Tolerance and Effect of Antipsychotics in children and adolescents with psychosis

An investigator-initiated, phase IV, randomised double-blind multi-centre trial of the benefits and harms of aripiprazole versus quetiapine in children and adolescents with psychosis

The TEA Trial

Protocol version 10 – November 2013 (ENGLISH)

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ClinicalTrials.gov: NCT01119014
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CTU number: TEA-DP-157-CT-53
Summary

Background The benefits and harms of antipsychotics are relatively well studied in adults. Numerous studies with adult patients have found treatment with antipsychotics to be more effective than placebo in terms of improving psychotic symptoms and preventing relapse. However, there is a lack of scientifically valid studies regarding the benefits and harms of antipsychotics in children and adolescents with psychosis. The indication of using antipsychotics in children and adolescents is based on knowledge that has primarily been extrapolated from studies of adults. This is problematic, since a large number of children and adolescents are treatment resistant and the prevalence of adverse reactions has been found to be larger in children and adolescents. Characterising the efficacy and tolerability of atypical antipsychotic drug treatment in children and adolescents with psychotic symptoms will lead to a more rational and individualised treatment, e.g., based on the specific psychopathological symptoms, cognitive deficits, and somatic status of patients. The identification of early indicators of later sustained clinical effects of antipsychotics is of great clinical relevance, as unnecessary long treatments with suboptimal effects can be avoided.

Objective The main objective of the TEA trial is to compare the efficacy and adverse reactions of two antipsychotics (quetiapine versus aripiprazole) in children and adolescents between 12-17 years of age with psychotic symptoms on psychopathology, cognitive deficits, and daily functioning. Furthermore, the trial will focus on adverse reaction profiles of the two antipsychotics as well as early predictors of later sustained clinical effects of these antipsychotics. Additionally we will investigate health-related quality of life after antipsychotic treatment for psychosis, and the perception of stigmatisation following a psychotic illness.

Intervention Intervention arm A will in a 9-day titration phase get quetiapine extended release, titrated up to 600 mg per day. The dose can be titrated up to 800 mg per day if needed for efficacy, or titrated down to a lower dose level if not tolerated. Intervention arm B will get aripiprazole in a 9-day titration phase with a final daily dose of 20 mg. The dose can be titrated up to 30 mg if needed for efficacy, or titrated down to a lower dose level if not tolerated. If participants cannot stick with their assigned treatment for the blinded 16 weeks of treatment, the investigator will unblind the intervention assigned to that participant and is free to choose any treatment in accordance with the patient. A sex and age matched healthy control group will be included to form a reference group for cognitive and somatic measures. The healthy controls will not receive any trial medication.

Design The trial is a Danish, randomised multi-centre trial. Patients will be randomised to a 16 weeks double-blind intervention period, with assessments of benefits and harms at 2 week, 4 weeks, and 12 weeks after randomisation. After the 16 weeks double-blind intervention period, the intervention is unblinded and the treating physician is free to choose any treatment. All participants will further be re-assessed at one year after the randomisation. The healthy controls will works as a control and standard group for somatic and cognitive measurements.

Trial size Total size is 200 participants: 100 in intervention arm A (quetiapine extended release); 100 in intervention arm B (aripiprazole). In addition 100 healthy volunteering controls will be examined.
Inclusion criteria non-organic and non-drug-induced psychosis; minimum one psychotic symptom that scores minimum 4 points on PANSS (‘Positive And Negative Syndrome Scale’); referred to participating psychiatric departments, where prescription of antipsychotic compound is considered; 12-17 years of age (both inclusive), both sexes; antipsychotic-naïve or previously received antipsychotic treatment for a psychotic illness for a maximum of one year within the last calendar year, patients who has received antipsychotic treatment for a maximum of one week (Lifetime, regardless of time) may also be included; both inpatients and outpatients; any intelligence quotient (IQ), and informed consent.

Exclusion criteria compulsory treatment; drug-induced or organic psychosis, severe chronic somatic illness or a history of severe head-trauma; no psychotic symptoms but prescribed antipsychotic treatment on the indication of, e.g., severe behavioural problems or tics; pregnancy; substance abuse (substance abuse is defined by F1x.2 Dependence syndrome); aggravation of psychosis; or lack of informed consent.

Outcome measures
Primary: Psychotic symptoms measured as changes in PANNS positive subscale.
Secondary: Negative symptoms, cognition; cognitive daily functioning; motor adverse reactions; metabolic adverse reactions; hormonal adverse reactions; cardiac adverse reactions; and early indicators (after 2 and 4 weeks of treatment) of sustained significant clinical effects on psychopathology.

