Better care for less money: cost-effectiveness of integrated care in multi-episode patients with severe psychosis

Karow A, Brettschneider C, Helmut König H, Correll CU, Schöttle D, Lüdecke D, Rohenkohl A, Ruppelt F, Kraft V, Gallinat J, Lambert M.

**Objective:** To compare cost-effectiveness of integrated care with therapeutic assertive community treatment (IC-TACT) versus standard care (SC) in multiple-episode psychosis.

**Method:** Twelve-month IC-TACT in patients with schizophrenia-spectrum and bipolar I disorders were compared with a historical control group. Primary outcomes were entropy-balanced cost-effectiveness based on mental healthcare costs from a payers' perspective and quality-adjusted life years (QALYs) as a measure of health effects during 12-month follow-up.

**Results:** At baseline, patients in IC-TACT (n = 214) had significantly higher illness severity and lower functioning than SC (n = 56). Over 12 months, IC-TACT had significantly lower days in inpatient (10.3 ± 20.5 vs. 28.2 ± 44.9; P = 0.005) and day-clinic care (2.6 ± 16.7 vs. 16.4 ± 33.7; P = 0.004) and correspondingly lower costs (€–55 084). Within outpatient care, IC-TACT displayed a higher number of treatment contacts (116.3 ± 45.3 vs. 15.6 ± 6.3) and higher related costs (€+1417). Both resulted in lower total costs in IC-TACT (mean difference = €–13 248 ± 2975, P < 0.001). Adjusted incremental QALYs were significantly higher for IC-TACT versus SC (+0.10 ± 0.37, P = 0.05). The probability of cost-effectiveness of IC-TACT was constantly higher than 99%.

**Conclusion:** IC-TACT was cost-effective compared with SC. The use of prima facie ‘costly’ TACT teams is highly recommended to improve outcomes and save total cost for patients with severe psychotic disorders.

**Significant Outcomes**

- Treatment within integrated care including therapeutic assertive community treatment (IC-TACT) was less costly and more effective compared with standard care in patients with severe psychotic disorders over a period of 12 months. Consequently, investments in team-based integrative care models pay off from the payers’, providers’, and patients’ perspective.

**Limitations**

- Possible selection bias due to the naturalistic study design with a historical control group and group differences regarding illness severity at baseline, though associated variables were included into the statistical analyses. The cost calculation focussed direct treatment costs, several other costs were not investigated. Consequently, costs are likely underestimated.
INTRODUCTION

Severe mental illness (SMI) is defined by considerable and persistent impaired functioning due to mental disorders (1). Epidemiological data indicate that 6-8% of the population with mental disorders suffer from SMI (2). About 60% of those suffer from a psychotic disorder, mainly schizophrenia (90% SMI lifetime risk), schizophrenia-spectrum disorders (60% risk), or bipolar-I disorder/major depressive disorder with psychotic symptoms (40% risk) (1).

People with psychotic disorders fulfilling SMI criteria present clinical and social challenges: (i) more than 80% suffer from comorbid mental disorders, mostly substance use disorders; (ii) approximately 80% of multiple-episode patients have chronic somatic disorders; and (iii) all patients present different areas of social disability (3, 4). Further important challenges include high rates of service disengagement, medication non-adherence, multiple relapses, and homelessness all of which lead to high treatment costs and low life expectancy (5–12).

According to the Organization for Economic Co-operation and Development (OECD 2014), there are three main evidence-based care models for people with SMI: (i) Early Intervention Services (EIS; (13)), (ii) Crisis Resolution Teams (CRT; (14)), and (iii) Assertive Community Treatment (ACT; (15)). Despite many similar core features, there are to date four different variations of ACT: (i) Classic ACT according to the original model (15), (ii) Flexible ACT a combination of ACT and case management (FACT; (16, 17)), (iii) Resource Group ACT, in which subjects themselves set the goals for their treatment (16, 18), and Therapeutic ACT (TACT; (19, 20)) with the following unique additional features: (i) the TACT team is embedded in an integrated care (IC) network of specialized psychosis in- and outpatient institutions (IC-TACT), (ii) the IC-TACT teams are specialized on the treatment of patients with severe non-affective and affective psychoses, and (iii) the IC-TACT team mostly consists of psychiatrists and psychologists with training in psychotherapy as a core feature of the intervention model. A further important difference is that IC-TACT is managed by a managed care organization (MCO) and financed by a yearly per-patient capitation rate with full responsibility for all care costs (21). The results of different studies investigating cost-effectiveness of integrative treatment models for severe mental disorders indicate superiority compared with standard care (7, 22, 23).

So far, the Integrated Care in Psychosis (ACCESS) model was evaluated in three consecutive studies: (i) ACCESS I, which compared IC in combination with TACT (IC-TACT) with standard care (SC) in 120 patients with first- or multiple-episode schizophrenia-spectrum disorders (19), (ii) ACCESS II, which is an ongoing long-term evaluation of all patients who are treated with IC-TACT after it was approved by health insurances in 2006 and extended to severe affective psychoses (3, 21, 24), and (iii) ACCESS III, which examined the efficacy of the IC-TACT model adaptation to early psychosis (20).

The aims of the present costs and cost-effectiveness analyses are the comparison of the ACCESS model to standard care in multiple-episode patients with severe psychotic disorders (ACCESS II, aged 18–65 years). Quality-adjusted life years (QALYs) were used as the measure of beneficial health effects, following the concept of cost-utility analyses as recommended by health economists (25). We hypothesized that the additional mental healthcare costs associated with IC-TACT would be below 50 000€ per QALY gained, a threshold for cost-effectiveness commonly regarded as acceptable by decision makers (26).

