Cost-Effectiveness of Comprehensive, Integrated Care for First Episode Psychosis in the NIMH RAISE Early Treatment Program

Robert Rosenheck*,1, Douglas Leslie2, Kyaw Sint1, Haiqun Lin1, Delbert G. Robinson1–6, Nina R. Schooler3–6, Kim T. Mueser8, David L. Penn8,10, Jean Addington9, Mary F. Brunette12,13, Christoph U. Correll14,16, Sue E. Estroff14, Patricia Marcy3, James Robinson18, Joanne Severe16, Agnes Rupp16, Michael Schoenbaum16, and John M. Kane1–6

1Department of Psychiatry and Public Health, Yale Medical School, New Haven, CT; 2Department of Public Health Sciences, Penn State College of Medicine, Hershey, PA; 3Psychiatry Research, Zucker Hillside Hospital, North Shore—Long Island Jewish, Glen Oaks, NY; 4The Feinstein Institute for Medical Research, Manhasset, NY; 5Departments of Psychiatry and Molecular Medicine, Hofstra North Shore LIJ School of Medicine, Hempstead, NY; 6Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Bronx, NY; 7Department of Psychiatry, SUNY Downstate Medical Center, Brooklyn, NY; 8Center for Psychiatric Rehabilitation, Departments of Occupational Therapy, Psychiatry, and Psychology, Boston University, Boston, MA; 9Department of Psychology, University of North Carolina-Chapel Hill, Chapel Hill, NC; 10School of Psychology, Australian Catholic University, Melbourne, Australia; 11Hotchkiss Brain Institute, Department of Psychiatry, University of Calgary, Calgary, Canada; 12Geisel School of Medicine at Dartmouth, Lebanon, NH; 13Bureau of Behavioral Health, DHHS, Concord, NH; 14Department of Social Medicine, University of North Carolina, Chapel Hill, NC; 15Nathan Kline Institute, Orangeburg, NY; 16National Institute of Mental Health, Rockville, MD

*To whom correspondence should be addressed; VA New England Mental Illness Research, Education and Clinical Center, VA Connecticut Health Care System, 950 Campbell Avenue, West Haven, CT 06516, US; tel: 203-932-5711, ext 3723, fax: 203-937-3472, e-mail: Robert.Rosenheck@Yale.Edu

This study compares the cost-effectiveness of Navigate (NAV), a comprehensive, multidisciplinary, team-based treatment approach for first episode psychosis (FEP) and usual Community Care (CC) in a cluster randomization trial. Patients at 34 community treatment clinics were randomly assigned to either NAV (N = 223) or CC (N = 181) for 2 years. Effectiveness was measured as a one standard deviation change on the Quality of Life Scale (QLS-SD). Incremental cost effectiveness ratios were evaluated with bootstrap distributions. The Net Health Benefits Approach was used to evaluate the probability that the value of NAV benefits exceeded its costs relative to CC from the perspective of the health care system. The NAV group improved significantly more on the QLS and had higher outpatient mental health and antipsychotic medication costs. The incremental cost-effectiveness ratio was $12 081/QLS-SD, with a .94 probability that NAV was more cost-effective than CC at $40 000/QLS-SD. When converted to monetized Quality Adjusted Life Years, NAV benefits exceeded costs, especially at future generic drug prices.

Key words: schizophrenia/cost-effectiveness/quality adjusted life years

Introduction

Research suggests that early intervention for psychotic disorders such as schizophrenia can improve outcomes,1–5 and 2 cluster randomized trials6,7 have demonstrated effectiveness in routine service settings. One unanswered question is whether the increased costs of comprehensive first episode psychosis (FEP) programs are offset by reduced inpatient costs, or whether the value of health benefits justifies the additional costs. While it has been reported that early intervention programs reduce hospital days in nonrandomized matched comparisons8–10 and in 1 randomized clinical trial (RCT),11 only 2 RCT-based cost-effectiveness analyses have been published.12,13 Both trials found non-significant reductions in costs, although when benefits were assigned monetary values, both suggested that the benefits outweighed costs, albeit at less than the 95% confidence level. Further evaluation of the cost-effectiveness of early intervention programs in real-world treatment settings is needed.

This study uses data from the Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP) to evaluate the cost-effectiveness of the Navigate (NAV) intervention package as compared to standard Community Care (CC) over 2 years from the perspective of the health care system.

