

# **A randomised clinical trial of the effect of two years versus five years specialized assertive intervention for first episode psychosis**

## **Aim**

With a randomised clinical trial we want to investigate if the positive short term outcomes (first 1-2 years), achieved with specialized assertive intervention programme (OPUS), can be maintained for five years if the specialized treatment is sustained over the first five years in comparison to only two years of specialised treatment followed by three years of standard treatment.

The aim is to compare the effect on clinical symptoms, substance abuse and institutionalisation and labour market affiliation of two-years versus five-years specialised assertive intervention programme (OPUS-treatment) for first episode psychosis

Hypothesis: It is possible to maintain the positive results of the intensive two-year intervention in another three year for those who keep receiving the specialized assertive intervention programme.

## **Background**

### Schizophrenia

Schizophrenia is a severe brain disease with complex pathogenetic and pathophysiological mechanisms and inadequate treatments. Schizophrenia is a disorder that afflicts the young, stays with them for life, and exerts tremendous suffering and burden for the patients themselves, for the relatives and for others. The primary features of schizophrenia and related disorders are psychotic symptoms (delusions, hallucinations) disorganization of thought and behaviour, and negative symptoms (poverty of thought and affect, apathy and emotional withdrawal)<sup>1</sup>, as well as depressive, manic and anxiety symptoms in the acute phase, and residual symptoms and cognitive impairments (deficits in memory, attention and concentration) and social disability in the longer term. The most serious implications of these disorders are their impact on peoples' lives through interference with their social and emotional maturation, education, employment, and important life transitions such as marriage and parenthood. Furthermore, psychosis is associated with very high rates of substance abuse, depression, suicide<sup>2</sup>, violence and legal problems, and evaluation of the direct cost of schizophrenia in different European countries indicate that these cost sum up to approximately two percent of national health expenditure<sup>3</sup>, a similar order of magnitude to cancer or ischemic heart disease. Moreover there are also huge indirect costs to society in terms of lost productivity. Thus such disorders represent a very serious public health problem with enormous economic and social costs to the public.

It is of utmost importance to identify possibilities for prevention and treatment. The evidence base for the treatment of psychotic disorders is underdeveloped<sup>4</sup>. Historically, randomised, controlled trials have been few in number and uneven in quality<sup>5</sup>. There is an urgent need for large investigator initiated, independent, non-commercial trials of complex interventions that can help us to prevent the invalidating and deteriorating course in many patients.

### First episode psychosis

The focus on first-episode psychosis arises because converging evidence suggest that the underlying illness process that affects biological, psychological and social domains undergo major deterioration around the peri-onset phase of illness. Hence this early phase of illness requires special attention. Delayed detection and treatment is a widespread problem and predicts poor clinical outcome<sup>6;7</sup>. The positive effects of ACT,<sup>8</sup> psycho-educational family intervention,<sup>9;10</sup> and social skills training<sup>11;12</sup> for chronic patient populations with psychosis are well documented. Interest in the possible

benefits of early specialized intervention for psychotic disorders<sup>13-15</sup> has been increasing. Such specialized early-intervention services are characterized by comprehensive, multi-modal and phase-specific treatment of first-episode psychosis, modified to suit the needs of this patient population (including intensive/assertive case management and family involvement).<sup>15</sup>