We aimed to assess whether the ACCESS model would continue to show better cost-effectiveness without selection bias in a ‘real world setting’ in patients with high illness severity, poor outcome, and higher annual cost. Finally, we aimed to establish if such a high-fidelity and personnel-intense IC-TACT team approach results in lower total costs and better cost-effectiveness mediated by ‘high-quality outpatient care = better outcome = lower inpatient costs = comparable or, possibly, lower overall costs’.
Methods

The data for the present analyses were derived from the ACCESS I (Standard Care) and II studies (IC-TACT) (3, 21, 24). All patients signed a declaration of consent regarding the use of their data. Study design, baseline data, and different clinical outcomes of ACCESS I and II studies have been published elsewhere, data of the cost-effectiveness analysis were not published before (24, 27–29). In brief, ACCESS II is a non-randomized implementation cohort study with consecutively enrolled patients from 2008 to 2014, receiving IC-TACT as defined below, using a historical control group of patients receiving SC from 2005 to 2008 (ACCESS I) in the same treatment system but in another catchment area and prior to the implementation of ACCESS care into daily clinical routine.

Integrated Care with Therapeutic Assertive Community Treatment (IC-TACT)

ACCESS is a managed care, integrated care model, which was first investigated at the university medical center in Hamburg, Germany, in 2005. ACCESS was designed to offer improved care to patients with non-affective and affective psychoses fulfilling criteria for SMI. The managed care network comprises various specialized psychosis institutions, spanning a network of inpatient units, day clinics, early detection services, a psychosis outpatient center, and private psychiatrists (20, 21). The IC-TACT teams have important core features, which are based on the original ACT model, that is, low therapist-patient ratio of 1:15 during 1st year of treatment (1:25 after 2nd year), a no drop out policy, 24-h daily crisis intervention service, high-frequent treatment contacts, and across-setting treatment continuity. Team members were highly educated psychosis experts consisting of a consultant psychiatrist, psychiatrists, psychologists, and nurses, all of which received training in cognitive behavioral (CBT), dynamic, and/or family psychotherapy. IC-TACT is a manualized intervention, whereby all therapeutic interventions are adapted to individual needs. Additional important components are as follows:

i specialization of all network facilities on psychotic disorders in people with SMI;

ii individualized, evidence-based and guideline-concordant, diagnosis-specific and intensive treatment with a focus on psychotherapy in addition to pharmacotherapy. This includes individual psychotherapy and family interventions provided by the IC-TACT team therapists, and group psychotherapy within the care network;

iii service provision within a catchment area network of institutions (private psychiatrists, social care and housing institutions etc.).

Standard Care (SC)

The control condition comprised a control group with comparable age, diagnoses, and stage of illness characteristics that were treated in a different catchment area in Hamburg (details with regard to comparability see below and (19)). The control group consisted of 56 patients with multiple-episode psychosis between 18 and 65 years (ACCESS-I). They had been treated between January 2005 and December 2008. Main differences in the SC group are (i) absence of an integrated care network including the TACT team, (ii) regular referral to an established private psychiatrist network with in most cases lower contact frequency, and (iii) treatment with quetiapine immediate release (QIR) at study entry, regardless of being pre-existing or newly initiated. Switching of QIR to other antipsychotics or antipsychotic augmentation therapy was allowed and did not lead to study termination (19). Participants in IC-TACT were treated with different antipsychotics based on clinician’s choice. In IC-TACT and SC, all other treatment was naturalistic, thus, all concomitant medications were allowed (e.g., other antipsychotics, benzodiazepines, mood stabilizer, antidepressants).

Assessments and outcome measures

Assessments analyzed for this study were carried out at baseline (T1), 6 (T6), and 12 (T12) months follow-up visits by trained raters who were independent of the treatment teams. The following variables were assessed: (i) sociodemographic characteristics including duration of psychosis/illness (DUP/DUI (30, 31)); (ii) diagnoses, confirmed with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I (32)); (iii) psychopathology (Brief Psychiatric Rating Scale (BPRS) (33) in IC-TACT and Positive and Negative Syndrome Scale, PANSS (34) in SC, severity of illness (Clinical Global Impressions-Severity scale (CGI-S) (35)), and functioning level (Global Assessment of Functioning scale (GAF) (36)). Quality of life was assessed with the Euro-QoL descriptive system (EQ-5D) (37), the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-18 (38)).

Service use data and cost calculation

Within each treatment arm, psychosis-related mental health service use data were assessed from the
Karow et al.

respective hospital databases. These databases cover inpatient and day-clinic care, treatment contacts in the outpatient center or at private psychiatrists, antipsychotic medications, and, only in the UKE catchment area, IC-TACT treatment contacts. Additionally, outpatient treatment contacts were collected from each participating private psychiatrist for both catchment areas. For the cost calculations of psychiatric inpatient, day-clinic, and outpatient care, unit costs were obtained from a guideline for cost calculation in health economic evaluation in Germany (39, 40) and adjusted for inflation to the year 2014 (see Table 1). Outpatient costs included the number of outpatient consultations at the outpatient centers of each hospital and private psychiatrists. The costs for IC-TACT of the University Medical Center Hamburg-Eppendorf were added to the regular outpatient costs in the IC-TACT group based on all salary, facility, and mobility costs for the ACT Employees. The costs of antipsychotic medications during outpatient care were calculated based on the officially listed German market prizes for 2014 (costs of inpatient and day-clinic care already include the bundled cost for drug treatment) (41). Switch to another antipsychotic and antipsychotic combination therapy were considered. All costs were adjusted to the year 2014 (date ACCESS-II data were obtained; Table 2).