Methods

The ETP study is part of the National Institute of Mental Health (NIMH) RAISE initiative. Details of the study, the clinical intervention, participant characteristics, and 2-year clinical outcomes, have been reported.
Subjects and Sites
A total of 404 individuals aged 15–40 who presented for treatment for a FEP and had taken ≤6 months of lifetime antipsychotics were enrolled between July 2010 and July 2012. A CONSORT diagram of recruitment was previously published. Written informed consent was obtained from adult participants and legal guardians for those under 18 years old. The study was approved by the Institutional Review Board (IRB) of the coordinating center and at participating sites. The NIMH Data and Safety Monitoring Board provided oversight. Thirty-four community mental health treatment centers were selected following a national invitation and selection process and randomly randomized equally to NAV or CC.

Intervention
NAV included 4 components: personalized medication management (assisted by a web-based decision support system, “COMPASS”); family psychoeducation; individual, resilience-focused illness self-management therapy; and supported education and employment. Robust differences were demonstrated between NAV and CC sites in the delivery of these interventions.

Weekly team meetings facilitated communication and coordination and NAV clinicians received training, on-site supervision, and external expert consultation. CC sites provided treatment according to clinician choice and service availability.

Assessments
Outcomes Trained clinician interviewers assessed the primary outcome measure, the Quality of Life Scale (QLS) using 2-way, live video conferencing. The preferred measure of outcome in cost-effectiveness analysis is the Quality Adjusted Life Year (QALY), a cardinal measure ranging from 0 to 1 (death to perfect health). Since methods for deriving QALY’s from the QLS have not been published, we used a one standard deviation change on the QLS (the QLS-SD; 18.8 points) as our unit of outcome.

Data were also collected during video-conference interviews on the Positive and Negative Syndrome Scale (PANSS). An algorithm that combines PANSS scores with side-effect indicators has been developed in recent years, and was used to generate a schizophrenia-specific measure of QALY’s. Equipercentile linking was used to estimate the number of QLS-SDs in a QALY. Equipercentile linking is a recently developed method for identifying corresponding points on correlated measures and has come into frequent use in psychiatric research recent years.

Service Use Research assistants documented service use from diverse sources of inpatient and outpatient care. Antipsychotic medication with daily doses, and other psychotropic and nonpsychotropic medication use was also documented based on patient self-report each month.

Costs. Unit costs of these services were estimated from published reports and administrative data sets from Medicaid, MarketScan® (a private sector claims data base), the Veterans Health Administration and State Mental Hospitals adjusted for inflation to July 2014 prices using the medical care component of the consumer price index from the US Bureau of Labor Statistics. Antipsychotic and other medication costs were estimated from discounted prices from the Federal Supply Schedule Prices for 2014. Since on-patent drugs will soon be generic, sensitivity analyses were also conducted in which drug-costs were considered at generic prices.

Costs of training conferences and on-site internal and expert external supervision for NAV were calculated from study administrative records. Training costs for CC sites included attendance at study-related conferences and bi-weekly routine staff supervision. These CC costs were small (6.5% as large as the NAV training and supervision costs) and were subtracted from estimated costs of NAV training to evaluate the incremental cost of training for NAV as compared to CC. These net training costs for NAV were distributed across visits as a proportion of direct per capita monthly health care costs per patient.

The unit of analysis for cost-evaluation is the total average 6-month health costs per patient ie, average monthly costs multiplied by 6 over 4 distinct 6-month periods totaling 24 months. Total costs addressed health services, medications, plus the marginal cost of training staff in the NAV intervention.

Statistical Methods
The initial evaluation of effectiveness on the QLS was the mixed model linear regression analysis presented previously that examined average QLS scores over the entire 24-month trial. Analyses of service use, cost components and total costs compared NAV and CC on average 6-month post-baseline service use and costs covering all 24 months. Six-month costs were examined to correspond to the timing of clinical assessments. These analysis used a mixed model including terms representing treatment group and categorical time, and estimated the least square mean service use and cost values by group and the significance of treatment differences. Untransformed measures provided the best fit. These analyses were conducted using 3-level mixed-effects linear regression models for repeated measures, which included a random intercept at client and site levels. Mixed models allow use of all
available data even when some data from some individuals are missing for some time points.