Time schedule Recruitment of participants starts medio 2010. Inclusion period is 4 years (medio 2010 – medio 2014). Follow-up period ends one year after the last participant has been randomised. Data analysis and presentation of results of the randomised trial (first 16 weeks) will happen in year 2014-2015, while data analyses and presentation of follow-up results will be in 2015-2016.

Ethical considerations All participants (and their parents) will receive full information (oral information and written information for parents and adolescents) about the trial to a level of their understanding, and will not be included in the trial without informed consent. The results from the TEA trial is expected to benefit the future treatment of children and adolescents with psychosis.

Safety It is not anticipated that the TEA trial will entail any particular risks or complications for participants. Adverse events and adverse reactions will be monitored closely in the trial.

Economy Funding is obtained from The Research Council for Health and Disease in 2007 (post doc scholarship, DKK 1,953,745 but only spent DKK 293,722); the Danish Association for Mental Health (DKK 50,000); Rosalie Petersen Foundation (DKK 60,000), The Psychiatric Centre for Children and Adolescents in Bispebjerg (a half-time clinical assistant for three years); the Capitol Region Psychiatry 2009 (Ph.D. scholarship, DKK 1,530,000 and general grant, DKK 880,000); A.P. Møller foundation (DKK 50,000); Research Institute for Biological Psychiatry, Sct. Hans Hospital 2009 (DKK 3,000,000 for genetic analyses). Tryg Fonden (DKK 2,000,000); Region Hovedstadens Forskningsfond, (DKK 2,475,000), 2010, Tryg Fonden 2011 (DKK 2,000,000), Psykiatrieforskningsfond Region of Southern Denmark (672,700), Psykiatrifonden (DKK 1,000,000), Tryg Fonden 2012 (DKK 1,000,000). Fund of 17-12-1981 (DKK 600.000), Region of the Capital Psychiatry Research Fund, (DKK 67.000 DKK),
Region of the Capital Strategic Research Fund (DKK 800.000), Knud and Dagny Andresens Fund (DKK 100.000), Psychiatric Research Fund of 1967 (DKK 30.000), Capital Region Psychiatry Research Fund (DKK 120.000), Danish Psychiatry Researcher development programme (DKK 30.000), Jacob Madsen and wife Olga Madsens (DKK 10.000), Timber trade Johannes Fogs Fund (DKK 25.000), The Brothers Hartmanns Fund (DKK 150.000), Aase and Ejnar Danielsens Fund (DKK 100.000), Doctor Sofus Carl Emil Friis and Wife Olga Friis legate (DKK 722.215). The sponsor, the steering group and investigators have no economic association to funding bodies.
Flow chart for patients

Inclusion - Week 0
Randomisation

- Treatment arm A (quetiapine extended release)
  12 weeks (double-blinded)

- Treatment arm B (aripiprazole)
  12 weeks (double-blinded)

Treatment discontinuation* before 12 weeks

The next upcoming follow-up is assessed at the timepoint of the discontinuation

Blinding broken†

Additional follow-up assessments

Follow up in week 52 after randomisation

Treatment continued for 12 weeks (blinded)

Follow up in weeks 2, 4, 12 after randomisation

Blinding broken† - Week 16*

The next upcoming follow-up is assessed at the timepoint of the discontinuation

Blinding is broken‡

Additional follow-up assessments

Follow up in week 52 after randomisation

Treatment continued for 12 weeks (blinded)

Follow up in week 52 after randomisation

Treatment discontinuation* before 12 weeks

Follow up in week 52 after randomisation

* after the blinding is broken the physician and patient is free to decide on any future therapy of choice.
† after clean data has been established regarding outcome measures for the participant.
Flow chart for healthy controls

Inclusion - Week 0

Follow up in weeks 12 and 52 after inclusion
## General information

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  - Hanne Børner, MD, Centre manager,

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- Lars Vedel Kessing, MD, Professor in clinical psychiatry, Psychiatric Centre, Rigshospitalet, Copenhagen University Hospital.
- Kristian Thorlund, MSc, statistician, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Doctoral Research Fellow at McMaster University, Canada.
- Jesper Brok, MD, Ph.D., Department of Paediatrics, Hvidovre Hospital, Copenhagen University Hospital.

Practicality

The trial investigators have pharmacological experience (e.g., (Fink-Jensen, 2000)) and experience from clinical studies with children and adolescents. In a previous cohort study, the investigators examined neurobiological, neuropsychological and psychosocial aspects of early onset psychosis in children and adolescents (Jepsen et al., 2009; Pagsberg et al., 2006; Pagsberg, 2004; Fagerlund et al., 2006; Fagerlund, 2004b). Two trials have examined the comparative effects of atypical and typical antipsychotics; and adjunctive treatment (with an acetylcholine esterase inhibitor, donepezil) on psychopathology and cognitive deficits in adult patients with schizophrenia (Fagerlund et al., 2007; Fagerlund et al., 2001; Fagerlund et al., 2004; Mackeprang et al., 2002).

