Despite evidence and consensus across international guidelines (2) that patients who have experienced an acute exacerbation of chronic obstructive pulmonary disease (AECOPD) should participate in pulmonary rehabilitation (PR) within 4 weeks after hospital discharge, the uptake of this treatment remains low (3). This is of concern, as PR has been shown to improve dyspnea, quality of life, and exercise capacity, and reduces hospital readmissions among patients with AECOPD (2). The authors rightly indicate that to date, very few studies have investigated the effects of interventions that aim to increase uptake of PR after an AECOPD (4). None of the existing published studies used a randomized controlled trial (RCT) design.

Barker and colleagues conducted an RCT to investigate the effects of an intervention, an educational video about PR, as an adjunct to usual care (1). Their primary outcome was uptake of PR within 28 days of hospital discharge. They concluded that a video delivered at hospital discharge did not improve uptake of PR. Although their RCT was well conducted, it does not appear that the authors applied behavioral theory to guide the key messages included in the video, nor was there a progressive and systematic framework guiding the development of their behavior-change intervention as suggested by the Obesity-related Behavioral Intervention Trials (ORBIT) model (5). The ORBIT model encourages investigators to complete a series of studies to define and refine the intervention (phase I) and to preliminarily test it (phase II) before conducting efficacy (phase III) and effectiveness (phase IV) trials, akin to the usual practice of pharmaceutical studies. These suggested steps for behavioral intervention development ensure that the treatment package includes essential components offered in an efficient way and, importantly, helps to ensure a clinically significant effect on the behavioral risk factor (5). Although this process can be long and laborious, it is a critical step to prevent a potential waste of resources—for example, by conducting a large RCT for a treatment that cannot impact the target clinical outcomes (5).

It seems that Barker and colleagues designed their RCT before they determined whether their video intervention included the essential components (e.g., a motivational communication style and the optimal frequency, duration, and timing of contacts to show the video). The video was only shown once at hospital discharge, a time that can be very overwhelming for patients and family members, and thus is not the best time to make such a decision (6). Indeed, 6 out of the 15 participants interviewed did not recall even watching the video at hospital discharge. Furthermore, at the outset of the RCT, the potential effect on behavioral risk factors (such as knowledge about PR, and self-efficacy/readiness for commencing PR) was not known, as no preliminary testing of these important mediate outcomes was performed. Finally, the rationale for their secondary outcomes is not clear. It is unlikely that an educational video shown once at hospital discharge would have an impact on PR completion rates and adherence, physical performance, or health-related quality of life.

The present study by Barker and colleagues addresses a very important question and was well conducted for an RCT. However, if the authors had used a theoretical framework such as the ORBIT model, they would have had the opportunity to strengthen their behavioral intervention and make it as effective as possible before conducting an RCT. It is important to emphasize the value of using a systematic, phased approach to develop a behavioral treatment before testing it in rigorous effectiveness trials.
posthospitalization pulmonary rehabilitation. They make some salient points and we appreciate the opportunity to respond.

Janaudis-Ferreira and colleagues emphasize the importance of a progressive and systematic framework to guide the development of an intervention, citing the Obesity-related Behavioral Intervention Trials (ORBIT) model developed by the NIH. In particular, they express concern that we paid insufficient attention to the development of the intervention before we conducted a randomized controlled trial.

Our team included experienced mixed-methods, qualitative, and implementation science researchers, as well as a patient and public involvement group. For details regarding the development of the intervention, we refer readers to the online supplement of our work (1). In summary, we used a methodology known as experience-based codesign (EBCD), which provides a framework whereby stakeholders (primarily patients and staff) can feel empowered and work together to improve experiences for patients and their families, as well as staff.

For those unfamiliar with EBCD, there are parallels to the ORBIT model and other frameworks for developing complex interventions. Following our original observation that there were low referral and uptake rates (2) for posthospitalization pulmonary rehabilitation even though it is an evidence-based and highly effective intervention (3), we conducted video-recorded qualitative interviews with patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease (COPD) and the hospital healthcare staff responsible for their care. Patients reported that little information about pulmonary rehabilitation was provided at the time of hospital discharge. Members of the healthcare staff described having limited personal knowledge about and experience with pulmonary rehabilitation and noted that time pressure was a barrier to providing information to patients. Clips from these videos, illustrating the key themes and experiences (known as “touch-points”), were subsequently combined and edited to produce a touch-points video. This edited video was then played at three key stakeholder feedback events: one for patients, one for healthcare professionals, and one for both patients and healthcare professionals. The priority that resulted from these stakeholder events was to develop an education package that would allow previous patients to tell prospective patients about the benefits of pulmonary rehabilitation in a visual manner that could be delivered without significantly affecting staff time. Codesign meetings were held to develop the intervention (creation and filming of the video) and to determine how and at which point in the patient pathway it would be delivered.

A feasibility study was conducted to compare delivery of the video via tablet computer with delivery of the video via patient bedside television systems. The latter was not taken forward owing to patients’ difficulties with accessing the video and the nonuniversal availability of bedside systems. During the feasibility study, both patients and staff found the video delivered by the tablet video to be acceptable and feasible, and we were able to estimate likely recruitment rates and the feasibility of the outcome measures. We also refined the delivery of the intervention to keep researchers blinded to treatment allocation. The development of the intervention and conduct of the feasibility study occurred between 2011 and 2015, equivalent to phases 1 and 2 of the ORBIT methodology. Our recently published randomized controlled trial (1) is the equivalent of ORBIT phase 3 (conducting an efficacy trial).