The incremental cost-effectiveness ratio (ICER) was calculated as the difference in average annualized total costs divided by the difference in effectiveness (improvement in the QLS from baseline). The uncertainty of differences in effectiveness and total cost was estimated using bootstrap sampling with replacement.\(^35\) For each of 5000 bootstrap samples, the differences in least square mean of total cost and of effectiveness between groups were calculated from mixed models with terms representing treatment and time. The ICER was calculated as the average group difference in cost divided by the average difference in effectiveness and its 95% confidence interval. These data show the proportion of observations in each quadrant of the cost-effectiveness plane.\(^35\)

Cost-benefit analysis was conducted using Net Health Benefits (NHB).\(^36\) This approach assumes that we do not know the monetary value of health outcomes like the QLS-SD. Instead, a range of estimates for the dollar value of one QLS-SD are examined in a sensitivity analysis in which each monetary estimate is multiplied by the change from baseline in QLS-SD for each patient at each time point. This yields an estimate of the economic value of health gains for each observation. Following conventions used in policy making for the value, or willingness to pay for a QALY,\(^37,38\) we monetized health status with estimates from $0 to $50,000/QALY/year in a sensitivity analysis. This yielded a monetized estimate of health gains for each client at each time point.

Annualized total health care costs (average 6-month costs ×2) were then subtracted from these estimated monetary health benefits to generate an estimate of average “annualized net health benefit” for each client at each of the estimated monetary values of a QLS-SD.

Mixed model regression analyses of the type described above were used to compare mean differences between the groups using annualized estimates of NHB from all 4 follow-up time points and adjusting for time and the baseline value of the NHB. These 3-level mixed-effects linear regression models included a random intercept at both client and site levels. To eliminate outliers, NHB data were winsorized at the fifth and 95th percentile.

Over the past decade, it has been increasingly recognized that policy makers have to make decisions even when findings do not meet the usual 5% standard of uncertainty used in scientific research. It is thus important to know the probability that one treatment will be more cost-effective than another, even when the uncertainty is greater than the conventional 5%.\(^35\) Using the method of Hoch et al,\(^39\) we calculated the probability that NAV had greater NHBs than CC at each of the estimated monetary values of the QLS-SD. This calculation was based on a 1-tailed test using the P-value associated with the coefficient representing treatment group in the regression analysis of NHB, computed as 1-p/2.\(^39\) These analyses allow plotting of a cost-effectiveness acceptability curve, which illustrates graphically the probability that that NAV was more cost-effective than CC at each estimated monetary value of a QLS-SD.\(^39\)

Marked differences in the effectiveness of NAV for clients with high and low duration of untreated psychosis (DUP: the time from the onset of symptoms of psychosis to the time of first antipsychotic medication treatment)\(^16\) were previously reported for this study.\(^9\) Accordingly we evaluated the impact of DUP as a moderator of bootstrapped ICERs and NHB comparisons. The interaction of DUP by treatment group was modeled as predicting NHB. Cost-effectiveness acceptability curves are presented for low and high DUP.

Finally, equipercentile linking\(^40\) of PANSS-based QALYs\(^22\) and the QLS-SD was used to estimate the number of QLS-SDs per QALY. Since there is an extensive literature on the economic value of a QALY, these results supported translation of QLS-SD outcomes into QALYs and related monetary values.

Analyses were performed using SAS version 9.3 (SAS Institute, Inc).

Results

The sample included 223 NAV and 181 CC patients with an average age of 23 years, 71.0% lived with families of origin, 73.6% had been previously hospitalized and 83.8% were taking antipsychotic medications at study entry. Average QLS scores were 52.6 (18.8), average PANSS scores were 76.6 (14.9), and 90% met criteria for schizophrenia spectrum disorder. Median DUP was 74 weeks. More extensive baseline data have been presented previously (table 1 of Kane et al\(^6\)).

On the primary outcome measure, the NAV group participants experienced significantly greater improvement over the 2-year assessment period than CC (group by time interaction, \(P < .02\)), with an effect size from baseline to final follow-up of 0.31 and 0.24 over the entire 2-year period.\(^6\) NAV participants also experienced significantly greater improvement on PANSS total scores.\(^6\)

Service Use

There were no significant differences during the 2-year follow-up period in inpatient service use, with 14% greater mental health or medical surgical days among NAV patients (table 1). In contrast, NAV clients received 6.5 (35%) more mental health outpatient visits per 6-month period (\(P = .05\)) than CC patients. NAV clients received 39.6% more clinical visits (eg, with psychiatrists and nurses; NS), 61.8% more rehabilitation visits (\(P < .001\)), and 646% more family treatment visits (\(P < .001\)), but 69% fewer peer support visits (\(P = .04\); table 1).
Costs

Despite having more days hospitalized, average 6-month inpatient costs were $86 lower (2.2%, NS) for NAV than CC clients (Table 2) because of 14.5% lower average per diem costs. Total average 6-month outpatient mental health costs were $491 (35.6%, \( P = .05 \)) greater for NAV.