Christian Gluud and Jørn Wetterslev at the Copenhagen Trial Unit have substantial experience with carrying out clinical trials. The Copenhagen Trial Unit (CTU), Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, is a multidisciplinary, non-profit unit for clinical intervention research with extensive experience in methodology and technology of randomised clinical trial and meta-analysis. Since 1995, the CTU has participated in the randomisation of about 20,000 participants in over 40 randomised clinical trials and published over 200 Cochrane protocols and over 110 Cochrane systematic reviews. The trial activities include development and conduct of large randomised trials such as CLARICOR, DIPOM, DANREHAB, PROXI, EXSTROKE, AREDIA-MYELOM, THALIDOMID, OPUS, CIMT, THALASSAEMIA, and TIA. CTU’s expertise covers development of clinical trial protocols, data management, e.g., development of electronic case record forms (e-CRFs), optically scanned paper CRFs, trial conduct, and statistical analysis. The CTU hosts the Editorial Team Office of The Cochrane Hepato-Biliary Group and has developed Trial Sequential Analysis software for
assessment of robustness in meta-analyses. CTU is staffed with experienced clinicians, epidemiologists, statisticians, information-technology engineers, and information specialists.

Dr. Christoff Correll has substantial experience in planning and carrying out pharmacological clinical trials in child-, adolescent, and adult psychiatry (Correll et al., 2003; Correll et al., 2005; Correll et al., 2007; Correll, 2008; Kumra et al., 2008).
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Abbreviations and definitions

AE  Adverse Event
AIMS  Abnormal Involuntary Movement Scale
AR  Adverse Reaction
ASAT  Aspartate Amino Transferase
BACS  Brief Assessment of Cognition in Schizophrenia
BARS  Barnes Akathisia Rating Scale
BMI  Body Mass Index
BRIEF  Behavioural Rating Inventory of Executive Functions
CGI-I  Clinical Global Impression, Improvement
CGI-S  Clinical Global Impression, Severity
CRF  Case Record Form
DIPI  Dimensions of Psychosis Instrument
DUP  Duration untreated psychosis
EPS  Extrapyramidal Side effects
GAPD  Global Assessment of Psychosocial Disability
GCP  Good Clinical Practice
HDL  High Density Lipoproteins
HRQoL  Health related quality of life
Healthy control  Healthy trial participant in the control group
ICD-10  International Classification of Diseases
IQ  Intelligence Quotient
K-SADS-PL  Kiddie-SADS-Present and Lifetime Version
KIDSCREEN-52  Health related quality of life questionnaire for children and young people and their parents.
LDL  Low Density Lipoproteins
PANSS  Positive and Negative Syndrome Scale
Participants  Covers both ‘patients’ and ‘healthy controls’
Patients  Trial participant who undergoes intervention
PAS  Premorbid Adjustment Scale
SAE  Serious Adverse Event
SCAN  Schedules for Clinical Assessment in Neuropsychiatry
SAR  Serious Adverse Reaction
SAS  Simpson-Angus Scale
SCoRS-DK  Schizophrenia Cognition Rating Scale – Danish version
UKU  ‘Udvalget for Kliniske Undersøgelser’ Side Effect Rating Scale
SUSAR  Suspected Unexpected Serious Adverse Reaction
TSH  Thyroid Stimulating Hormone
UKU  ‘Udvalget for Kliniske Undersøgelser’ Side Effect Rating Scale
WAIS-III  Wechsler Adult Intelligence Scale (III)
WAIS-IV  Wechsler Adult Intelligence Scale (IV)
WISC-III  Wechsler Intelligence Scale for Children (III)
WISC-IV  Wechsler Intelligence Scale for Children (IV)
1. **Background**

1.1 **Early onset psychosis**

Early onset of psychosis in childhood and adolescence (i.e., before age 18) is correlated with the same clinical, cognitive, aetiological and epidemiological components as illness onset in adulthood. Yet, it is characterised by a more insidious illness onset, more negative symptoms and thought disorders, more disorganised behaviour, more pre-morbid neurobiological and neuropsychological vulnerability indicators, developmental delays, and a higher prevalence of familial diagnoses within the schizophrenia spectrum (Eggers, 1999; Remschmidt and Theisen, 2005).