Statistical analysis

Statistical analyses were carried out using SPSS (version 22.0; Chicago, Illinois, USA) and STATA (STATA Corp., College Station, Texas, USA, Release 14).

In order to assess the cost and cost-effectiveness of IC-TACT versus SC, we employed a two-stage approach consisting of a preprocessing and estimation stage. As we used a control group from a different catchment area, study groups were not randomized. To achieve comparability in terms of sociodemographic and disease specific characteristics, we used the reweighting technique of Entropy Balancing in the preprocessing stage (42) and balanced for the second moment, that is, mean and variance. IC-TACT was balanced for the covariates age, sex, partnership status, work status, diagnosis, and duration of the psychotic prodrome, the number of previous hospital admissions. Due to the nature and size of the historical control groups, we were unable to balance for all covariates. Unbalanced covariates (illness duration, number of previous psychiatric hospitalizations, baseline GAF, baseline PANSS, baseline EQ-5D, and Q-LES-Q-18 total score) were considered at the estimation stage. Entropy Balancing was performed in STATA 14 by means of the Ebalance program developed by Hainmueller (43).

In the estimation stage, we calculated mean differences in QALY and costs between IC-TACT and SC over a time horizon of 12 months. Differences in QALY were assessed by ordinary least square (OLS) regression controlling for the unbalanced covariates linearly. Cost differences were measured by generalized linear models (GLM) with gamma family and log link function. GLM for cost differences were controlled for the same covariates as the OLS for QALY differences.

The economic evaluation was performed as a cost-utility analysis considering total costs and QALY as effect measures. QALYs are calculated by weighting the duration of health states with preference-based valuations of health-related quality of life (so-called ‘utilities’) for these particular health states (44). Utilities were based on the EQ-5D index (25, 37), using linear interpolation of EQ-5D index scores between measurement points (37). In the present study, EQ–5D index scores from the UK were used (45, 46). As a point estimator of cost-effectiveness, we calculated the incremental cost-effectiveness ratio (ICER), that is, the ratio of the differences in mean costs and mean health effects between the ACT and the SC during the 12-month follow-up period:

$$\text{ICER} = \frac{C_{\text{ACT}} - C_{\text{SC}}}{P_{\text{ACT}} - P_{\text{SC}}} = \frac{\Delta C}{\Delta E}$$

The ICER indicates the mean additional mental healthcare costs, which have to be spent in the IC-TACT group in order to gain one additional QALY versus the SC group. To provide information on cost-effectiveness considering uncertainty, we calculated cost-effectiveness acceptance curves (CEAC) based on the net-monetary benefit (NMB) approach (47). The patient-specific NMB is defined as $NMB_i = E_i \times \lambda - C_i$, where $\lambda$ is the willingness to pay for one QALY.

To calculate the CEAC, a series of OLS regression analyses with patient-specific NMB considering different willingness-to-pay margins ($€ per

| Variable                                      | Direct Costs (€)  |
|-----------------------------------------------|-------------------|
| Outpatient Treatment Private Psychiatrist     | 49.86 per contact |
| Outpatient Treatment Psychiatric Hospital     | 209.00 quarterly  |
| Inpatient Treatment                           | 339.71 per day    |
| Day Clinic Treatment                          | 220.81 per day    |

Table 1. Average inpatient, day-clinic and outpatient treatment costs adjusted to the year 2014 in Germany (39, 40)
Cost-effectiveness in severe psychosis

Table 2. Baseline variables of patients with multiple-episode psychosis in integrated care including therapeutic assertive community treatment (IC-TACT) versus standard care (SC)

