I was one of the fortunate few. A mere 29 months after receiving my first set of donor lungs, I was gifted a second pair. I was finally free from BOS, at least temporarily, and could return to “normal” -- whatever that meant. In honor of my organ donors, I competed in the Tough Ruck marathon race toting a twenty-pound pack, with commendable results. It was quite a comeback for someone who had required a walker six months earlier.

But despite my renewed physical competence and Herculean efforts to create a healthy, productive future, the specter of BOS remains omnipresent. In the lung transplant world, we are acutely conscious that it can strike without notice, leaving broken lives and families in its bitter wake. I can only hope and pray that when I come face-to-face with BOS again, treatments will have significantly evolved. Given the gross inadequacy of current therapies and the unlikelihood of a third transplant, it is improbable I will survive my next encounter. We desperately require additional research aimed toward a better understanding of BOS, the development of innovative therapies, and grounds for renewed hope.

## JOHN ROST

Hello, my name is John and I live in North Texas. I received a bilateral lung transplant in January of 2015 due to Idiopathic Pulmonary Fibrosis. My disease was likely familial as my father passed from the same thing in 2011. I am in chronic rejection and living with Bronchiolitis Obliterans Syndrome (BOS). Chronic rejection and BOS are such a chilling thought to me that I still have a hard time saying the words without reading them from text. My rejection is categorized as Stage 3, which basically means that I've lost more than 50% of my peak baseline lung function.

My transplant was a success. I woke up breathing on my own and was discharged from the hospital in 9 days. I had some early issues, the most intense being a moderate/severe acute rejection triggered by one of our common coronaviruses. After we resolved these early issues, things went very well. My post-transplant FEV-1 was averaging around 3 liters. FEV -1 is the amount of air I can forcefully blow out in 1 second and it is a test that I perform at least once a day. Over the next 18 months, we increased my FEV-1 to over 5 liters. I was exercising and training to compete in a strength competition with kettlebells and things were looking great. Then, in August 2015, I started pravastatin as a preventative for both acute and chronic rejection.

I was enjoying that 5-liter FEV-1 for about 4 months before it started to drop. In another 4 months, I was back down to 3 liters. This decrease in lung function triggered conversations about chronic rejection and I started taking Azithromycin for BOS in December of 2016.

During a 4-day hospital stay several months later, we found that I had, and this is a quote, “Gastroesophageal reflux to the level of the clavicles noted in the supine position”. A follow up bronchoscopy found stomach fluids in my lungs. This meant I would either go on a feeding tube or receive a Nissen Fundoplication. The Nissen was performed in May of 2017 and my BOS stabilized for nearly a year before my lung function started dropping again. We decided to get more aggressive in treating my BOS and I underwent a Thymoglobulin treatment in April of 2018.

Thinking about it now, Thymo would be a very scary proposition in the era of COVID as it knocked my CD3/CD4 T-Cells down to <25. As a point of reference, my CD3 started at 2234. Fortunately, my treatment was early enough in the year that I could recover some immune system function before the cold and flu season started.

The Thymoglobulin stabilized my rejection for about a year before something triggered my BOS and my lung function started slowly dropping once again. At this point, my transplant team recommended Extracorporeal Photopheresis (ECP), but the procedure was denied by Medicare. As ECP was the only treatment left to try, this was a big disappointment. It was even more disappointing since CMS had published Medicare documents recommending ECP for BOS as early as 2011.

Towards the end of 2019, our hospital began participating in a Medicare-sponsored ECP clinical trial and I was the second patient to start the treatment. After one year, my FEV-1 had increased to 2.1 liters, higher than it had been for the two previous years. This meant hope, not just for me and my family, but for all lung transplant recipients and even candidates who read about and study post-transplant issues and mortality.

The treatment protocol has improved several times during my treatment and is now much easier on my body. The primary side effect I experienced, and one that has been resolved by protocol changes, was a pulmonary embolism that sent me to the ICU with a catheter in my neck. I am currently on the maintenance stage of this treatment which means that I go in for treatment once a month. The treatment consists of two days of apheresis, and I usually do them on a Wednesday and Thursday. I chose these days so if there is an issue on Friday, I can go into the clinic and be seen and maybe avoid a trip to the ER.

My lung function has dropped a bit of late and I do have some concern that I have triggered chronic rejection once again. I contracted COVID last September and spent 10 days in the hospital. Recovering from COVID and getting my meds stabilized triggered an acute rejection in December. My current average daily FEV-1 is now below 2 liters.