1.2 **Lack of evidence of effect and tolerability in children and adolescents**

The effect and tolerability of antipsychotics are relatively well studied in adults. Numerous trials with adult patients have shown treatment with antipsychotics to be more effective than placebo in terms of improving psychotic symptoms and preventing relapse (Joy et al., 2006; Fleischhacker et al., 2003; Woods et al., 2001). Similarly to adult patients, stable antipsychotic treatment has been shown to improve the long-term prognosis of adolescent patients (Lieberman et al., 2001). Only few clinical trials have studied antipsychotic treatment in children and adolescents with psychosis, and most of these have only studied a single compound (Armenteros and Davies, 2006; DelBello et al., 2008; Kumra et al., 1998; Findling et al., 2003; Sholevar et al., 2000; Zalsman et al., 2003; Cheng-Shannon et al., 2004; Jensen et al., 2006). Two placebo-controlled double-blind trials have been published; one comparing the atypical compound olanzapine with placebo in adolescent bipolar mania (Tohen et al., 2007) and the other comparing the atypical compound aripiprazole with placebo in adolescents with schizophrenia (Findling et al., 2008b). Other placebo-controlled studies are underway, but have to date only been presented as abstracts (for overview, see Correll, 2008; Sikich, 2008). Very few randomised clinical trials have compared an atypical antipsychotic to other antipsychotic compounds.

There are three randomised open-label trials (Ratzoni et al., 2002; van Bruggen et al., 2003) and seven double-blind trials published to date (Kumra et al., 1996; Kumra et al., 2008; Shaw et al., 2006; Sikich et al., 2004; Sikich et al., 2008; Arango 2009). These trials include only very small patient samples, and combined, they have reported results from fewer than 300 patients. Even though some antipsychotics have been found to be effective and safe in children and adolescents (Sikich et al., 2004; Kapetanovic and Simpson, 2006), there is limited knowledge about their specific pharmacokinetics and pharmacodynamics. The indication of using these compounds in children and adolescents is based on knowledge that has primarily been extrapolated from trials conducted in adults. This is problematic, since the prevalence of adverse reactions has been found to be larger in children and adolescents (Findling, 2001; Lewis, 1998; Arango 2009) and a larger number of patients are treatment resistant (Arango et al., 2004).

1.3 **The effect of antipsychotics on cognitive deficits and daily functioning**

Cognitive deficits are core symptoms of schizophrenia and other psychotic disorders (Addington et al., 2003; Heaton et al., 2001). To a larger extent than psychotic symptoms, cognitive deficits are of crucial importance for the prognosis of patients, in terms of social function and work skills...
(Green, 1996). There continues to be an unfulfilled need for treatment of cognitive deficits and therefore also daily functioning in these patients (Fagerlund, 2004a; Harvey and Keefe, 2001; Woodward et al., 2005; Nuechterlein et al., 2005; Green et al., 2005). Only one clinical trial on the effect of antipsychotics on cognitive deficits among children and adolescents has been published. The trial was designed as a single-blinded randomised trial (Robles et al. 2009). Meta-analyses of trials including adult patients have found that typical antipsychotics neither improve nor worsen cognitive deficits, with small effect sizes of limited clinical relevance (Harvey and Keefe, 2001; Woodward et al., 2005).

1.4 Early predictors of later effect of antipsychotics on psychotic symptoms

It is common clinical practice to assess the effectiveness of antipsychotics for 8 to 12 weeks. This time frame is partly arbitrarily defined, and in part based on older studies (White and Wang, 1983), which indicated that antipsychotics exert their effects on dopamine cell firing after treatment for at least 21 days (Li et al., 2006; Agid et al., 2006; Kapur et al., 2005; Agid et al., 2003). PET and SPECT brain scan studies of both typical and atypical antipsychotics have shown that D2 receptor occupancy occurs within hours after treatment initiation and that a lasting blockade can be observed within the first days after administration (Nordstrom et al., 1992; Tauscher et al., 2002). Specific antipsychotic effects, which can be distinguished from non-specific sedative effects, can be observed within the first 24 hours (Kapur et al., 2005). Nevertheless, there is no question that the robust clinical effects are only apparent after several weeks of antipsychotic treatment, and that the improvements in efficacy continue for months afterwards. However, studies have shown that the largest effect of antipsychotics occur during the first 2 weeks, compared to any other subsequent 2-week period. A large meta-analysis based on data from 7450 adult patients, showed that the antipsychotic effect during the first 2 weeks of treatment was approximately three times larger than the effect in the following two weeks (Agid et al., 2003). Similarly, a larger improvement is seen within the first month after treatment initiation than in the following year (Agid et al., 2006). Another meta-analysis showed that approximately 70% of the improvement in psychotic and global clinical symptoms within the first year occurred during the first four weeks of treatment (Leucht et al., 2005). A study of acutely psychotic schizophrenic patients showed that all patients with less than a 20% improvement on BPRS (Brief Psychiatric Rating Scale) after one week of antipsychotic treatment, were classified as ‘non-responders’ after four weeks of treatment (Correll et al., 2003). All of the above-mentioned studies have been performed in adult patients; similar, studies on early predictors of late clinically significant effects of antipsychotics have not been reported in children and adolescents.