| Variable | IC-TACT (n = 214) | SC (n = 56) | IC-TACT vs SC T(df); P/χ²(df); P |
|----------|------------------|-------------|----------------------------------|
| **Demographic details** | | | |
| Age, mean (SD), y | 39.4 (14.2) | 37.6 (11.7) | −0.57(101.6); 0.33 |
| Sex, N(%) | 95 (44.4) | 32 (57.1) | 2.91(1); 0.06 |
| Partnership, N(%) | 175 (81.8) | 43 (76.8) | 0.71(1); 0.253 |
| Employment/occupation N(%) | 51 (23.8) | 8 (14.3) | 2.37(1); 0.084 |
| Independent living N(%) | 145 (67.8) | 30 (53.6) | 3.92(1); 0.035 |
| **Illness details** | | | |
| Diagnostic distribution, N(%) | | | 26.95(7); <0.001 |
| Schizophrenia | 129 (60.3) | 32 (57.1) | 35.9(1); <0.001 |
| Schizoaffective disorder | 27 (12.6) | 9 (16.1) | 13.6(1); 0.001 |
| Schizophreniform disorder | 5 (2.3) | 9 (16.1) | 3.27(1); 0.047 |
| Delusional disorder | 9 (4.2) | 3 (5.4) | 0.711(1); 0.253 |
| Psychotic disorder NOS | 7 (3.3) | 3 (5.4) | 0.06(1); 0.48 |
| Bipolar Disorder | 34 (15.9) | 0 (0) | 0.07(1); 0.33 |
| Severe Depression with Psychosis | 3 (1.4) | 0 (0) | 0.06(1); 0.48 |
| Comorbid psychiatric disorder lifetime (without SUD), N(%) | 160 (74.8) | 18 (32.1) | 35.9(1); <0.001 |
| Substance use disorder lifetime (SUD), N(%) | 135 (63.1) | 20 (35.7) | 13.6(1); 0.001 |
| Suicide attempts in the past, N(%) | 85 (39.7) | 15 (26.8) | 3.27(1); 0.047 |
| Number of suicide attempts in the past, median (quartiles)† | 2 (1, 7) | 1 (1, 3) | 0.16(1); 0.87 |
| Family history for any psychiatric disorder, N(%)‡ | 118 (55.1) | 31 (55.4) | 0.01(1); 0.98 |
| Family history for psychotic disorder, N(%) | 56 (25.2) | 11 (19.6) | 1.18(1); 0.25 |
| Traumatic events in the past, N(%) | 148 (69.2) | 40 (71.4) | 0.06(1); 0.48 |
| Duration of untreated illness, median (quartiles), weeks † | 152.1 (48.9, 270.1) | 182.5 (75.9, 341.1) | 1.6(268); 0.11 |
| Duration of untreated prodrome, median (quartiles), weeks † | 87.1 (26.1, 206.7) | 153.2 (52.1, 217.3) | 0.46(268); 0.64 |
| Duration of untreated psychosis, median (quartiles), weeks † | 21.6 (4.4, 52.1) | 27.6 (8.7, 52.1) | 1.3(68); 0.2 |
| Number of previous hospitalizations, mean (range) | 5 (0-30) | 3 (0-7) | 0.47(246); <0.001 |
| **Baseline scores of assessment scales**§ | | | |
| CGI-S, Global Clinical Impression scale–Severity score | 5.7 (0.9) | 5.0 (0.8) | −5.9(99); <0.001 |
| GAF score, mean (SD) | 36.9 (11.7) | 44.5 (11.7) | 4.32(46); <0.001 |
| PANSS total score, mean (SD)† | 139.9 (33.0) | 94.3 (18.1) | −13.7(162); <0.001 |
| Q-LES-Q-18 total score, mean (SD)§ | 2.3 (0.6) | 3.0 (0.2) | 12.0(248); <0.001 |

CGI-S, Global Clinical Impression scale–Severity score; GAF, Global Assessment of Functioning scale; PANSS, Positive and Negative Syndrome Scale; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire.

†Mann–Whitney U-Test for non-normal distributed data was used.
‡First and second degree relatives.
§Duration of untreated psychosis, prodrome, and illness were log transformed for statistical tests.
*BPRS of ACCESS II was transformed into PANSS (53).

All statistically significant differences are printed in bold.

Results

Sociodemographic and clinical data
A total of 214 patients were treated in IC-TACT and 56 patients in SC; of which 191 (89.3%) in IC-TACT versus 45 (80.3%) in SC completed one-year treatment. Altogether, 34 (12.6%) patients dropped out of treatment. There was a trend for more drop outs in SC (χ² = 3.19(1); P = 0.064).

Median time till drop out was 150 days (IQR: 96, 330) in IC-TACT and 92 days (IQR: 90, 182) in SC (F = 8.2(30.3); P = 0.085).

Comparability of the IC-TACT and SC groups was achieved by Entropy Balancing. Means and variances of balanced covariates were nearly identical. Patients were on average 39 years old, 53% were female, 81% were single, and 78% were unemployed, 65% lived independently. Most patients suffered from schizophrenia (59.6%) or...
schizoaffective disorder (13.3%). Between-group differences regarding duration of untreated psychiatric illness were non-significant (IC-TACT: 139.9 ± 33.0; SC: 94.3 ± 18.1; T = -13.7(162); P < 0.001), CGI (IC-TACT: 5.7 ± 0.9; SC: 5.0 ± 0.8; T = -5.9(99); P < 0.001), GAF (IC-TACT: 36.9 ± 11.7; SC: 44.5 ± 11.7; T = 4.3(246); P < 0.001) and number of previous hospital admissions (IC-TACT: 5 (0–30); SC: 3 (0–7); T = 0.47(246); P = 0.001). Furthermore, the Q-LES-Q-18 total score at baseline was significantly lower for patients in IC-TACT versus SC (IC-TACT: 2.3 ± 0.6; SC: 3.0 ± 0.2; T = 12.0(248); P < 0.001).

Service utilization. Treatment services were used more frequently by patients in IC-TACT versus SC patients. The mean number of outpatient contacts during the 12-month observation period was 116.3 ± 45.3 in IC-TACT vs. 15.6 ± 6.3 in SC patients (T = -31.3(239,3); P < 0.001). Conversely, the number of patients admitted to inpatient or day-clinic care was significantly lower for IC-TACT versus SC patients, that is, inpatient admission: IC-TACT: n = 64 (29.9%) vs. SC: n = 30 (53.6%); (χ² = 10.2(1); P < 0.001) and day-clinic admission: IC-TACT: n = 9 (4.2%) vs. SC: n = 14 (25.0%); (χ² = 24.3(1); P < 0.001). Similarly, the number of beddays was significantly lower in IC-TACT than SC patients, that is, inpatient beddays: IC-TACT: 10.3 ± 20.5; SC: 28.2 ± 44.9; T = 2.9(61.2); P = 0.005; day-clinic days: IC-TACT: 2.6 ± 16.7 days; SC: 16.4 ± 33.7 days (T = 2.3(62.3); P = 0.004).