Table 1. Average 6-Month Measures of Service Use Over 24 Months: Navigate vs Community Care

<table>
<thead>
<tr>
<th>Service Use (Average Nights or Visits per Patient per 6-Month Interval)</th>
<th>Community Care</th>
<th>Navigate</th>
<th>Mean</th>
<th>SE</th>
<th>Mean</th>
<th>SE</th>
<th>Difference</th>
<th>% Difference</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient/residential days</td>
<td></td>
<td></td>
<td>3.96</td>
<td>1.87</td>
<td>6.55</td>
<td>1.73</td>
<td>2.59</td>
<td>65.40</td>
<td>1.02</td>
<td>.31</td>
</tr>
<tr>
<td>Mental health or medical surgical inpatient days</td>
<td></td>
<td></td>
<td>3.07</td>
<td>1.00</td>
<td>3.51</td>
<td>0.89</td>
<td>0.44</td>
<td>14.33</td>
<td>0.33</td>
<td>.74</td>
</tr>
<tr>
<td>Mental health inpatient days</td>
<td></td>
<td></td>
<td>2.86</td>
<td>1.01</td>
<td>3.29</td>
<td>0.90</td>
<td>0.43</td>
<td>15.03</td>
<td>0.32</td>
<td>.75</td>
</tr>
<tr>
<td>Medical surgical inpatient days</td>
<td></td>
<td></td>
<td>0.24</td>
<td>0.10</td>
<td>0.22</td>
<td>0.09</td>
<td>-0.02</td>
<td>-8.33</td>
<td>0.10</td>
<td>.92</td>
</tr>
<tr>
<td>Residential/nursing home days</td>
<td></td>
<td></td>
<td>0.63</td>
<td>1.26</td>
<td>3.05</td>
<td>1.16</td>
<td>2.42</td>
<td>38.13</td>
<td>1.42</td>
<td>.16</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td></td>
<td></td>
<td>20.79</td>
<td>2.65</td>
<td>27.24</td>
<td>2.48</td>
<td>6.45</td>
<td>31.02</td>
<td>1.78</td>
<td>.08</td>
</tr>
<tr>
<td>Emergency department visits</td>
<td></td>
<td></td>
<td>0.53</td>
<td>0.09</td>
<td>0.42</td>
<td>0.08</td>
<td>-0.11</td>
<td>-20.75</td>
<td>0.89</td>
<td>.37</td>
</tr>
<tr>
<td>Medical surgical outpatient visits</td>
<td></td>
<td></td>
<td>1.85</td>
<td>0.59</td>
<td>1.82</td>
<td>0.55</td>
<td>-0.03</td>
<td>-1.62</td>
<td>0.03</td>
<td>.98</td>
</tr>
<tr>
<td>Mental health outpatient visits</td>
<td></td>
<td></td>
<td>18.44</td>
<td>2.46</td>
<td>24.97</td>
<td>2.30</td>
<td>6.53</td>
<td>35.41</td>
<td>1.94</td>
<td>.05</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td>5.02</td>
<td>0.98</td>
<td>7.01</td>
<td>0.93</td>
<td>1.99</td>
<td>39.64</td>
<td>1.48</td>
<td>.14</td>
</tr>
<tr>
<td>Rehabilitation</td>
<td></td>
<td></td>
<td>8.13</td>
<td>1.35</td>
<td>13.16</td>
<td>1.26</td>
<td>5.03</td>
<td>61.87</td>
<td>2.72</td>
<td>.0066</td>
</tr>
<tr>
<td>Family</td>
<td></td>
<td></td>
<td>0.43</td>
<td>0.58</td>
<td>3.21</td>
<td>0.55</td>
<td>2.78</td>
<td>646.51</td>
<td>3.50</td>
<td>.0005</td>
</tr>
<tr>
<td>Peer support, self-help group, and club house</td>
<td></td>
<td></td>
<td>4.51</td>
<td>1.14</td>
<td>1.39</td>
<td>1.05</td>
<td>-3.12</td>
<td>-69.18</td>
<td>2.02</td>
<td>.04</td>
</tr>
</tbody>
</table>

Note: *Mixed models included terms for treatment and categorical time with random intercepts for individual and site.

\( ^{\text{b}} \)Least square means from mixed models. Totals may not add up to sum of components because separate models were conducted for each variable.