1.5 Health-related quality of life (HRQoL)

In adult patients, it has been found that use of HRQoL, so that health personnel has a measure for the individual patient's quality of life, can have a beneficial effect on the doctor-patient communication and on the patient satisfaction (Thastum, M., 2008). Measuring quality of life may also shed light on the advantages and disadvantages from medication or therapy - from the patient's perspective. Results from measuring quality of life may therefore have implications for the clinical decisions taken in relation to, for example changes in medication. HRQoL also increases the doctor's detection rate for psychosocial and functional problems in patients.
Children and adolescents with psychotic disorders often have impaired daily functioning. Health-related quality of life can be used to measure the proportion of a person's quality of life that relates to their health status. The quality of life assessment can include many different aspects such as the individual's ability to form social relationships, physical and mental functioning and the child's or adolescent's ability to attend to school activities. Furthermore, the quality of life assessment is used to measure the child's or adolescent's assessment of the pros and cons of the medication or therapy that s/he receives (Thastum, M., 2008).

In children and adolescents with psychosis, there is only performed a few studies and common to them is that they only had small populations (Rademacher, J. et al, 2007; Stewart, M. et al, 2009). Thus, there are no randomised blinded clinical trials or studies on Danish children and adolescents treated with antipsychotics.

1.6 Stigma
Studies show that adults with mental disorders largely suffer from the stereotypes that exist about mental illness (Link, BG. et al., 2001). This can lead to the stigmatization - and the stigma may contribute to social exclusion and have implications for the ability to form social relationships or their connection to, e.g., the labour market. Stigma can also have consequences for the possibility of early detection and treatment because the patient fails to seek treatment.

Until now, the stigmatization of children and adolescents with mental disorders is poorly understood, despite the fact that the stigma that children and adolescents experience takes place in a completely different context than that of adults, and one can therefore not draw an immediate parallel between the two. Furthermore, the few existing studies focus primarily on the prejudices the child's or the adolescent's parents experience and the prejudices surrounding the world has towards the children with mental disorders, and not on the child's or the adolescent's own experiences (Mukolo, A. et al, 2010).

1.7 Motion disturbances
Motion disturbances in patients with schizophrenia are often related to the antipsychotic treatment, which can have an impact on the patients wellbeing, quality of life and compliance. Additionally motion disturbances have also been demonstrated prior to medical treatment in adult schizophrenic adults (Rogers, D. 1985, Wolff. AL et al 1999) while knowledge of motor disturbances in children and adolescents is lacking. The assessment of motor symptoms has often been limited to the use of observer-based rating scales that inherently are subject to inter-observer variability, which means that even trained clinicians underestimate the prevalence of motors symptoms when using observer-based assessment tools (Dean, CE. et al., 2004, Lohr, JB et al., 1992, Wolff, AL et al., 1999).

In cooperation with the Danish Technical University (DTU Compute) we have started a work of developing a Kinect™-based instrument (Computer vision based human motion capture), that can quantify primary and secondary movement patterns objectively before and after initiation of medical treatment. The instrument appeal to younger patients, since the motion disturbances is registered, while the patient is playing the computer game.
1.8 Pilot study
The investigator group has tested the psychiatric materials of the TEA trial in a pilot study. The pilot study took place at Bispebjerg University Hospital, Child- and Adolescent Psychiatric Department, during 2007. As part of the pilot study, a focus group was set up, consisting of psychotic patients and their parents, presently connected to the department. The purpose of the focus group was to obtain feedback from patients and parents regarding the materials, and study design and program. After the pilot study, certain appropriate changes in the investigation programme were made as a result of responses from patients and parents, and investigator evaluation of the applicability of instruments.

1.9 The importance of investigator-initiated studies
The pharmaceutical companies involved have sponsored most randomised trials comparing the effects of different antipsychotics in adult patients. Analyses of randomised trials have found that conclusions from these trials favour the compound of the sponsor (Als-Nielsen et al., 2003; Kjaergard and Als-Nielsen, 2002). Therefore, there is considerable need for investigator-initiated, independent, comparative randomised trials (Lieberman, 2006).

2. Objectives
The objectives of the TEA trial are to:

Examine the efficacy of antipsychotics in children and adolescents between 12-17 years of age with psychosis; the effect is measured as:

- a. psychopathology, primary outcome measure of interest: Severity of psychotic symptoms (PANSS positive subscale);
- b. cognitive deficits, primary outcome measure of interest: Global BACS cognitive score;
- c. cognitive daily functioning, primary outcome measure of interest: Global executive function, SCoRS-DK.
- d. Health-related quality of life, primary outcome measure of interest: KIDSCREEN-52 score.