### Rationale for the trial

Through state funding it was possible to carry out the OPUS trial, in which we included 547 patients with first-episode psychosis and thereby established the largest trial in first-episode psychosis in the world. The effects of OPUS treatment was clearly better than standard treatment, and the results were published in high impact journals and six researchers defended Ph.D.-theses based on results from the trial. Thereby it was possible for Danish researchers to play a pioneering role in demonstrating that it was possible to improve clinical outcome through a specialised early intervention service.<sup>13</sup> The Danish OPUS trial and the English LEO (Lambeth Early Onset) trial<sup>14</sup> of the short-term (two years) benefits of this specialized approach have confirmed that patients treated in a specialized early intervention service have higher rates of adherence, lower rates of relapse and substance abuse, fewer negative symptoms, better functional outcomes, decreased use of inpatient services, and improved user satisfaction after two years, compared to patients treated in standard treatment. However, results from five-year follow-up show that many of the encouraging findings were not sustainable at five-year follow-up, three years after the experimental treatment ended, apart from the finding that significantly more patients who received OPUS treatment were able to maintain independent living (as opposed to living in an institution for mentally ill).<sup>16</sup> This suggests that many of the initial advantages of specialized treatment were lost once the patients were transferred to regular care. Thus, the evidence basis for the duration of specialised treatment is lacking, and it is likely that two years of treatment is too short.

It has been hypothesized that there is a critical period up to five years after onset of illness, which represents a window of opportunity where a long-term course can be influenced.<sup>17</sup> It is possible that extending the specialized assertive intervention service up to five years will allow the beneficial effects to continue beyond this high-risk period, through consolidation of improved social and functional outcome. We therefore propose as the next and utmost important step to carry out a secondary preventive trial of two years versus five years of specialized assertive intervention. The project will thereby provide clinicians and planners of mental health services with the needed high level of evidence for planning of the duration of services for first-episode psychosis patients. The cost-benefits of a specialized assertive intervention sustained for the entire critical period are also equally important to establish.

### Perspectives

The results of the OPUS trial have influenced the planning of treatment for first episode patients in all Danish Regions and in other countries. The assertive and supportive approach has changed the organisation of psychiatric treatment putting more emphasis on continuity of care, treatment tailored to meet patients' needs, integration of social aspects, labour market affiliation and health care, focus on rehabilitation and family involvement. The psychiatric treatment has developed to a more flexible organisation, better suited to meet the needs of the patients and to help the relatives to continue to play the roles as supportive caregivers. If the positive two-year results can be maintained for a longer period, it will influence the prognosis for the patients and be of great importance for health care planning.

## **Methods**

### **Design**

The design is an open label randomized design given the nature of the question. Patients and care providers cannot be kept blind to treatment allocation. Prior to randomization all patients will have received treatment for first-episode psychosis in one of the five OPUS-teams in the Capitol Region or in one of the three teams in Region Midt. OPUS teams incorporate modified assertive case management, rational pharmacotherapy, family psycho-educational intervention, group interventions to aid with recovery, social skills training, cognitive behaviour therapy when indicated, and crisis intervention. OPUS-treatment is tailored to meet patients' needs. After 1½ years treatment in OPUS teams, patients will be randomised to another 3½ years OPUS-treatment or versus ½ year OPUS-treatment and thereafter referral to standard treatment.

### **Participants**

Patients, aged 18-35 years, with first episode psychosis in schizophrenia spectrum, treated for 1½ year in the five OPUS teams in the Capitol Region and the three OPUS teams in Region Midt and who will give informed consent to participate in the study can be included.

We plan to recruit 225 patients for the trial in 2009 and 75 patients in 2010. This is realistic as each of the OPUS teams discharge approximately 40 patients per year. Patients will fulfil ICD 10 diagnostic criteria for schizophrenia or schizophrenia like psychosis (F20, F22-F29).

### **Randomisation**

The included patients will be randomised to either ½ or 3½ years further specialised assertive intervention in OPUS teams. Researchers will independent and blinded for treatment allocation, randomisation will be centralised and computerised with concealed randomisation sequence (carried out by Copenhagen Trial Unit). Block size will be unknown to researchers and clinicians, and randomization will be stratified for treatment site (eight sites) and symptom severity (none or mild versus more severe negative symptoms). Informed consent will be obtained prior to patients being randomized. Patients, who are randomised to only ½ year further specialised treatment, will be transferred to standard treatment after six month.

### **Outcome measures**

Negative symptoms, measured with Schedule for Assessment of Negative Symptoms in Schizophrenia, SANS) are the primary outcome measure. Psychotic symptoms, substance abuse, user satisfaction, adherence to treatment, compliance with medication, suicidal behaviour, use of bed days, ability to live independently, and labour market affiliation are secondary outcome measures.