Costs, QALYs, and ICER. On average, the mean unadjusted difference in total 12-month costs favored IC-TACT versus SC (IC-TACT: €9850 ± 7483 [median: €6890]; SC: €18 215 ± 17 456 [median: €11 236]; mean difference: €-8365; Robust SE: €2415; P < 0.001). After adjustment, the mean difference was €-13 248; Robust SE: €2975; P < 0.001) in favoring IC-TACT. The adjusted cost of hospital care (inpatient and day-clinic) was lower for subjects in IC-TACT versus SC (€-55 084; Robust SE: €31 758; P = 0.08), while costs for outpatient care were significantly higher for subjects in IC-TACT compared with SC (€+1417; Robust SE: €479; P = 0.003; Fig. 1).

On average, patients in the SC group gained non-significantly more unadjusted QALYs than patients in the IC-TACT group (SC: 0.63 ± 0.26 QALY; IC-TACT: 0.56 ± 0.23 QALY; mean difference: 0.07 ± 0.30 [robust SE: 0.04], P = 0.16). However, after adjustment, the mean gain of QALYs during the 12-month follow-up period was significantly higher in the IC-TACT versus the SC group. The adjusted mean difference was 0.10 QALY ± 0.37 (Robust SE: 0.05; P = 0.05). The mean incremental costs and gain of QALYs for mental health care showed the dominance of IC-TACT compared with SC. The reported results proved to be robust on the CEAC. Independent from the chosen willingness-to-pay margin, the probability of cost-effectiveness was continuously higher than 99% (Fig. 2).

Discussion

Patients with SMI, who need extended and intensive multimodal treatment, are at high risk of receiving substandard care with all its negative

![Fig. 1. 12-month outpatient and hospitalization costs of IC-TACT (n = 214) versus standard care (SC; n = 56) in multiple-episode psychosis (age 18–65).](image-url)
consequences for their chance of achieving symptomatic remission as well as symptomatic and functional recovery (48–50). Consequently, studies investigating the cost-effectiveness of therapeutic interventions for SMI are needed in order to inform healthcare decision makers about the most effective evidence-based and affordable healthcare strategies.

IC-TACT treatment in the ACCESS model was associated with significant lower inpatient and higher outpatient cost compared with SC. Importantly, the cost savings in the inpatient sector exceeded excess cost in the outpatient sector. Therefore, after calculating total costs, IC-TACT was cost saving while delivering superior care and leading to improved outcomes in people with severe psychotic disorders. Additionally, QoL increased significantly during the 12-month treatment, either in IC-TACT or SC settings. However, the increase of QoL with IC-TACT was significantly larger compared with SC. Considering both, costs and QALY, the probability of cost-effectiveness at a generally agreed upon threshold of willingness to pay of 50 000€ per QALY was higher than 99%, for patients with severe psychosis treated with IC-TACT (44). This finding means that there is a maximum 1.0% probability of error, indicating that IC-TACT is a cost-effective treatment approach. These results are in line with other recent ACT studies (51, 52). The results of the present quasi-experimental effectiveness trial study extend the prior results of ACCESS I to the real world treatment setting, in which IC-TACT is implemented in daily routine care.

The observed superiority can only be achieved by high-quality and high-quantity outpatient care with a combination of case management and home treatment. Outpatient treatment services were used far more frequently by patients in IC-TACT and the number of patients admitted to inpatient or day-clinic care was lower compared with SC. Results of the present study further indicate that the superior effectiveness of IC-TACT is dependent on the specification of the manualized treatment model and the standard of care, which is in line with our previous results (7). The integrated care model comprises a high fidelity of IC-TACT teams with a recovery-oriented, multimodal treatment approach, who are specialized on patients with schizophrenia-spectrum and bipolar disorders with high illness severity and low functioning (45, 46).

Limitations and strengths
The present study was not randomized, but rather used historical control groups. This approach might have introduced bias due to secular trends and differences in delivery and quality of SC. Although we do not have reason to believe that SC would have been substantially altered in the region where the study took place over a two-year period,
we cannot exclude this possibility. Nevertheless, the naturalistic design and setting also allowed us to include patients with an illness severity that is likely much more generalizable and reflective of usual care settings than in RCTs, with PANSS total scores ranging from 120 to 140 in the IC-TACT and 90-95 in the SC groups, and with CGI-S scores of 6 (‘severely ill’) in the IC-TACT and 5 (‘markedly ill’) in the SC groups. Moreover, treatment groups differed significantly with regard to sociodemographic and clinical variables at baseline. However, we applied the reweighting method of Entropy Balancing to balance the comparison groups with regard to relevant covariates in order to address this issue. This adjustment was successful to a great extent as indicated by our ability to precisely adjust the means and variances of different relevant covariates between the groups. Furthermore, patients in SC received QIR at study entry, though switching to any other antipsychotics or antipsychotic augmentation or augmentation of other drugs was allowed. It is very likely that this had caused a selection bias toward patients with lower levels of illness in the SC group. However, this difference could also be interpreted as conservative bias that would strengthen the results.