Looking to the future, we need more effective and less invasive treatments to preferably prevent, and if not prevent, treat all chronic rejections. Treatments that can be started earlier by identifying chronic rejection in very early stages will allow future patients to maintain higher lung function and quality of life for much longer. I've been asked about what the ideal treatment would look like. To me the ideal treatment would be similar to Azithromycin, a small pill or inhaler that is easy to take, has minimal side effects, and makes a noticeable improvement in lung function.

Thanks for giving me the time to share a bit of what living with BOS is like. I am very blessed in finding a treatment that has helped me, many others have not been so fortunate.

## JEN WEBER

When I was first diagnosed with Bronchiolitis Obliterans Syndrome (BOS) about 2.5 years after my second double lung transplant, I thought my life was about to end. I believed this because I'd experienced a very swift rejection episode 2.5 years after my first double lung transplant. My first rejection episode kicked off a lengthy ICU odyssey, on a ventilator with a tracheostomy, that lasted over 6 months until my retransplant. I didn't believe with this BOS diagnosis that there would be another way forward.

I am glad I was wrong.

When I received my BOS diagnosis, I was still working full-time, leading an active lifestyle of traveling, volunteering in my community, and spending time with my family and friends. I was, however, steadily losing lung function and had experienced a few episodes of acute rejection prior to this diagnosis. I was born with Cystic fibrosis (CF) which caused my original double lung transplant and I was no stranger to living with chronic lung disease. What was different with BOS was the unpredictable nature of it. With CF, I had largely understood the progressive nature and had a strict daily treatment regimen. With lung transplant and subsequent BOS, it was much more unpredictable and I had to get comfortable living with uncertainty.

With BOS there is no typical day. I could take the same medications every day, and some days experience extreme breathlessness no matter what. My daily treatment regimen for BOS includes twice-a-day anti-rejection medication and various meds to combat immune suppression, (which is in excess of 20 pills), two inhalers, along with using supplemental oxygen. I had to learn to manage unpredictable breathlessness and coughing from things like taking a shower and climbing steps, and constantly monitoring my blood oxygen saturations with strenuous activities. Keeping in regular contact with my medical teams any time something is "off" or not at my baseline was another adjustment, as I learned it was critical to catch any virus or infection early, or ensure my BOS had not caused further lung disease progression. Never knowing when feeling poorly was just a bad day or a temporary setback, rather than a warning sign of something worse ahead was probably the most challenging part of learning to living with BOS/chronic lung rejection.

Despite this I still tried to control as much of my prognosis as I could. I educated myself on the limited treatment options, remained as active as possible, and even resumed pulmonary rehab when my lung function continued to drop. I also focused on nutrition and maintaining my weight, both difficult when you have CF. Continuing to pursue aggressive treatment options like photopheresis and antirejection therapies helped me feel like I was leaving no stone unturned in my fight to retain my lung function and quality of life.

I have been forced to make accommodations, just as any person might in the face of a major health issue. I had to give up my full time profession, practicing law, 2.5 years ago, which was difficult for me. Still, I've been able to navigate life with BOS, an undeniably life-altering experience, by refocusing on my health and pursuing interests outside of my previous profession.

While there is still just as much uncertainty as the day I was diagnosed, I don't fear the future so much as trust that I'll face it the same way I face the obstacles of today.

Life with BOS is hard. In addition, I also still have CF and its complications, diabetes and pancreatic insufficiency chief among them. Some weeks all I do is go to lab visits and doctors appointments, juggling lengthy photopheresis treatments, transfusions, and consults with specialist for a variety of organ systems affected by the aggressive medications I take to control my chronic rejection.

Several of these medications have side effects that sometimes cause chronic pain, chronic kidney disease, and chronic nausea which make it near impossible to eat. My lungs retain carbon dioxide and I can't sleep without using a non-invasive ventilator to help alleviate crushing headaches. When I travel, I bring oxygen, my non-invasive ventilator, and enough medication to get through the week. This often makes my luggage look like a mini-hospital. And don't get me started on the complex insurance and billing processes that often involve hours on the phone, sorting out pre-authorizations and correcting medical codes and what pharmacies are the correct providers for which meds. The stamina and organization required to manage meds and treatments convince me I am stronger than I think most days, and my life itself is like running a Fortune 500 company!

