In response to Schulz, we used risk factors for severe Covid-19 illness as defined by the Centers for Disease Control and Prevention. Severe illness included but was not limited to death. These patient characteristics do imply a risk for hospitalization, as evidenced by the 158 of 511 patients (30.9%) who reached the primary outcome — a rate much higher than the rates in other trials involving outpatients with Covid-19.

We agree that more study is required regarding the treatment of immunodeficient patients, including those with cancer. There remain many questions regarding dosing, pharmacokinetics, and patient selection that cannot be addressed in a single trial investigating the use of convalescent plasma in one particular outpatient population with Covid-19.

Finally, we are in the process of analyzing both baseline and subsequent antibody levels in the trial participants over 30 days. We hope that the trajectories of the antibody responses in individual patients will provide insight into disease progression and will help in the design of future studies.

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Since publication of their article, the authors report no further potential conflict of interest.

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Triple Therapy for Cystic Fibrosis Phe508del–Gating and –Residual Function Genotypes

TO THE EDITOR: Given that the minimal clinically important difference in the percentage of predicted forced expiratory volume in 1 second (FEV₁) is considered to be 5 percentage points, the between-group difference of 3.5 percentage points in the percentage of predicted FEV₁ with elexacaftor–tezacaftor–ivacaftor, as compared with active control treatment, that is reported by Barry et al. (Aug. 26 issue) is unlikely to be clinically relevant. Changes of this magnitude, reported in previous studies, have aroused questions regarding whether the efficacy of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies may be considered to be suboptimal. This hypothesis is supported by the finding that cystic fibrosis modulator therapy may have only a small effect on the need for therapies to address symptoms.

Against the background of modest therapeutic benefit and very high drug acquisition costs, it is not surprising that CFTR modulator therapies have been found not to be cost-effective. A colleague and I have found incremental cost-effectiveness ratios of approximately €400,000 ($460,000) per quality-adjusted life-year for ivacaftor and lumacaftor plus ivacaftor. The reality is that CFTR modulator therapy frequently offers poor value for the money and a very high opportunity cost of millions of dollars per year.

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THE AUTHORS REPLY: Patients with cystic fibrosis heterozygous for the Phe508del mutation and a gating or residual function mutation who were treated with elexacaftor–tezacaftor–ivacaftor had lung-function improvement on top of standard care that included effective CFTR modulators. There is no generally accepted minimal clinically important difference for lung-function improvement in patients with cystic fibrosis. Because cystic fibrosis is characterized by progressive loss of lung function, even maintenance of lung function is a treatment goal. Previous CFTR modulator regimens yielding similar magnitudes of improvement in lung function have been associated with clinically meaningful improvements in rates of change in lung function, pulmonary exacerbations, and hospitalizations.

Whether estimates of quality-adjusted life-years can truly capture the systemic value of CFTR modulator therapy is debatable. With elexacaftor–tezacaftor–ivacaftor therapy, additional benefits are likely to be based on the degree of decrease in the sweat chloride concentration, a clear indicator that the basic defect has been addressed. A large natural history study of sweat chloride showed that concentrations in the range observed in response to elexacaftor–tezacaftor–ivacaftor therapy were associated with markedly lower risks of death, hospitalization, and complications.

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3. Cystic Fibrosis Foundation. CF Foundation leaders provide expertise during ICER public meeting. 2020 (https://www.cff.org/node/826).

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The authors reply:

Since publication of their article, the authors report no further possible conflict of interest.