With respect to the economic analysis, it has to be noted that the presented cost calculations have the following limitations: (i) neither costs for concomitant medications other than antipsychotics nor for non-mental health services were included, (ii) costs for the implementation of a new IC-TACT team, for example, a lower than optimal case load at beginning, were not considered, (iii) 10% of patients dropped out of treatment without differences between IC-TACT versus SC, although a trend for more drop outs in SC was observed. Taking all of these aspects into account, costs of treatment in both IC-TACT and SC are likely underestimated. Furthermore, from a societal perspective, it must be noted that several important costs, such as indirect costs due to lost productivity or supported accommodation caused by disease related disability, or the emotional costs of the psychological burden for caregivers, were not included in the present analyses. Regarding the productivity losses, we can make the educated guess that the consideration of productivity losses could make IC-TACT even more favorable. This assumption is based on the lower number of inpatient admissions and beddays. Every day in hospital is a day a patient cannot work and hence a day of lost productivity. However, this is just an assumption. Whether patients who were not in the hospital were able to work or on sick leave we do not know.

Nevertheless, despite these limitations, this study has the strengths of a prospective design, the investigation of a recovery-oriented, interdisciplinary, and team-based treatment approach under real world conditions with a focus on people with SMI, and the assessment of indicated cost-effectiveness of the IC-TACT treatment model over SC. Clearly, economic analyses will yield different results in different healthcare settings. However, it is ubiquitous that inpatient costs are much higher than outpatient care costs. Thus, saving substantially on inpatient care would likely translate into considerable cost savings in most, if not all, treatment settings. Nevertheless, this premise requires testing through application of IC-TACT in other countries and healthcare systems.

To conclude, the cost utility analyses of this study in patients with schizophrenia-spectrum and bipolar disorders treated with IC-TACT or SC confirmed that treatment within the ACCESS model was less costly and more effective compared with SC. Differences in treatment costs in IC-TACT compared with SC revealed cost savings, though the present IC-TACT intervention was carried out by highly educated and therefore ‘costly’ psychosis experts staff specifically trained in the delivery of care to psychotic patients that was tailored to the needs of patients with severe psychosis. In addition, treatment with IC-TACT resulted in a large shift of costs from inpatient to outpatient care. Consequently, the results confirmed the benefit of recovery-oriented, interdisciplinary, and team-based treatment approaches for people with SMI with the core features: specialization on psychosis with SMI, low therapist-patient ratio, no drop out policy, 24-h daily crisis intervention, high-frequent treatment contacts, across-setting treatment continuity and need adapted treatment including individual and group psychotherapy.

Acknowledgements

The authors express their gratitude to all participating patients and health professionals, who were involved in the integrated care of the participating patients.

Conflict of Interest

Prof. Karow and Prof. Lambert have been consultants and/or advisors to or have received honoraria from: AstraZeneca, Bristol-Myers Squibb, Lilly Deutschland GmbH, Janssen Cilag GmbH, Lundbeck GmbH, Otsuka Pharma GmbH, Roche Deutschland Holding GmbH, Sanovi Aventis, Trommsdorff GmbH & Co. KG. Prof. Correll has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Angelini, Boehringer-Ingelheim, Gerson Lehrman Group, Indivior, IntraCellular Therapies, Janssen/
Cost-effectiveness in severe psychosis

disorders and their influence on 4-year outcomes of integrated care treatment (ACCESS II study). Schizophr Res 2017;193:377–383.
4. CONUS P, COTTON S, SCHMIELMANN BG et al. Rates and predictors of 18-months remission in an epidemiological cohort of 661 patients with first-episode psychosis. Soc Psychiatry Psychiatr Epidemiol 2017;52:1089–1099.
5. FLEISCHBACHER WW, CETKOVICH-BARMASS M, DE HERT M et al. Comorbid somatic illnesses in patients with severe mental disorders: clinical, policy, and research challenges. J Clin Psychiatry 2008;69:514–519.
6. LAMBERT M, CONUS P, COTTON S et al. Prevalence, predictors, and consequences of long-term refusal of antipsychotic treatment in first-episode psychosis. J Clin Psychopharmacol 2010;30:565–572.
7. KAROW A, REIMER J, KÖNGH HH et al. Cost-effectiveness of 12-month therapeutic assertive community treatment as part of integrated care versus standard care in patients with schizophrenia treated with quetiapine immediate release (ACCESS trial). J Clin Psychiatry 2012;73:e402–e408.
8. MENNEAR M, BRIAND C. Implementing a continuum of evidence-based psychosocial interventions for people with severe mental illness: part 1-review of major initiatives and implementation strategies. Can J Psychiatry 2014;59:178–186.
9. BRIAND C, MENNEAR M. Implementing a continuum of evidence-based psychosocial interventions for people with severe mental illness: part 2-review of critical implementation issues. Can J Psychiatry 2014;59:187–195.
10. GÖNÉE U, WEIDMANN S, ARNOLD K et al. S3 guideline on psychosocial therapies in severe mental illness: evidence and recommendations. Eur Arch Psychiatry Clin Neurosci 2014;265:173–188.
11. DE HERT M, CORRELL CU, BOBES J et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry 2011;10:52–77.
12. DE HERT M, COHEN D, BOBES J et al. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. World Psychiatry 2011;10:138–151.
13. CORRELL C, GALLOW B, PARMAR A et al. Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis: A Systematic Review, Meta-analysis, and Meta-regression. JAMA Psychiatry. 2018 Jun 1;75:555–565. doi: 10.1001/jamapsychiatry.2018.0623.
14. MURPHY SM, IRVING CB, ADAMS CE et al. Crisis intervention for people with severe mental illnesses. Cochrane Database Syst Rev 2015;12:CD001087.
15. MARSHALL M, LOCKWOOD A. Assertive community treatment for people with severe mental disorders. Cochrane Database Syst Rev 2011;4:CD001089.
16. NORDEN T, NORGANDER T. Absence of positive results for flexible assertive community treatment. What is the next approach? Clin Pract Epidemiol Ment Health 2014;10:87–91.
17. NUGTER MA, ENGELSREI B, BÄHLER M et al. Outcomes of FLEXIBLE assertive community treatment (FACT) implementation: a prospective real life study. Community Ment Health J 2016;52:898–907.
18. VAN VELDHUIZEN R et al. Flexible ACT & resource-group ACT: different working procedures which can supplement and strengthen each other. A response. Clin Pract Epidemiol Ment Health 2015;11:12–15.

