compared between groups, and in the event of baseline differences, we specified criteria for including variables as covariates in the outcome analyses (briefly, variables needed to differ significantly and be correlated with outcome). Of the prespecified variables, NAVIGATE participants differed significantly from community care participants on four measures. NAVIGATE had significantly more males (77.6% compared with 66.2%; $p=0.05$); NAVIGATE had a smaller proportion of participants with prior hospitalization (76.3% compared with 81.6%; $p<0.05$); NAVIGATE participants had worse total scores on the Positive and Negative Syndrome Scale ($p<0.02$); and NAVIGATE had fewer participants attending school at baseline (16.0% compared with 26.0%; $p<0.02$). Three out of the four differences would suggest a worse prognosis in the experimental NAVIGATE group, contrary to Dr. Amos's contention of a worse prognosis among community care participants. Table 2 of the article shows which variables met the statistical analysis plan criteria for inclusion as a covariate in each analysis.

Furthermore, we do not agree with the additional suggestion that differences in the number of potential participants screened at NAVIGATE sites and at community care sites resulted in selection bias. Screening results can vary between community sites for any number of reasons, including different referral patterns or the personalities of the screeners. However, consistent and systematic application of inclusion and exclusion criteria is key. RAISE-ETP utilized a cadre of well-trained clinical professionals who were blinded to site and cluster assignment in order to select participants on the basis of standardized diagnostic and assessment interviews. As noted above, this strategy minimized potentially confounding differences between treatment and control groups. In addition, for clustered randomization at site level, we used site-level random effects to account for any potentially unmeasured differences between the two treatments.

Regarding the duration of untreated psychosis, as Dr. Amos suggests, our study sample size was chosen based upon power to detect differences across conditions in quality of life and not in duration of untreated psychosis.

As Dr. Amos noted, the difference in mean duration of untreated psychosis between conditions was small in comparison with the standard deviations in this measure. Unlike Dr. Amos, we believe that the selection of statistical tests was appropriate. These analyses showed no significant difference with two tests of duration of untreated psychosis (the p value of the comparison of the mean duration of untreated psychosis was 0.35 unadjusted and was 0.33 adjusted, and the p value for the median duration of untreated psychosis was 0.35). These results did not meet the statistical plan criteria for the inclusion of duration of untreated psychosis as a covariate, and thus we believe that our exclusion of duration of untreated psychosis from the variables included as covariates was warranted.

Although the duration of untreated psychosis was not significantly different between groups at baseline, it did emerge as a significant moderator of several outcomes. We did not comment on the Treatment and Intervention in Psychosis study because a discussion of whether reducing the duration of untreated psychosis would change outcomes was beyond the scope of our article. We found that stratifying comparisons by duration of untreated psychosis was associated with significant differences in outcomes. We did not seek to explain the mechanism behind this difference.

The statement in our earlier article (2) that none of the sites withdrew after randomization referred to the potential risk that sites would initiate withdrawal because of disappointment in their cluster-randomized assignment. We did discontinue two sites due to poor enrollment.

We appreciate the opportunity to address Dr. Amos's concerns, but we believe that given the nature of this study, we have done everything appropriate to demonstrate that our conclusions are valid and follow the data as closely as possible.

REFERENCES

1. Kane JM, Robinson DG, Schooler NR, et al: Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE Early Treatment Program. Am J Psychiatry 2016; 173:362–372
2. Kane JM, Schooler NR, Marcy P, et al: The RAISE early treatment program for first-episode psychosis: background, rationale, and study design. J Clin Psychiatry 2015; 76:240–246

John M. Kane, M.D.
Delbert G. Robinson, M.D.
Nina R. Schooler, Ph.D.
Haiqun Lin, M.D., Ph.D.
Robert A. Rosenheck, M.D.
Robert K. Heinssen, Ph.D., A.B.P.P.
For the RAISE-ETP Study Group

From the Division of Psychiatry Research, Zucker Hillside Hospital, Northwell Health, Glen Oaks, N.Y.; the Feinstein Institute for Medical Research, Manhasset, N.Y.; the Department of Psychiatry, SUNY Downstate Medical Center, Brooklyn, N.Y.; the Department of Psychiatry, Yale Medical School, and Yale School of Public Health, New Haven, Conn.; and the Division of Services and Intervention Research, NIMH, Rockville, Md.

The authors' disclosures accompany the original article.

This reply was accepted for publication in February 2016.

Am J Psychiatry 2016; 173:535–536; doi: 10.1176/appi.ajp.2016.15111427r

Comment on Analyses and Conclusions of "Microglial Activity in People at Ultra High Risk of Psychosis and in Schizophrenia: An [^{11}C]PBR28 PET Brain Imaging Study"

TO THE EDITOR: Theories relating the etiology of schizophrenia to immune response date back more than a century (1). Therefore, the recent [^{11}C]PBR28 positron emission tomography (PET) study by Bloomfield et al. (2), published in the January 2016 issue of the *Journal*, is an important one with implications for early diagnosis and therapeutic strategies. However, we outline concerns with respect to the outcome measures and analyses used in this study to arrive at the conclusion that microglial activation is elevated in

patients with schizophrenia and in persons at ultra high risk for psychosis.