Despite the hard times and continued uncertainty, I live with optimism because while BOS needs further research, treatment and understanding, I'm grateful that my medical teams have worked together with me to keep my gifted lungs working to the best of their ability. I once read, "You can't deny the diagnosis, but you can challenge the verdict" and that is how I intend to continue pushing back against my BOS. Thanks for listening to my story.

## Appendix 4

### Testimonies submitted by email

#### TOM NATE

Hello! My name is Tom Nate and I'm the President of Second Wind Lung Transplant Association as well as a two-time double lung transplant survivor. I'm 67 years old and, as you might have guessed, not exactly an ideal candidate for a third double lung transplant.

As a child, I was diagnosed with Kartagener's Syndrome and bronchiectasis. In May 2007, I received my first bilateral lung transplant. Surgery took nearly 14 hours and my wife was told to prepare for the worst. My new lungs kept filling with blood and I required a heart-lung machine just to stay alive. 12 months, 2 bronchoscopies, and a 20% reduction in FEV1 later, chronic rejection was confirmed.

After experiencing another 20% reduction in lung function, I began photophoresis in July 2008. Since ECP is used off-label for the treatment of lung transplant rejection, it isn't covered by insurance. My pulmonologist had to fight the insurance company while my FEV1 dropped another 10%. It quickly became clear that I needed a second transplant. I was healthy enough to do well but there was <1% chance of finding a match.

At the time, my son was 4 years old and my wife was exhausted from my first transplant. I had to decide whether a second go around would be worth my son having a fighting chance of having a father to help raise him. In September 2008, I went on the list for a second transplant.

Several months later, I woke up unable to breathe and was rushed to the hospital. The pulmonologist told me I had 2 weeks to live and I went into cardiac arrest and organ failure that very night. My body was swollen from kidney failure and I was unable to talk due to a deep tracheostomy. I didn't wake up for 3 weeks.

Once I regained consciousness, my wife focused on raising our son while I focused on my own care. On top of having to suction mucus from my lungs 3x-4x/daily, I was able to convince the hospital to let me serve as the test case for use of a portable ventilator. I had a ventilator for the apartment and a separate ventilator for my scooter. I learned to talk through an electrolarynx. I learned to become attuned to how my body was feeling so I could catch issues before they spiraled out of control.

In September 2010, I learned that I was a perfect match for a bilateral lung transplant from a young, male donor. The doctor cautioned me that I was a high risk patient and my second bilateral transplant would likely be more challenging than the first. Instead, the second surgery only took 6 hours and I was able to raise my arms, wave, get out of bed, and walk the very next morning. My surgeon said, "Tom, you've been through hell. Don't go home and live in a bubble." We know you went through a lot between BOS and your two bilateral transplants. What would a new therapy that could ensure patients don't have to go through a similar hell mean and what would this therapy look like?

## CHERYL KEELER

I was recently diagnosed with BOS. On August 3rd, I had 17 and a half years post transplant. My transplant date is February 3, 2005. That is certainly a long time. My doctor, Dr. Marie Budev (Director of the Heart Lung Transplant Center at Cleveland Clinic) said she would have been surprised if I didn't have BOS. I have nodules as follows: 2 in my lungs, several in my stomach and several in my large colon. CCF is starting with my colon. I'm having a colonoscopy on September 12th then we will go from there. I believe they are looking for cancer. Some of you may remember my name. I was Vice President of Second Wind for about 6 years and President of Second Wind for 5 years. It was a great pleasure serving on the Board and interacting with all of you for years. I think it was 2018 when I was in ICU for about a month in Cleveland because I couldn't breathe. It was a really difficult time and I resigned from the Board then. I remember one of our Board Members had BOS for ten years and lived her life as best she could. She was an inspiration to all of us. I hope you are all living life to the fullest. Bless you.



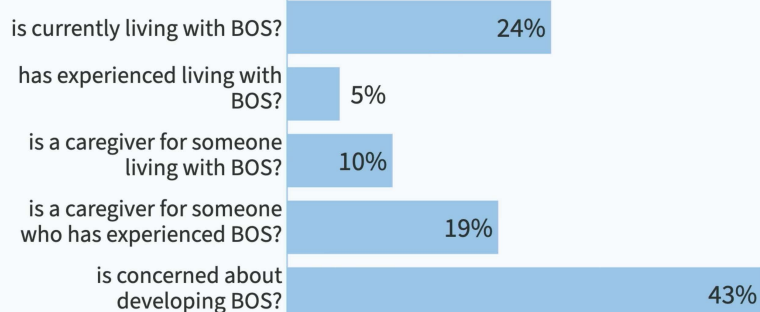
## APPENDIX 5

### LIVE POLLING QUESTIONS

#### POLLING QUESTION 1

Are you a person living who: Is currently living with BOS? Has experienced living with BOS? Is a caregiver/care partner for someone living with BOS? Is a caregiver/care partner for someone who has experienced BOS? Are you someone who is concerned about developing BOS?