Table 2. Average 6-Month Measures of Health Service-Related Costs Over 24 Months: Navigate vs Community Care

<table>
<thead>
<tr>
<th>Costs (Per 6 Months)</th>
<th>Community Care</th>
<th>Navigate</th>
<th>Mean</th>
<th>SE</th>
<th>Mean</th>
<th>SE</th>
<th>Difference</th>
<th>% Difference</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All mental health and medical surgical inpatient costs</td>
<td>$3780</td>
<td>1069</td>
<td>$3694</td>
<td>941</td>
<td>$-86</td>
<td>-2.28</td>
<td>0.06</td>
<td>.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residential and nursing home costs</td>
<td>$38</td>
<td>63</td>
<td>$159</td>
<td>58</td>
<td>$121</td>
<td>318.42</td>
<td>1.42</td>
<td>.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient service costs</td>
<td>$1626</td>
<td>203</td>
<td>$2100</td>
<td>191</td>
<td>$474</td>
<td>29.15</td>
<td>1.71</td>
<td>.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department costs</td>
<td>$68</td>
<td>12</td>
<td>$54</td>
<td>10</td>
<td>$-14</td>
<td>-20.59</td>
<td>0.9</td>
<td>.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical surgical outpatient costs</td>
<td>$180</td>
<td>56</td>
<td>$175</td>
<td>52</td>
<td>$-5</td>
<td>-2.78</td>
<td>0.06</td>
<td>.95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health outpatient costs</td>
<td>$1379</td>
<td>185</td>
<td>$1870</td>
<td>174</td>
<td>$491</td>
<td>35.61</td>
<td>1.94</td>
<td>.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total service costs (excluding medications)</td>
<td>$5534</td>
<td>1144</td>
<td>$5948</td>
<td>1017</td>
<td>$414</td>
<td>7.48</td>
<td>0.27</td>
<td>.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total medication costs</td>
<td>$1292</td>
<td>210</td>
<td>$1957</td>
<td>196</td>
<td>$665</td>
<td>51.47</td>
<td>2.32</td>
<td>.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic medication</td>
<td>$1060</td>
<td>191</td>
<td>$1739</td>
<td>177</td>
<td>$679</td>
<td>64.06</td>
<td>2.61</td>
<td>.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychotropic medications</td>
<td>$102</td>
<td>27</td>
<td>$114</td>
<td>25</td>
<td>$12</td>
<td>-11.76</td>
<td>0.32</td>
<td>.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonpsychotropic drugs</td>
<td>$140</td>
<td>30</td>
<td>$102</td>
<td>26</td>
<td>$-38</td>
<td>-27.14</td>
<td>0.97</td>
<td>.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total medication costs using generic costs for antipsychotics</td>
<td>$350</td>
<td>55</td>
<td>$362</td>
<td>51</td>
<td>$12</td>
<td>3.43</td>
<td>0.15</td>
<td>.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic medication using generic costs</td>
<td>$102</td>
<td>10</td>
<td>$137</td>
<td>9</td>
<td>$35</td>
<td>34.31</td>
<td>2.58</td>
<td>.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total costs (services and medication)</td>
<td>$6743</td>
<td>1088</td>
<td>$7856</td>
<td>957</td>
<td>$1113</td>
<td>16.51</td>
<td>0.77</td>
<td>.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total costs (services and medication plus training costs)</td>
<td>$6719</td>
<td>1137</td>
<td>$8556</td>
<td>998</td>
<td>$1837</td>
<td>27.34</td>
<td>1.22</td>
<td>.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total costs (services and medication using generic APS costs plus training costs)</td>
<td>$6019</td>
<td>1260</td>
<td>$7088</td>
<td>1127</td>
<td>$1069</td>
<td>17.76</td>
<td>0.63</td>
<td>.53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: *Mixed models included terms for treatment and categorical time with random intercepts for individual and site: 6-month least square means over 24 months. APS, antipsychotic medication.

\( ^{\text{b}} \)Least square means from mixed models. Totals may not add up to sum of components because separate models were conducted for each variable.
differences in total medication costs, although NAV antipsychotic costs remained slightly greater by $35 ($P = .01$).

Total clinical service costs (ie, excluding medications) were 7.5% greater for NAV than CC ($P = .79$), while this cost difference increased to $1113 ($P = .44$) when medication costs were included and to $1837 (27.3%, $P = .22$) when the marginal cost of NAV training (amounting to 9% of all health care costs) was added. Although training actually had no effect at all on CC costs the additional cost for NAV training appears to lower the costs for CC because of the statistical modeling of least square means in table 2.

When generic costs for antipsychotic medications were applied, total cost differences were reduced by almost half to $1069 greater for NAV ($P = .53$; table 2).