Contributors

The study was conducted as Investigator-Initiated Trial (IIT) in collaboration of the Psychosis Centre of University Medical Center Hamburg-Eppendorf (AK, ML, TB, BGS, and DN) and the Department of Psychiatry of the Asklepios Westklinikum Hamburg. The first and senior authors (AK and ML) developed the research question, the study design, and conducted the study together with the ACCESS study group. AK, CB, CC, BGS, HHK, DS and ML conducted the data analysis strategy, had access to the raw data, analyzed the data, interpreted the data, and wrote the manuscript. All authors have read and contributed to the final version of the manuscript.

Role of Funding Source

The ACCESS I study was conducted as Investigator-Initiated Trial (IIT) funded by an Educational Grant of AstraZeneca Germany. AstraZeneca had no role in developing the research question and data analysis strategy, analyzing the raw data, interpreting the data, or writing the manuscript. AstraZeneca had the right to comment on the final draft of this manuscript before submission to the Journal. AstraZeneca agreed to publication without material change. The ACCESS II study was funded by the participating health insurances (AOK Rheinland, DAK, HEK, IKK Classic).

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. DELESPAUT PH. Consensus regarding the definition of persons with severe mental illness and the number of such persons in the Netherlands. Tijdschr Psychiatr 2013;55:427–438.
2. BAGALMAN E, NAPLI A. Prevalence of Mental Illness in the United States: Data Sources and Estimates, in Library of Congress. Congressional Research Service. Washington, D.C.: U.L.G.D. Department, Editor. 2015.
3. LAMBERT M, RUPPELT F, SEM A-K et al. Comorbidity of chronic somatic diseases in patients with psychotic
25. ROSENHECK A et al. Cost-effectiveness of early intervention in first-episode psychosis: economic evaluation of a randomised controlled trial (the OPUS study). Br J Psychiatry 2012; 202:35–41.

26. ROTH ET AL. The Hamburg-model of integrated care for patients with psychosis: Part 1. Rationale, treatment concept and results of the pre-study. Psychiatr Prax 2014;41:257–265.

27. LAMBERT M, BOCK T, DAUBMANN A et al. The Hamburg-model of integrated care for patients with psychosis: Part 1. Rationale, treatment concept and results of the pre-study. Psychiatr Prax 2014;41:257–265.

28. LAMBERT M, SCHOTTLE D, SENUTTA M et al. Early detection and integrated care for adolescents and young adults with severe psychotic disorders: rationales and design of the Integrated Care in Early Psychosis Study (ACCESS III). Early Interv Psychiatry 2016;12:96–106.

29. KAROW A, BOCK T, DAUBMANN A et al. The Hamburg-model of integrated care for patients with psychosis: Part 2. Results of the clinical course over 2- and 4-years of treatment. Psychiatr Prax 2014;41:266–273.

30. McGorry P, COPOLOV DL, SINGH BS. Royal park multidagnostic instrument for psychosis: Part I. Rationale and review. Schizophr Bull 1990;16:501–515.

31. McGorry P, SINGH BS, COPOLOV DL, PARK ROYAL. Multidagnostic instrument for psychosis: Part II. Development, reliability and validity. Schizophr Bull 1990;16:517–536.

32. VENTURA J, LIBERMAN RP, GREEN MF et al. Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I-P). Psychiatry Res 1998;79:163–173.

33. OVERALL JE, GORHAM DR. The brief psychiatric rating scale. Psychol Rep 1962;10:799–812.

34. KAY SR, FIEBEE A, OPLE LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276.

35. HARO JM, KAMATH SA, OCHOA S et al. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand Suppl 2003;416:16–23.

36. GUY W. ECDEU Assessment Manual for Psychopathology, revised. Rockville: National Institute of Mental Health 1976 (DHHEW Pub. No. (ADM) ): p. 76–338.

37. GROUP E. EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 1999;16:199–208.

38. RITZER M, KURS R, GIEß A et al. Validity of an abbreviated quality of life enjoyment and satisfaction questionnaire (Q-LES-Q-18) for schizophrenia, schizoaffective, and mood disorder patients. Qual Life Res 2005;14:1693–703.

39. KRAUTH C, HESSEL F, HANSMEEER T et al. Empirical standard costs for health economic evaluation in Germany – a proposal by the working group Methods in Health Economic Evaluation. Gesundheitswesen 2005;67:736–748.

40. BOCK JO, BRETTSCHEIDER C, SELM H et al. Calculation of standardised unit costs from a societal perspective for health economic evaluation. Gesundheitswesen 2015;77:53–61.

41. Rote Liste. Arzneimittelverzeichnis für Deutschland. Frankfurt/Main: Rote Liste Service GmbH; 2014.

42. HAUSMÜLLER J. Entropy balancing for causal effects: A multivariate reweighting method to produce balanced samples in observational studies. Political Anal 2011;20:25–46.