##### 1. Are you a person who:



#### POLLING QUESTION 2

How do you identify? Female, male, non-binary, or maybe you prefer not to answer. Again, we want to get a sense for who we have in the audience

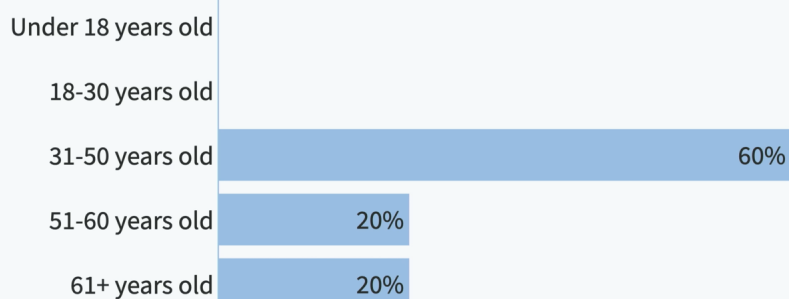
##### 2. How do you identify?



#### POLLING QUESTION 3

For patients and caregivers in the audience, how old are you? We have categories to select from under 18 years old, 18-30 years old, 31-50 years old, 51-60 years old or over 60 years old.

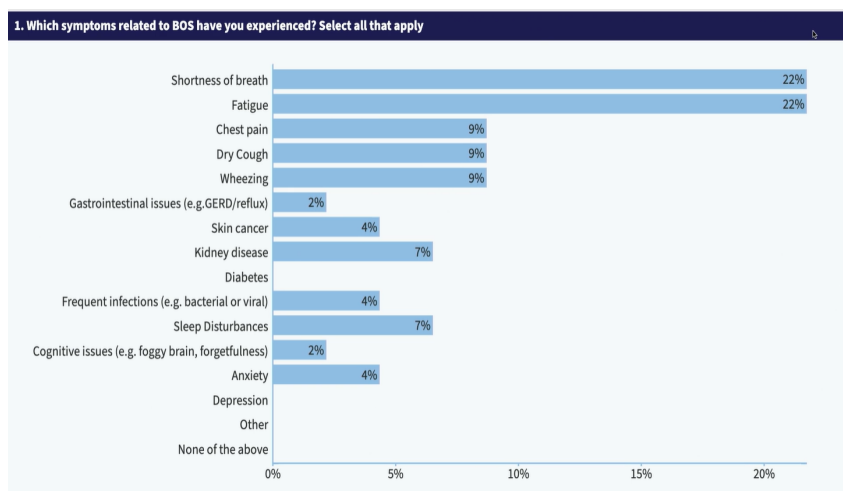
##### 3. How old are you?



## TOPIC 1 POLLING QUESTIONS

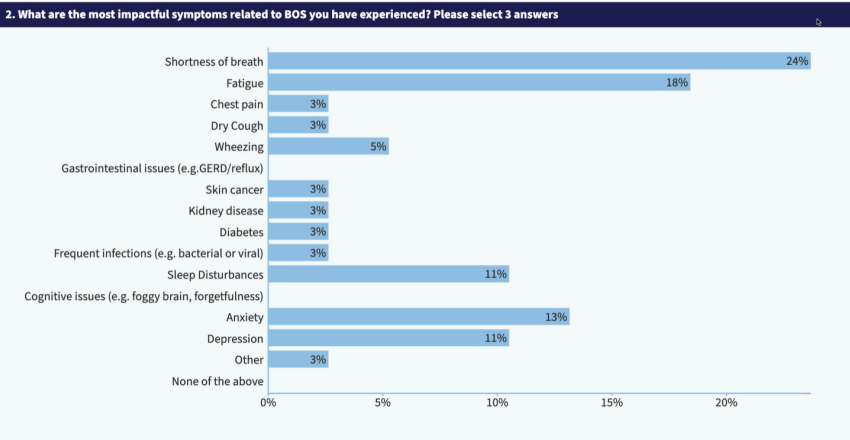
1. Which symptoms related to BOS have you experienced? Please select all that apply.  
The symptoms listed for you to choose from are:

- Shortness of breath,
- Fatigue,
- Chest pain,
- Dry Cough,
- Wheezing,
- Gastrointestinal issues (e.g. GERD/reflux),
- Skin cancer,
- Kidney disease,
- Frequent infections (e.g. bacterial or viral),
- Sleep Disturbances,
- Cognitive issues (e.g. foggy brain, forgetfulness),
- Anxiety,
- Depression or
- Other if you have experienced another symptom, not listed here, you can select, or
- None of the Above, if you have not experienced any symptoms.