Determining the primary outcome measure to be used in any PET study is critical and has been the topic of considerable effort to ensure consistency in the field (3). Traditionally, for PET radiotracers that lack a true reference region, the regional distribution volume (V_T) is used as the outcome measure; in the present study, the failure to find any significant between-group differences with this measure is a concern (see Table S5 in the data supplement that accompanies the online version of the original article). The authors used an alternative outcome measure, distribution volume ratio, as their primary outcome measure in this study. The distribution volume ratio was arrived at by normalizing a region of interest V_T to total brain V_T. This approach is problematic because [^{11}C]PBR28 binding in the region of interest is represented in both the numerator and the denominator. In addition, total brain V_T is vulnerable to differences in white and gray matter ratios, cortical and subcortical region volumes, etc., making this measure undesirable to use for normalization. The authors evaluated the bias of total brain V_T normalization by comparing it with normalization in two regions with low translocator-protein (TSPO) activity (the cerebellum and white matter). Unfortunately, these region-based approaches do not clarify whether the higher distribution volume ratio values in schizophrenia subjects and in ultra-high-risk subjects are a result of greater microglial activation in the region of interest or of lesser microglial activation in the cerebellum (or white matter). In fact, data in Table S2 (in the data supplement that accompanies the online version of the original article) shows cerebellum V_T at a trend level lower in schizophrenia subjects compared with control subjects, thereby supporting the latter possibility. We acknowledge the fact that recent [^{11}C]PBR28 studies have advocated the use of simplified outcome measures, such as distribution volume ratio and standardized uptake value, to reduce within-group variability in clinical studies. Nevertheless, prior to use, it is critical to demonstrate concurrence between distribution volume ratio and V_T and to ensure that the disease does not affect binding in the region used for normalization, as shown for the cerebellum in Alzheimer's disease (4). Unfortunately, the findings reported with distribution volume ratio in this article fail to meet this rigorous standard.

There are additional statistical concerns in this data set. For example, in Table S6 and Figure S3 in the online data supplement (data for control subjects and for ultra-high-risk subjects were partitioned by genotype), there are large standard deviations and no apparent difference in the means; in the first grouping in Figure S3, the estimated standard deviation is approximately 0.5. However, in the table, the standard deviation is listed as 0.016. Assuming that this standard deviation is a modified one arrived at by covarying for age, this represents a 97% reduction in standard deviation. This would suggest that all the variance in the [^{11}C]PBR28 distribution volume ratio data is explained by age. To our knowledge, such a large effect for age is not evident in any published [^{11}C]PBR28 data set. Congruent with this line of thinking is the authors' own modest r statistic of 0.31 for the distribution volume ratio versus age in Table S3. The r statistic would have to be much higher in these data for nearly all the variance in the distribution volume ratio to be explainable by age.

In summary, it may have been beneficial to the field to see these data published as a negative study utilizing the standard outcome measure of V_T with a discussion of the distribution volume ratio findings as a secondary analysis. Interestingly, such a result would have been consistent with the only other study in schizophrenia that used a second-generation TSPO radioligand (5).

REFERENCES

1. Khandaker GM, Cousins L, Deakin J, et al: Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry 2015; 2:258–270
2. Bloomfield PS, Selvaraj S, Veronese M, et al: Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [^{11}C]PBR28 PET brain imaging study. Am J Psychiatry 2016; 173:44–52
3. Innis RB, Cunningham VJ, Delforge J, et al: Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 2007; 27:1533–1539
4. Lyoo CH, Ikawa M, Liow JS, et al: Cerebellum can serve as a pseudo-reference region in Alzheimer disease to detect neuroinflammation measured with PET radioligand binding to translocator protein. J Nucl Med 2015; 56:701–706
5. Kenk M, Selvanathan T, Rao N, et al: Imaging neuroinflammation in gray and white matter in schizophrenia: an in-vivo PET study with [18F]-FEPPA. Schizophr Bull 2015; 41:85–93

Raj Narendran, M.D.
W. Gordon Frankle, M.D.

From the Department of Psychiatry, University of Pittsburgh Medical Center; and the Department of Psychiatry and Radiology, University of Pittsburgh.

Dr. Narendran has received research grants from NIDA, NIMH, and the National Institute on Alcohol Abuse and Alcoholism; he also has received payments for participation in the Food and Drug Administration Psychopharmacology Drug Advisory Committee. Dr. Frankle reports no financial relationships with commercial interests.

This letter was accepted for publication in February 2016.

Am J Psychiatry 2016; 173:536–537; doi: 10.1176/appi.ajp.2016.15111417

Response to Narendran and Frankle: The Interpretation of PET Microglial Imaging in Schizophrenia

TO THE EDITOR: We thank Drs. Narendran and Frankle for their interest in our study (1) and for the opportunity to address the issues raised. The first issue is why we used distribution volume ratio and not distribution volume (V_T) as the main outcome measure. V_T measures rely on having reliable measurements of the plasma input function and on having no systematic group differences in free parent radiotracer plasma levels. For 18kD translocator-protein (TSPO) tracers, the free fraction is very small (<5%; approximately 2% in our study), making measurement unreliable (2). In addition, plasma proteins may bind to >50% of TSPO tracers in plasma (3). In disorders such as schizophrenia,