Examine the tolerability of antipsychotics in children and adolescents between 12-17 years of age with psychosis, concerning:

- a. motor adverse reactions;
- b. metabolic adverse reactions;
- c. hormonal adverse reactions;
- d. cardiac adverse reactions;
- e. other side effects, including psychological

Identify early indicators (after 2 and 4 weeks of treatment with two different atypical antipsychotics) of sustained clinically significant effects on psychopathology assessed after 12 weeks and after one year after inclusion into the trial.

Examine the difference in health-related quality of life in healthy children and adolescents and children and adolescents with psychosis, respectively. Examine the change in quality of life
during the course of antipsychotic treatment for psychosis, and the experience of stigma as a result of mental illness.

In cooperation with the Danish Technical University (DTU Compute) to develop a Kinect™-based instrument that can quantify movement patterns objectively. To investigate patterns of movement in children and adolescents with psychoses compared with a healthy control group. Additionally, to investigate changes in motion patterns before and after the initiation of treatment with antipsychotics among TEA patients.

2.1 Hypotheses
The primary hypothesis:
- Quetiapine extended release and aripiprazole exert different efficacy and adverse reaction profiles.

The secondary hypotheses:
- Antipsychotic efficacy in children and adolescents after two or four weeks of treatment predict the later effect of antipsychotics on psychopathology (i.e., after 12 weeks of double-blind treatment and at 52 weeks after randomisation).
- Cognitive function:
  1. At baseline, there will be significantly more cognitive deficits among the patients than among the healthy controls.
  2. Antipsychotic medical treatment (aripiprazole or quetiapine) will after 12 weeks improve the cognitive deficits only to a smaller extend.
  3. Quetiapine and aripiprazole have different effects on cognitive deficits among children and adolescents after 12 weeks treatment.
  4. The cognitive deficits will at baseline as well as after 12 weeks of medical treatment be moderately associated with different ratings of cognitive daily functioning, but only weakly associated with psychopathological ratings.

- Cognitive daily functioning:
  1. At baseline, there will be significantly more cognitive daily functioning disorders among the patients than among the healthy controls.
  2. Antipsychotic medical treatment (aripiprazole or quetiapine) will after 12 weeks only to a smaller extend improve the cognitive daily functioning disorders.
  3. Quetiapine and aripiprazole have different effects on the cognitive daily functioning disorders among children and adolescents after 12 weeks of treatment.
  4. Cognitive daily functioning will at baseline as well as after 12 weeks medical treatment be weakly correlated with ratings of psychopathology.

- Quality of life and stigmatization:
  1. At the time of inclusion the patient group’s quality of life will be lower than that of the healthy controls’.
  2. Quality of life will increase after 12 (and 52) weeks of treatment.
  3. Assessments of quality of life will be inversely correlated with the patient’s disease intensity (score on PANSS DIPI, CGI and GAF).
  4. The trial participants who exhibit cognitive difficulties will assess their quality of life differently than children or adolescents without cognitive difficulties.
5. The majority of patients will experience stigmatization 52 weeks after psychosis onset time.
6. At week 52 the patients’ experience of stigmatization will be correlated with the patient's quality of life.

• Motion disturbances
  1. A positive association between the motion activity parameters (Kinect™) and the ratings of the clinical rating scales with respect to bradykinesia and rigidity.
  2. A decrease in spontaneous movement, lower velocity of movement and a less steep learning curve in regard to motoric movement measured with the Kinect-based instrument among the non-medicated psychotic patients compared to the healthy controls.
  3. An association between reduced velocity of movement and an increased score of decreased affect (PANSS item).
  4. An abnormal pattern of movement prior to the initiation of medical treatment predicts later development of additionally changed/abnormal motion patterns.

2.2 The relevance of the trial

The comparison of different antipsychotic compounds
It is problematic that the choice between different antipsychotic compounds for children and adolescents is not based on solid evidence. The clinical effect varies between compounds and between patients. Characterising the efficacy and tolerability of atypical antipsychotics in children and adolescents with psychotic symptoms will lead to a more rational and individualised treatment, e.g., based on the specific psychopathological symptoms, cognitive deficits, and somatic status of patients. This will be of great relevance for clinical practice.

Characterising the efficacy of antipsychotics on cognitive deficits and daily functioning
There are no antipsychotic compounds with the registered indication of improving cognition in psychotic patients. Studies of the efficacy of antipsychotics such asquetiapine and aripiprazole on cognition are of considerable clinical relevance.

Identification of early predictors of later sustained effects
The identification of early indicators of later sustained clinical significant effects of antipsychotics is of great clinical relevance with respect to identifying patients that do not benefit sufficiently from treatment with one compound, but might benefit from an early relatively quick switch to another compound. This topic has not been investigated in children and adolescents previously.