43. HAUSMÜLLER J, XU Y. Ebalance: A Stata package for entropy balancing. J Stat Softw 2013;54:7.

44. RICHARDSON G, MANEA A. Calculation of quality adjusted life years in the published literature: a review of methodology and transparency. Health Econ 2004;13:120310.

45. BROOKS R, RABIN R, DE CHIARO F. The measurement and valuation of health status using EQ-5D: a European perspective. Amsterdamin: Kluwer 2003.

46. HERTH RA, CHERNEW ME, MILLER E et al. Willingness to pay for a quality-adjusted life year: in search of a standard. Med Decis Making 2000;20:332–342.

47. LAMBERT M, BOCK T, DAUBMANN A et al. The Hamburg-model of integrated care for patients with psychosis: Part 1. Rationale, treatment concept and results of the pre-study. Psychiatr Prax 2014;41:257–265.

48. LAMBERT M, SCHOTTLE D, SENUTTA M et al. Early detection and integrated care for adolescents and young adults with severe psychotic disorders: rationales and design of the Integrated Care in Early Psychosis Study (ACCESS III). Early Interv Psychiatry 2016;12:96–106.

49. KAROW A, BOCK T, DAUBMANN A et al. The Hamburg-model of integrated care for patients with psychosis: Part 2. Results of the clinical course over 2- and 4-years of treatment. Psychiatr Prax 2014;41:266–273.

50. McGorry P, COPOLOV DL, SINGH BS. Royal park multidagnostic instrument for psychosis: Part I. Rationale and review. Schizophr Bull 1990;16:501–515.

51. McGorry P, SINGH BS, COPOLOV DL, PARK ROYAL. Multidagnostic instrument for psychosis: Part II. Development, reliability and validity. Schizophr Bull 1990;16:517–536.

52. VENTURA J, LIBERMAN RP, GREEN MF et al. Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I-P). Psychiatry Res 1998;79:163–173.

53. OVERALL JE, GORHAM DR. The brief psychiatric rating scale. Psychol Rep 1962;10:799–812.

54. KAY SR, FIEBEE A, OPLE LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276.

55. HARO JM, KAMATH SA, OCHOA S et al. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand Suppl 2003;416:16–23.

56. GUY W. ECDEU Assessment Manual for Psychopathology, revised. Rockville: National Institute of Mental Health 1976 (DHHEW Pub. No. (ADM) ): p. 76–338.

57. GROUP E. EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 1999;16:199–208.

58. RITZER M, KURS R, GIEß A et al. Validity of an abbreviated quality of life enjoyment and satisfaction questionnaire (Q-LES-Q-18) for schizophrenia, schizoaffective, and mood disorder patients. Qual Life Res 2005;14:1693–703.

59. KRAUTH C, HESSEL F, HANSMEEER T et al. Empirical standard costs for health economic evaluation in Germany – a proposal by the working group Methods in Health Economic Evaluation. Gesundheitswesen 2005;67:736–748.

60. BOCK JO, BRETTSCHEIDER C, SELM H et al. Calculation of standardised unit costs from a societal perspective for health economic evaluation. Gesundheitswesen 2015;77:53–61.

61. Rote Liste. Arzneimittelverzeichnis für Deutschland. Frankfurt/Main: Rote Liste Service GmbH; 2014.

62. HAUSMÜLLER J. Entropy balancing for causal effects: A multivariate reweighting method to produce balanced samples in observational studies. Political Anal 2011;20:25–46.

63. HAUSMÜLLER J, XU Y. Ebalance: A Stata package for entropy balancing. J Stat Softw 2013;54:7.

64. RICHARDSON G, MANEA A. Calculation of quality adjusted life years in the published literature: a review of methodology and transparency. Health Econ 2004;13:120310.

65. BROOKS R, RABIN R, DE CHIARO F. The measurement and valuation of health status using EQ-5D: a European perspective. Amsterdamin: Kluwer Academic Publishers; 2003.

66. PAPAZANNOI D, BRAZIER J, PARRY G. How valid and responsive are generic health status measures, such as EQ-5D and SF-36, in schizophrenia? A systematic review. Value Health 2012;14:907–920.

67. HOCH JS, BRIGGS AH, WILAN AR. Something old, something new, something borrowed, something blue: a framework for the marriage of health econometrics and cost-effectiveness analysis. Health Econ 2002;11:415–430.

68. LAMBERT M, KAROW A, LECERTY S et al. Remission in schizophrenia: validity, frequency, predictors, and patients’ perspective 5 years later. Dialogues Clin Neurosci 2010;12:393–407.

69. JAASKELAINEN E, JUOLA P, HRVDÖVINEN N et al. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull 2013;39:1296–1306.

70. CARBON M, CORRELL CU. Clinical predictors of therapeutic response to antipsychotics in schizophrenia. Dialogues Clin Neurosci 2014;16:505–524.

71. KILLASPY H, KINERTY S, BERRINGTON P et al. Randomised evaluation of assertive community treatment: 3-year outcomes. Br J Psychiatry 2009;195:81–82.

72. MCCROME P, CRABBE TKJ, POWER P et al. Cost-effectiveness of an early intervention service for people with psychosis. Br J Psychiatry 2010;196:377–382.

73. LEECH T, ROTH P, DAVIS JM et al. Equipercentile linking of the BPRS and the PANSS. Eur Neuropsychopharmacol 2013;23:956–959.