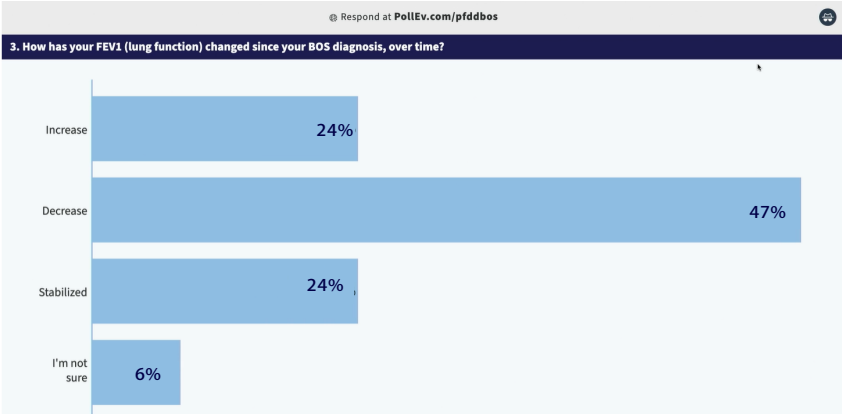


# TOPIC 1 POLLING QUESTIONS

2. What are the most impactful symptoms related to BOS you have experienced? Here, we would like you to select the 3 symptoms you consider most burdensome or have impacted you the most. The answer choices are the same as the previous poll.



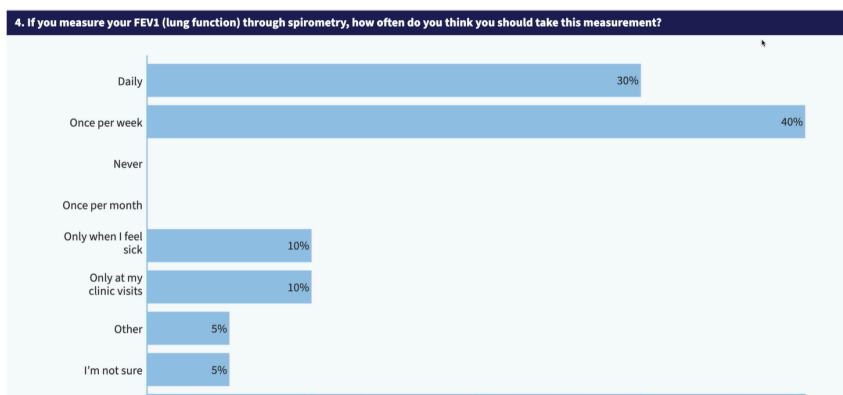
3. How has your FEV1 (lung function) changed since your BOS diagnosis, over time? Have you experienced an increase in lung function or your FEV1, or a decrease? Has your lung function stabilized? Or are you unsure?



## TOPIC 1 POLLING QUESTIONS

4. If you measure your FEV1 (lung function) through spirometry, how often do you think you should take this measurement? You can choose from the following:

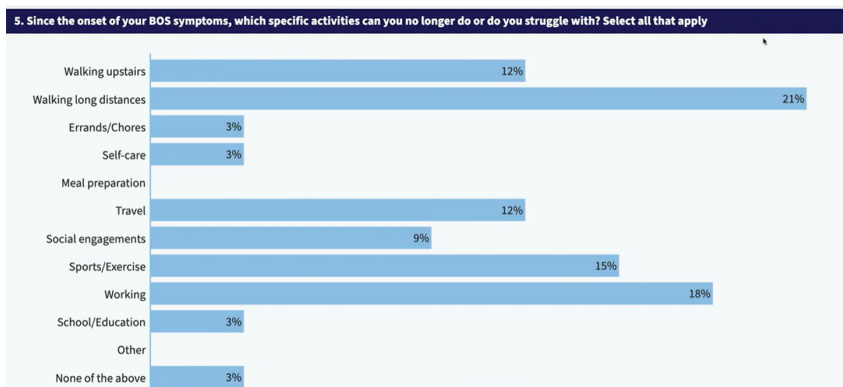
- Never,
- Daily,
- Once per week,
- Once per month,
- Only when you feel ill or sick, or
- Only at your clinic visits?
- Other if you think your lung function should be measured at some other time interval, or if you are unsure and you can see this is an answer option as well.