Measuring health related quality of life and experience of stigma
In adult patients, it has been found that use of HRQoL, so that health personnel has a measure for the individual patient's quality of life, can have a beneficial effect on the doctor-patient communication and on the patient satisfaction (Thastum, M., 2008). In addition, HRQoL measurements have clinical significance in the choice of, e.g., the treatment plan and changes in medication. HRQoL also increases the doctor's detection rate for psychosocial and functional problems in patients. Few studies have examined HRQoL in children, and no studies have measured HRQoL in psychotic children and adolescents (Thastum, M., 2008).
There is evidence that adults with mental disorders are largely stigmatized by their communities and that patients greatly stigmatize themselves. This stigmatization may contribute to social exclusion and have implications for the ability to form social relationships or their connection to, e.g., the labour market. Stigma can also have consequences for the possibility of early detection and treatment because the patient fails to seek treatment. Thus, there are several international studies of adults' experience of stigma, but there are no studies to illustrate the psychotically ill children's experience of being stigmatized (Link, BG. Et al, 2001).

**Measurement of motion disturbances with Kinect™**

Examination of involuntary movements among children and adolescence is time-consuming and can at times be difficult to conduct. With Kinect™ (Microsoft Xbox) an economically affordable and precise movement tracking unit has become available. Since the release of Kinect Windows Software Development Kit (SDK) in June 2012 several research projects with application of Kinect to i.e. rehabilitation (Chang, YL et al., 2011) and treatment of stroke patients plus surgical navigation is started (Haro, BB et al. 2012, Leong, JHJ et al., 2006, Padoy, N et al. 2012, Reiley, CE et al., 2008).

3. **Eligibility criteria**

3.1 **Patients**

**Inclusion criteria**

- **Diagnosis:** Children and adolescents with a non-organic and non-drug-induced psychosis, meeting the criteria for ICD-10 diagnoses: F20, F22-F29 and F30.2, F31.2 F31.5, F32.3 and F33.3. This is verified with a semi-structured psychopathological interview using K-SADS-PL (Kaufmann 1997) four weeks after inclusion into the trial.

- **Psychopathology:** Children and adolescents with psychotic symptoms, scoring ≥ 4 on at least one of the following PANSS items: P1 (delusions), P2 (conceptual disorganisation), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution) or G9 (unusual thought content); and a total PANSS score > 60. The treating physician has decided to prescribe an antipsychotic compound.

- **Age:** 12-17 years (both inclusive).

- **Sex:** Both sexes are included.

- **Previous treatment:** Patients must be antipsychotic-naïve or only have received a limited amount of treatment with antipsychotics previously. As a maximum, the treatment with antipsychotics for a psychotic illness must have been within the previous calendar year, or, maximum one week’s treatment (lifetime, regardless of time).

- **Somatic illness:** No somatic contraindication to planned medication, documented by standard somatic examination

- **Written informed consent.**

**Exclusion criteria**

- **Compulsory treatment:** Patients that are compulsorily hospitalised against their will are excluded. If their status changes to voluntary hospitalisation, patients can be included. If the patient is already included in the trial and is briefly detained, confined, or subjected to other forceful treatment according to the Danish Psychiatric Care Act (‘Psykiatriloven’),
both the patient and parents have to agree to remain in the trial if exclusion is to be avoided. Compulsory treatment in the form of, e.g., brief forced immobilisation or single instances of forced medication, are not causes for exclusion.

- **Diagnoses**: Patients with drug-induced or organic psychosis, severe chronic somatic illness, or a history of severe head-trauma are not included. Patients that do not have psychotic symptoms but are prescribed antipsychotic treatment on the indication of, e.g., severe behavioural problems or tics are not included.

- **Pregnancy**: Pregnant or lactating patients are not included (a pregnancy test is undertaken at inclusion). Female participants, that are sexually active, must use safe contraception throughout the trial period (see section 6.4). A pregnancy test (urine sample) is also taken throughout the trial if suspicion of pregnancy is present, e.g., if the participant is changing status from not sexually active to sexually active.

- **Substance abuse**: People with severe alcohol or drug abuse are not included (substance abuse is defined by F1x.2 Dependence syndrome). Possible abuse is monitored both by interviewing participants and by taking a urine sample at inclusion and at 4, 12 and 52 weeks follow-up (if there is suspicion of substance abuse), testing for the presence of cocaine, amphetamine, cannabis, opiates, methamphetamine (inclusive for ecstasy), and benzodiazepines. When severe abuse is suspected during the trial, an ad hoc urine sample is taken. Brief periods of large alcohol/cannabis intake are not a cause of exclusion from the trial; however, cognitive and other examinations are not carried out while patients are under the influence of drugs or alcohol.