Instruments: Schedule for Clinical Assessment in Neuropsychiatry (SCAN)<sup>18</sup>, Schedule for assessment of positive and negative symptoms in schizophrenia (SAPS and SANS)<sup>1</sup>, Client Satisfaction Questionnaire (CSQ)<sup>19</sup>, Life Chart Schedule (LCS)<sup>20</sup>, and cognitive functions<sup>21</sup>.

Register based information: Vital status, cause of death<sup>22</sup>, use of mental health services<sup>23</sup>, living in an institution for mentally ill, labour market affiliation, sick leave, early age pension<sup>24</sup>, use of antipsychotic medication can be extracted from the unique, complete, longitudinal Danish registers.

### **Power calculation**

We want to be able to detect a difference of 0.4 point in negative dimension, measured with SANS. Based on our previous findings, we expect the patients treated in OPUS to have 1.42 in negative dimension and standard patients to have 1.84; standard deviation is expected to be 1.2.<sup>25</sup> With the 0.05 level of significance and with power 0.8, 129 patients were required for each study group and 150 patients will be included because 15 percent attrition is expected.

## **Data analyses**

Analysis will be based on intention-to-treat principles. Data from all patients will be included in the group to which random assignment is made. The characteristics of patients that are lost to follow-up will be compared with those that remain in the study. Continuous outcome measures will be analysed in a repeated measurements model with unstructured variance matrix. This approach assumes that the distribution of missing data can be estimated from the information from previous interviews. The condition for using this method is the assumption that data are missing at random when taking into consideration the information extracted from baseline interviews... In this model baseline values of the scales are included<sup>26</sup>. Dichotomous outcomes will be analysed with logistic regression with baseline values of the variable included as covariates.

## **Treatments**

The trial is pragmatic, comparing two versus five years of specialised, assertive intervention programme (OPUS) defined by a set of protocols.

### *Specialised assertive intervention programme (OPUS)*

The integrated treatment consisted of three core elements; Assertive Community Treatment, family treatment and social skills training. Eight multidisciplinary teams has been established and trained to provide specialised assertive intervention. Caseload is 1:10. The patients are designated a primary staff member, who are responsible for maintaining the contact and to coordinate the treatment within the team, but also across social services and other institutions involved in the treatment. Patients will be visited in their homes or other places in their community or at their primary team member's office according to the patients' preferences. The team will offer psycho educational family treatment to all patients. The team will always try to get in contact with at least one family member and motivate the family to participate in a psycho educational group.

### *Standard treatment*

Patients, who are randomised to two years of specialised assertive intervention, will be transferred to standard treatment, when the two-year period is running out. Standard treatment usually offers the patient treatment at a community mental health centre. Home visits are possible but office visits is the general rule. The caseload of staff members vary between 1:20 and 1:30. The transition to standard treatment will be carried out gradually and as gentle as possible.

## **Economy**

Two large Danish Regions, The Capitol Region and Region Midt, has offered to fund the intervention part of a trial comparing the effects of two years versus five years OPUS treatment with 21 million DKK over a five year period and thereby made it realistic to conduct such trial.

## **Project organisation and management**

The trial will be carried out in the Capitol Region and in Region Midt, and will be based in Psychiatric Centre Bispebjerg, where a series of interventional trials in different phases of schizophrenia spectrum disorders is conducted, from the early prodromal phase, to the early psychotic phase, and to later phases with specialized intervention for co-morbid substance abuse and neurocognitive deficits. The project group consists of Professor Merete Nordentoft, Professor Ole Mors, Professor Preben Bo Mortensen, Dr. Anne Thorup, Dr. Lone Petersen, Dr Pia Jeppesen and Dr. Mette Bertelsen, who are well-estimated experts in psychopathology, psychiatric epidemiology and psychosocial treatment in schizophrenia.