**Incremental Cost Effectiveness Ratios and Bootstrap Analyses**

Dividing the aggregate difference in average “annualized” total costs ($3674) by the aggregated benefit of 0.25 QLS-SDs yields an arithmetic ICER of $14 696/QLS-SD. Bootstrap analysis yielded somewhat smaller average costs per 6-month period for an ICER of $12 081/QLS-SD (figure 1) and with 95% of all observations falling in the upper right quadrant of the cost effectiveness plane, representing greater benefits and greater costs for NAV.

**Low and High DUP**

In the original QLS analysis, the NAV-CC effect size gain of 0.57 among low-DUP patients was substantially higher than the .07 observed among high-DUP patients. Among low-DUP patients (table 3), the NAV group had “fewer” mental health or medical/surgical inpatient days per 6-month period and $3778 (56.7%, $P = .34$) “lower” inpatient costs. In contrast, among high-DUP patients, the NAV group averaged “more” inpatient days per 6-month period, and $1820 (63%, $P = .29$) “higher” inpatient costs (table 3).

As a result, among low-DUP patients, NAV total costs averaged $1368 per patient per 6 months less than CC (14.8%, $P = .72$), while among high-DUP patients, NAV showed increased costs of $3839 (64%, $P = .05$) per patient per 6 months (table 3).

Related bootstrap analyses show an ICER of only $1035/QLS-SD among low-DUP patients (figure 2), compared to an ICER of $41 307/QLS-SD among high-DUP patients (figure 3), with wide 95% confidence intervals.

Finally, the ICER using generic costs for antipsychotic medications (figure 4) was only $6501/QLS-SD, still with 81% of observations in the quadrant representing greater costs and greater benefits. When calculated with generic antipsychotic costs, the ICER among high-DUP clients declined from $41 307/QLS-SD to $29 516/QLS-SD (figure not shown).

**NHB Analysis**

There is a .80 probability that NAV is cost-effective in comparison with CC if a QLS-SD is valued at $20 000 (figure 5); a .90 probability if the QLS-SD is valued at $30 000; and the scientifically normative .95 probability if the QLS-SD is valued at $40 000 or more.

Evaluation of the interaction of treatment assignment by DUP in a model of NHB showed a significant interaction, even at $0 value of one QLS-SD ($t = 2.43, $P = .016$). In the low-DUP sub-group, there is a .83 probability that NAV is cost-effective in comparison with CC if one QLS-SD is valued at only $10 000 (figure 6) and a .94 probability if the QLS-SD is valued at only $20 000. Among the high-DUP sub-group (figure 7), in contrast, there is a less than even probability (.31) that NAV is more cost effective than CC if 1 QLS-SD is valued at $20 000; and only a modestly greater than average probability (.64) if a QLS-SD is valued at $50 000.

**Conversion to QALYs**

A highly significant correlation of 0.36 ($P < .0001$) was found between the QLS and the PANSS-derived measure of QALY’s. Equipercentile linking of these data shows that a one unit change in the QLS-SD represents a 0.14 change in QALY’s, or, reciprocally, that 7 QLS-SDs = 1 QALY.

The overall ICER of $12 081/QLS-SD thus equates to $7 	imes 12 081 = $84 567 per QALY, while the low-DUP ICER equates to $7245/QALY, the high-DUP ICER to $289 149/QALY, and the generic antipsychotic prices ICER to $45 507/QALY. High-DUP clients evaluated with generic drug costs had an ICER of $206 612/QALY.

Reexamination of the NHB analysis from the QALY perspective suggests that there is a .90–.95 probability...
that NAV is more cost effective than CC at dollar values of $210 000/QALY to $280 000/QALY. In the low-DUP group, there is a .94 probability that NAV is more cost-effective than CC at $140 000/QALY, although among high-DUP patients there is only a .65 probability chance that NAV is more cost-effective than CC at $350 000/QALY, all below the upper-range estimates of the monetized value of a QALY (see discussion below).

Discussion
This study used 3 strategies to evaluate the cost-effectiveness and cost-benefit of NAV in comparison to CC in a
2-year cluster randomized trial. First, mixed linear models showed greater NAV effectiveness, and greater total costs than CC with 26% of the increased costs attributable to increased outpatient service costs, 36% to greater medication costs, and 9% to additional training costs. There was no significant reduction in inpatient costs with NAV, similar to 2 previous RCT cost-effectiveness analyses of FEP treatment.\textsuperscript{12,13} The increase in medication costs was presumably driven by guidance from the COMPASS decision support system that encouraged the use of second generation antipsychotics with favorable metabolic side effect profiles and also long acting antipsychotic formulations for adherence enhancement, despite their greater cost.