## TOPIC 1 POLLING QUESTIONS

5. Since the onset of your BOS symptoms, which specific activities can you no longer do or do you struggle with? Here, you can select all that apply. The answer options listed are

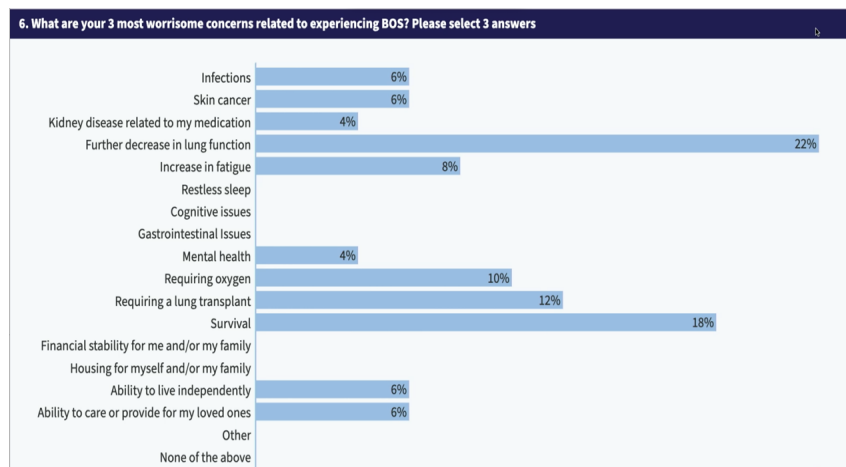
- Walking upstairs,
- Walking long distances,
- Errands or Chores,
- Self-care,
- Meal preparation,
- Travel,
- Social engagements,
- Sports/Exercise,
- Working,
- School/Education,
- Other,
- None of the Above.



## TOPIC 1 POLLING QUESTIONS

6. What are your 3 most worrisome concerns related to experiencing BOS? Please select up to 3. The answer options listed are:

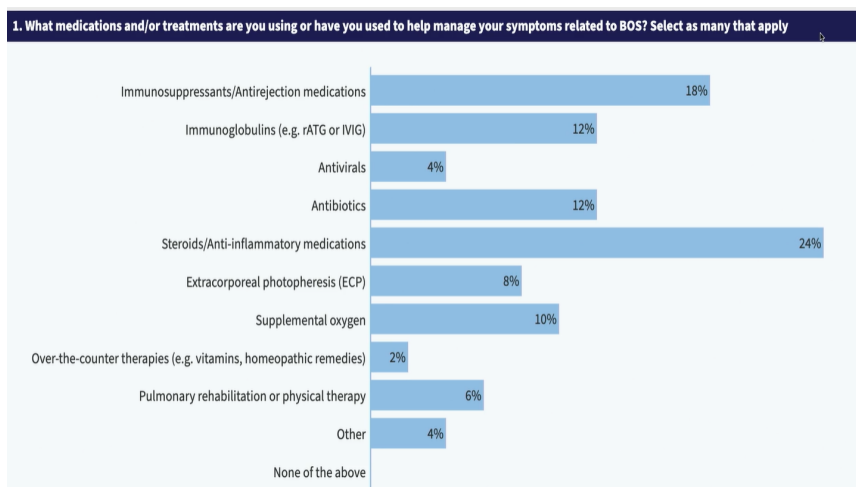
- Infections,
- Skin cancer,
- kidney disease related to your medication,
- Further decrease in lung function,
- Increase in fatigue,
- Restless sleep,
- Cognitive issues,
- Gastrointestinal issues,
- Mental health,
- Requiring oxygen,
- Requiring a lung transplant due to BOS,
- Survival,
- Financial stability for you or your family,
- Housing for you or your family,
- The ability to live independently,
- Your ability to care or provide for your loved ones, or
- Other if there are other concerns not listed here or
- None of the above, if none of these are concerning to you.