The local management of the project will be led by Professor Merete Nordentoft. The Ph.D.-students involved in the project will benefit from being involved with researchers who have worked with clinical and epidemiological research in schizophrenia spectrum disorders for many years, and from the excellent opportunities for international collaboration.

The centralised randomisation procedures will be planned together with Copenhagen Trial Unit. Professor, dr. sc. Philip Hougaard will supervise the statistical analyses.

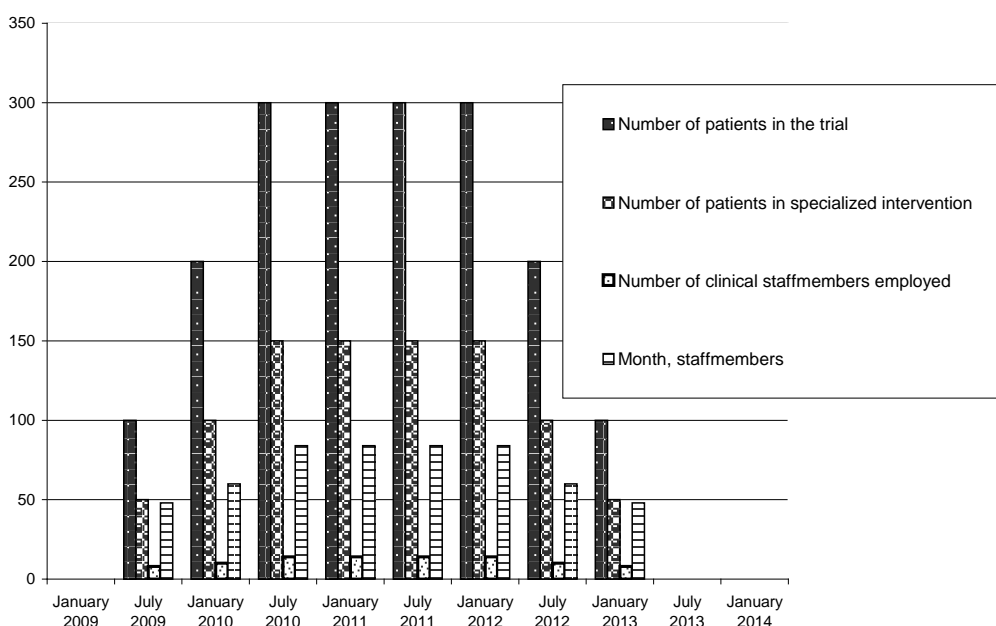
Blinding of researchers will be ensured by carefully instructions to patients not to reveal the treatment group they have been randomised to. If patients in spite of instructions reveal their treatment allocation to the researcher, the evaluation will be carried out by another person in the research group who then will be kept blinded. Meetings will be arranged to ensure programme fidelity and interrater reliability. Baseline interviews will be carried out by a Ph.D.-student and research nurses, trained in all instruments used in the study. Follow-up interview interviews will be carried out by research nurses and two Ph.D.-students (one in Copenhagen and one in Aarhus). The themes for the Ph.D.-studies will be planned by the project group.

### International collaboration

The research group has a close collaboration with the PEPP project in Montreal through the Principal Investigator in the PEPP-projects, Professor Ashok Malla, Douglas Hospital Research Centre (McGill University). An application, with Merete Nordentoft as co-applicant, for a comparison of two years versus five years specialised treatment in Montreal was submitted to CIHR, and the researchers expect answer to their application in autumn 2008. In the meantime the Canadians are conducting the trial as a pilot project at one centre in Montreal.

The research group has a close collaboration with Professor Tom Craig at Institute of Psychiatry London, principal investigator in the LEO trial and Dr. Paddy Power, leader of the LEO Unit, Lambeth Hospital. In London, the researchers behind the LEO trial have planned to seek funding for an extension trial like the one described, and through the international collaboration, we will ensure that the results of the trials in Copenhagen, London and Montreal can be compared.

Number of patients and clinical staff members in the trial



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