The second method, using bootstrap analysis of ICERs, confirmed findings of greater benefits and cost for NAV. The greatest cost-effectiveness was observed among low-DUP clients and when generic drug prices were used (as is likely to be the case in the future).\textsuperscript{32} The third analytic approach, using NHB, found a .95 probability that NAV was more cost-effective than CC if the QLS-SD is valued at $40 000. Among the low-DUP samples there was a .94 probability that NAV was more cost-effective at only $20 000/QLS-SD, while among the high-DUP patients there was a .31 probability at $20 000 and only a .64 probability that NAV was cost-effective compared to CC at $50 000.
Thus in all 3 analyses, NAV was both more effective and more costly than CC, with considerably greater cost-effectiveness among low-DUP clients than among high-DUP clients, and when generic drug prices were used for antipsychotics.

Monetary Value of Clinical Improvement

The remaining feature of our analysis was a cost-benefit analysis based on an estimate of the monetary value of one QLS-SD, since the ultimate meaning of both ICER and NHB analyses hinges on the estimated willingness-to-pay for, or dollar value of, a QLS-SD. Using data collected with the algorithm for estimating QALYS from the PANSS, we estimated that there are 7 QLS-SDs in one QALY. Using this figure, ICERs for NAV ranged from $7245/QALY to $45 507/QALY, with the exception of the high-DUP group, which ranged from $200 000/QALY to $300 000/QALY. NHB analysis, further, suggests that there is a 0.90–0.95 likelihood that NAV is more cost-effective than CC at dollar values of $210 000/QALY to $280 000/QALY.

There is an extensive literature on the monetary value of a QALY[37,38,41] which has been estimated to range from $50 000 (in 1984 dollars) to $117 000 (in 2014 inflation-adjusted dollars) to $183 000–$264 000 in a recent analysis of expenditures and costs in the US health care system[38] and by some methods to as high as $400 000/QALY. Thus ICER and NHB estimates presented here all suggest that the value of clinical improvements for NAV compared to CC fall under the published range of estimates for the ceiling value of a QALY although for high-DUP patients this is limited to estimates based on generic drug prices.

Two previous cost-benefit analyses of FEP programs using the NHB approach[12,13] found no statistically significant cost savings for FEP early intervention. However, they reported greater NHBs for FEP treatment when they took the monetary value of clinical improvement into consideration in a cost-benefit analysis. Benefits in these studies were measured at £1000–£10 000 for “full vocational recovery” in the first case,[13] and £2000 per point on the 0–100 Global Assessment of Function (GAF) scale in the second.[12] When these monetized benefits were added to inpatient cost savings, the claim for cost-effectiveness was strengthened, although the greater cost-benefit for FEP treatment still fell short of the .95 probability level. However, “full vocational recovery” was not operationally defined and neither study presented a justification for the monetary value they assigned to these clinical outcomes. Claims of cost-effectiveness in these studies thus rest on assumptions that are incompletely substantiated.

The multistep estimation method used here provides a firmer foundation than had previous been available for concluding that the health benefits of NAV exceed their costs and thus pass the “cost-benefit” test.

Limitations

Several limitations of this study require comment. First, the conditions of a randomized trial like RAISE-ETP may not be generalizable to real-world practice since all sites that volunteered for RAISE-ETP were capable and motivated to successfully implement a comprehensive, integrated care FEP program with existing non-research sources of funding. As a result, CC sites most likely offered a level of FEP care that was superior to usual FEP treatment in the US, thus minimizing observed differences between NAV and usual treatment. In several other RCTs of FEP programs,[2,4,5] rates of hospitalization among control groups were 37% to 71% over 12 months, 1.5 to 3.5 times greater than the 20% seen in the first 12 months for CC in this study. This difference suggests that the lack of more favorable NAV-CC differences in inpatient care and costs may reflect an exceptionally good performance at keeping hospital utilization low at CC sites in this study. If CC subjects in the present study had performed similarly...

Fig. 6. Cost effectiveness acceptability curve (Navigate vs Community Care [NAV vs CC]; low duration of untreated psychosis [DUP]).

Fig. 7. Cost effectiveness acceptability curve (Navigate vs Community Care [NAV vs CC]; high duration of untreated psychosis [DUP]).
to control groups in previous trials cited above, the differentially greater costs associated with NAV might have been reduced to zero or might even have been reversed to as much as $7000 in savings. Generalizability of these results is thus uncertain as RAISE-ETC may have artificially increased CC effectiveness and reduced CC costs.