## TOPIC 2 POLLING QUESTIONS

1. Our first polling question asks what medications and/or treatments are you using or have you used to help manage your symptoms related to BOS? We want you to select as many that apply from the options listed. Do you take:

- Immunosuppressants or
- Anti Rejection medications,
- Antivirals,
- Antibiotics,
- Steroids/Anti-inflammatory medications,
- Extracorporeal photopheresis (ECP),
- Supplemental oxygen,
- Over-the-counter therapies (e.g. vitamins, homeopathic remedies)?
- Is pulmonary rehabilitation or physical therapy part of your treatment plan?
- Other, if you have taken or used another treatment, you can select 'Other' or
- None of the Above if you are not taking any medication.

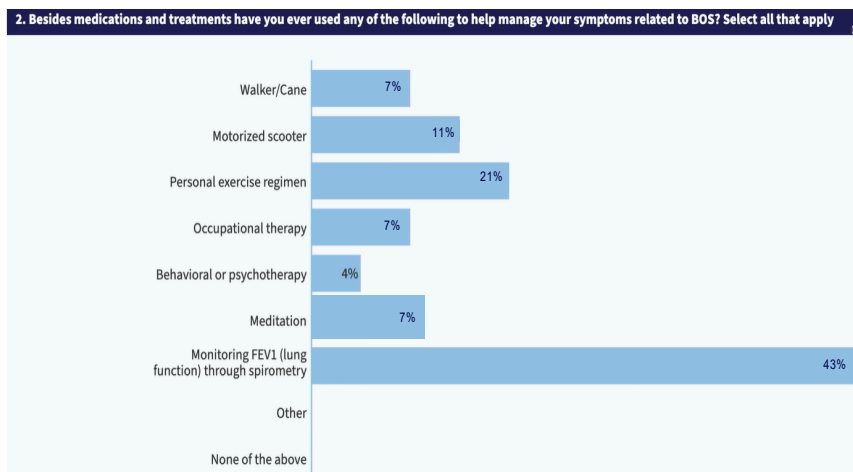


## TOPIC 2 POLLING QUESTIONS

2. Besides medications and treatments have you ever used any of the following to help manage your symptoms related to BOS? Here we ask you to select all that apply.

Have you used a:

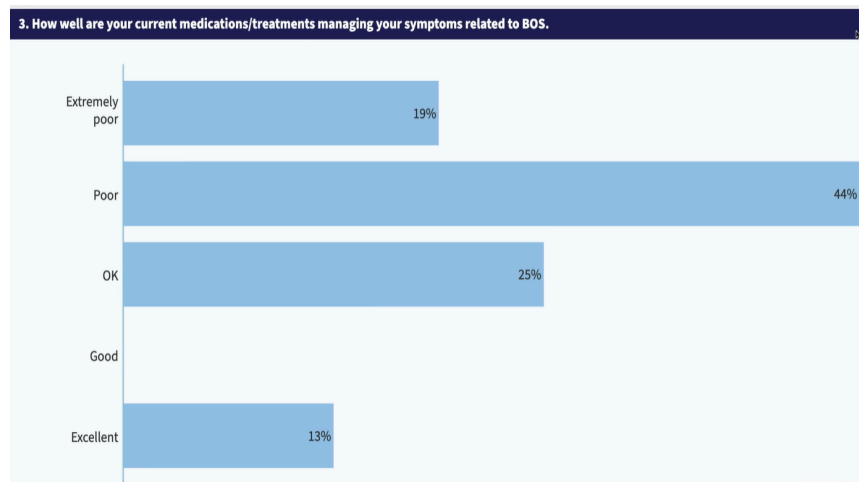
- Walker or a cane,
- Motorized scooter,
- Personal exercise regimen,
- Occupational therapy,
- Behavioral or psychotherapy,
- Meditation,
- Monitoring FEV1 (lung function) through spirometry,
- Other, for any other medications or treatments or
- None of the above might apply to you.



## TOPIC 2 POLLING QUESTIONS

3. How you think these treatments are working. How well are your current medication(s)/treatment(s) managing your symptoms related to BOS. We want to know what you think.