Janaudis-Ferreira and colleagues speculate that if we had used the ORBIT model to develop the intervention, we would have had the opportunity to strengthen the behavioral component of the intervention with a view to making it more effective. As we acknowledged in our paper, there were several reasons why the video may have not had an adjunctive effect over standard care (delivery of a COPD discharge bundle), including the lack of an added counseling element. However, during the EBCD process, stakeholders (patients and staff) appreciated that a priority for the intervention was that it should be low cost (with staff time being the most expensive component of behavioral interventions) and easily implementable.

We note recent work from the team of Drs. Bourbeau and Janaudis-Ferriera in which they tested a pulmonary rehabilitation taster session for patients hospitalized with acute exacerbation of COPD (4). Although they used the ORBIT methodology, the intervention they developed was only acceptable to six out of 31 patients (19%) (4). Furthermore, they largely used a quantitative approach to assess the feasibility, acceptability, and safety of their intervention. We propose that had Janaudis-Ferriera and colleagues incorporated a qualitative methodology such as EBCD (which empowers patients and other stakeholders to codesign an intervention), they might have produced a more patient-friendly and feasible intervention that could be evaluated in an efficacy trial.
Two-edged Sword?

Treatment of Drug-Resistant Tuberculosis: A
ATS/CDC/ERS/IDSA Clinical Practice Guidelines for
Treatment of Drug-Resistant Tuberculosis: A
Two-edged Sword?

To the Editor:

On the basis of individual patient data (IPD) meta-analysis of observational studies (1), the World Health Organization released the consolidated guidelines on drug-resistant tuberculosis (TB) treatment in 2019 (2). Shortly afterward, using a data set modified from the aforementioned IPD, the American Thoracic Society (ATS)/CDC/European Respiratory Society (ERS)/Infectious Diseases Society of America (IDSA) published their official clinical practice guidelines for the treatment of drug-resistant TB (3). The ATS/CDC/ERS/IDSA have recommended the use of linezolid and bedaquiline to treat all patients with multidrug-resistant TB (MDR-TB), regardless of the drug-susceptibility testing results. Although the present guidelines have substantiated the role of linezolid and bedaquiline in the treatment of fluoroquinolone-resistant MDR-TB, the IPD meta-analysis findings might have been overextrapolated (4), with findings regarding the use of linezolid and bedaquiline for the management of fluoroquinolone-resistant MDR-TB applied to fluoroquinolone-susceptible MDR-TB. Retrospective analysis of linezolid in better-defined cohorts with MDR-TB have suggested that linezolid would be useful largely in the treatment of more complicated MDR-TB (5). Whether adding bedaquiline to fluoroquinolone would improve treatment outcomes of fluoroquinolone-susceptible MDR-TB is still being evaluated in stage 2 of the STREAM (Evaluation of a Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with Multidrug-Resistant Tuberculosis) trial. Furthermore, selection bias and inadequate control of confounding in the IPD meta-analysis might have yielded some findings that cannot be readily explained on a biologically plausible basis. Although the ATS/CDC/ERS/IDSA have explicitly stated that their guidelines were based on evidence of very low certainty (3), their categorical recommendation regarding use of linezolid and bedaquiline may pose a two-edged sword for TB control programs worldwide.

Intuitively, the pros of including linezolid and bedaquiline in a standard regimen for all types of MDR-TB may be greater simplicity for programmatic implementation and lesser need for drug-susceptibility testing. However, the major cons probably lie in the concern for patient safety and tolerance, especially when the standard regimen in universally applied to many patients with MDR-TB worldwide. The first global report of surveillance of adverse events in the treatment of drug-resistant TB has suggested a substantial risk of serious adverse events related to the use of linezolid and, possibly, bedaquiline (6). The underlying mechanism, clinical impact, and optimal monitoring of some potentially serious toxicities, such as those pertaining to the cardiovascular and neurological systems, are not yet fully understood. Furthermore, the expertise and resources required for monitoring such adverse drug reactions likely overwhelm capacity in a large number of MDR-TB programs with high disease burdens, particularly when comorbidities such as diabetes mellitus and HIV infection prevail. It cannot be overemphasized that suboptimal management of drug toxicities significantly contributes to poor treatment adherence and eventually contributes to unfavorable treatment outcomes.

Linezolid resistance is now mounting in many parts of the world. Rapid emergence of resistance against bedaquiline would be formidable for global TB control. Use of linezolid and bedaquiline in selected patients with MDR-TB may facilitate the optimal use of resources in a programmatic setting for management of drug adverse reactions and curtailment of drug resistance.

Directly observed treatment in the holistic patient care package likely contributed to the high treatment success rates of optimized background regimens in Trial 213 (7) and in the STREAM trial (8). With advances in rapid detection of drug resistance, optimized background regimens or shorter World Health Organization MDR-TB regimens may still have a place in the programmatic treatment of fluoroquinolone-susceptible MDR-TB in some parts of the world (8), at least currently.

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