Second, our method for determining the number of QLS-SDs per QALY, and hence the monetary value of documented clinical outcomes, is novel. Each step in the process was based on empirical data, but the validity, reliability and generalizability of the methods used, has not been replicated. We relied on a broad range of published estimates with consistent results favoring NAV.

Third, we note that inpatient service use is strongly influenced by the local supply of inpatient beds and local clinical practice patterns. Treatment-related reductions in hospitalization and related cost savings are limited where the baseline supply and utilization of inpatient services is low to begin with and the RAISE-ETP sample averaged only 3 mental health inpatient days per client per month. NAV showed lower rates of hospitalization at 12 months than other recent demonstrations of multimodal FEP treatment (20% for NAV vs 32% for the RAISE Connection program and 23% for the STEP program), reflecting generally low levels of inpatient use at both NAV and CC sites.

Fourth, it should be acknowledged that RAISE-ETP, with a total sample of 404 participants clustered in 34 sites, was not adequately powered for cost-effectiveness analysis. Since the distribution of cost data was highly non-normal, differences in results across our methods of analysis are in part attributable to a relative lack of statistical power (as evidenced by the wide confidence intervals of the bootstrap analyses), although the overall findings are highly consistent.

Finally, we note that although RAISE-ETP has a longer duration of follow-up than many previous studies of FEP interventions, it cannot speak to the very long-term benefits that may accrue over decades in what can be a life long illness. In addition, the analysis was conducted from the perspective of the health care system, and thus did not address costs to patients’ families or other social welfare systems.

Conclusion

This study showed that a comprehensive service package for FEP can improve quality of life, albeit at increased costs. However, the value of the achieved clinical benefit appears to justify these additional expenditures, especially for clients with shorter DUP, and when generic prices for antipsychotic medication are applied.

Funding

This work was supported with funds from the American Recovery and Reinvestment Act and from the National Institute of Mental Health, under Contract No. HHSN271200900019C. The contents of this article are solely the responsibility of the authors and do not necessarily represent the views of National Institute of Mental Health or the US Department of Health and Human Services.

Acknowledgments

J.M.K. has been a consultant for Alkermes, Amgen, Bristol-Myers Squibb, Eli Lilly, EnVivo Pharmaceuticals (Forum), Forest, Genentech, H. Lundbeck, Intra-Cellular Therapies, Janssen Pharmaceutica, Johnson and Johnson, Merck, Novartis, Otsuka, Pierre Fabre, Reviva, Roche, Sunovion, and Teva; he has received honoraria for lectures from Bristol-Myers Squibb, Genentech, Janssen, Lundbeck, and Otsuka; and he is a shareholder in MedAvant and in Vanguard Research Group. D.G.R. has been a consultant to Asubio, Otsuka, and Shire; and he has received grants from Bristol-Myers Squibb, Janssen, and Otsuka. N.R.S. has served on advisory boards or as a consultant for Abbott, Alkermes, Amgen, Eli Lilly, Forum (formerly EnVivo), Janssen Psychiatry, Roche, and Sunovion; she has received grant or research support from Genentech, Neurocrine, and Otsuka; and she has served on a data monitoring board for Shire and on the faculty of the Lundbeck International Neuroscience Foundation. M.F.B. has received grant support from Alkermes. C.U.C. has been a consultant or adviser to or has received honoraria from AbbVie, Actavis, Actelion, Alexza, Alkermes, Bristol-Myers Squibb, Cephalon, Eli Lilly, Genentech, Gerson Lehrman Group, Intra-Cellular Therapies, Janssen, Johnson and Johnson, Lundbeck, MedAvant, Medscape, Merck, Otsuka, Pfizer, ProPhase, Reviva, Roche, Sunovion, Supernus, Takeda, Teva, and Vanda; and he has received grant support from Bristol-Myers Squibb, Janssen Johnson and Johnson, Novo Nordisk, Otsuka, and Takeda. P.M. is a shareholder in Pfizer. J.R. has received grant support from Otsuka and is a shareholder in Pfizer. The authors and their associates provide training and consultation about implementing NAVIGATE treatment that can include compensation. These activities started only after data collection for the manuscript was completed. At the time of publication, D.G.R. had received compensation for these activities. K.T.M., D.L.P., R.R., J.A., S.E.E., J.S., H.L., K.S., A.R., and M.S. report no financial relationships with commercial interests.

References

2. Alvarez-Jimenez M, Parker AG, Hetrick SE, McGorry PD, Gleeson JF. Preventing the second episode: a systematic