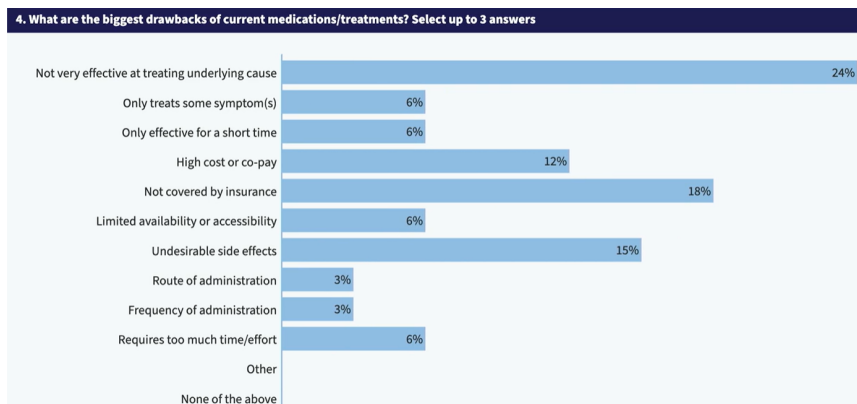
- Extremely poor,
- Poor,
- OK,
- Good or
- Excellent



## TOPIC 2 POLLING QUESTIONS

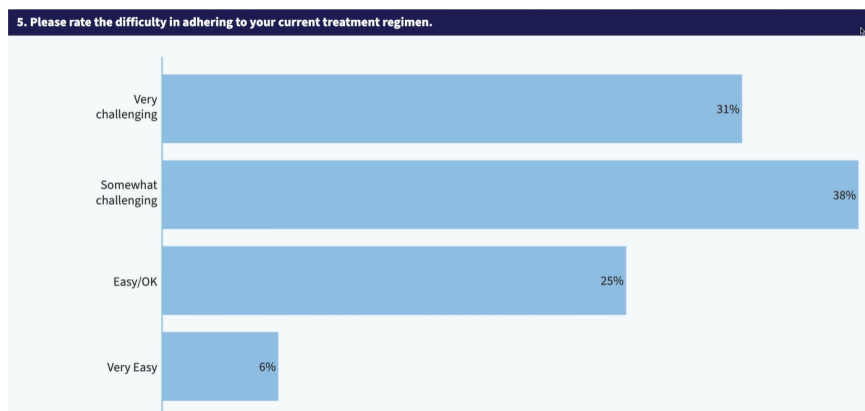
4. What are the biggest drawbacks of current medications/treatments? For this question we are asking you to select up to 3 answers. Which of the following options do you feel are the biggest downside or drawback to your medications?

- Not very effective at treating the underlying cause,
- Only treat some symptoms, or are they only effective for a short time?
- Do they cost a lot or have a high co-pay, or
- They are not covered by your health insurance or
- Have limited access or availability?
- Undesirable side effects,
- The route of administration, or
- The frequency of administration.
- Too much time or effort.
- Other, if you have another answer, or
- None of the above if that applies to you.



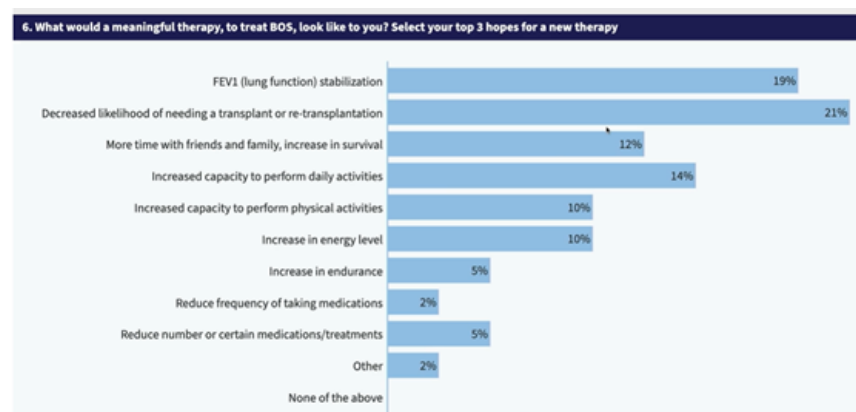
## TOPIC 2 POLLING QUESTIONS

5. Please rate the difficulty in adhering to your current treatment regimen. Do you feel it is very challenging, somewhat challenging, easy or OK, or very easy?



6. What would a meaningful therapy, to treat BOS, look like to you? Select your top 3 hopes for a new therapy. The options listed are:

- FEV1 (lung function) stabilization,
- Decreased likelihood of needing a transplant or re-transplantation,
- More time with friends and family,
- increase in survival,
- Increased capacity to perform daily activities,
- Increased capacity to perform physical activities,
- Increase in energy level, Increase in endurance,
- Reduce frequency of taking medications,
- Reduce number or certain medications/treatments,
- Other, or
- None of the above.



## Appendix 6

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