- **Aggravation**: Patients may be excluded if there is a significant worsening of clinical state during the course of the trial (i.e., increases of 30% or more from baseline on the PANSS total score).

- **Allergy and intolerance**: Patients with allergy towards the investigational drugs, or is lactose intolerant are not included.

- **Lack of informed consent**.

### 3.2 Healthy controls

#### Inclusion criteria

- **Matching**: Healthy controls (n=100) are included, in the way that they are matched to the first 100 patients included in the study (i.e., corresponding to the number of patients required in each treatment group). They will be matched according to:
  - age;
  - sex; and
  - socioeconomic status (based on Denmark's Statistical Socioeconomic Classification system)

- **Informed consent**.

#### Exclusion criteria

- **Psychopathology**: People with a previous psychotic disorder (ICD 10, F20-F29 and F30.2, F31.2, F31.5, F32.3 and F33.3) or current psychiatric disorder (multiaxial axis 1) are not included. This is verified partly by excluding persons with a prior psychotic diagnose using data from the CPR-registry and 'Psykiatrisk Centralregister' and partly by
diagnostic screening using K-SADS-PL as part of the eligibility assessment before inclusion into the study of healthy controls. The presence of psychotic psychiatric diagnoses in first-degree relatives is also a cause for exclusion.

- **Somatic illnesses:** People with severe chronic somatic illness or a history of severe head-trauma as well as current medicinal treatment judged to influence assessments and test results are not included.
- **Intelligence:** People with known mild mental retardation (i.e., IQ between 50-70) prior to inclusion are excluded; however, if mild mental retardation is found during the study, participants are not excluded, since they must be considered a marginal part of the normal distribution. People with moderate to severe mental retardation (i.e., IQ < 50) are excluded.
- **Pregnancy:** For reasons of possible bias by somatic assessments, pregnant and lactating controls will be excluded (pregnancy test should be performed on female control subjects where suspicion of pregnancy is present.
- **Substance abuse:** People with severe alcohol- or drug abuse are excluded (substance abuse is defined by F1.x.2 Dependence syndrome). Possible abuse is monitored both by interviewing participants and by taking a urine sample at inclusion and at 4, 12 and 52 weeks follow-up (if there is suspicion of substance abuse), testing for the presence of cocaine, amphetamine, cannabis, opiates, methamphetamine (inclusive for ecstasy) and benzodiazepines. Brief periods of large alcohol/cannabis intake are not a cause of exclusion from the study; however, cognitive and other examinations are not carried out while participants are under the influence.
- **Lack of informed consent.**

4. **Trial design**

**Patients**
The benefits and harms of antipsychotics on psychopathology, cognitive deficits, cognitive daily functioning, and adverse reactions are studied for one year. A specific comparison of the two drugs’ effects and side effects is assessed after 12 weeks of blinded antipsychotic treatment and at one year (i.e., 36 weeks after the participant is unblanded in week 16) after randomisation. Week number is always counted from the day of randomisation. Furthermore, early predictors of sustained significant clinically important effects on psychopathology are studied.

**Week 0**
If the patient meets all the inclusion criteria and none of the exclusion criteria s/he is moved on to inclusion assessments. The patient is then randomisation to either intervention arm A (quetiapine extended release) or treatment arm B (aripiprazole).

**Intervention period (week 1 to 16)**
Participants enter a randomised, double-blind, 16 week antipsychotic treatment period. During the first 9 days the assigned antipsychotic intervention is uptitrated and adjusted to the
participant. Benefits and harms are assessed at three time points during the intervention period (in weeks 2, 4 and 12). During week 12 to week 16 the participants will be continued on blinded trial medication administered in accordance to symptoms as during week 0 to week 12. During this blinded period all data regarding benefits and harms must be cleaned. For each individual participant declaration of clean file must occur before week 16, after which the unblinding of employed intervention may occur.

**Weeks of assessments**
Assessments are made at inclusion when drug-naïve (week 0), and at weeks 2, 4, 12, and 52 after randomisation.

**Discontinuing the intervention**
See section 9.3 "Breaking of the randomisation code" and section 9.4 "Discontinuation of the intervention and/or exclusion from the trial".

**Healthy controls**
Healthy controls are included to form a reference population for cognitive and somatic measures as well as blood tests and urine tests. They are assessed at inclusion (week 0) and in week 12 and 52 after inclusion. Healthy controls will not receive any trial intervention.

### 4.1 Outcome measures

**Primary outcome**
- Psychopathology: PANSS positive scale (PANSS ‘Positive and Negative Syndrome Scale’) (Kay, 1991).

**Secondary outcomes**

**Psychopathology**
- Other PANSS scales (negative scale and general symptoms)
- DIPI (Dimensions of Psychosis Instrument) (Mizrahi et al., 2006);
- CGI-S (Clinical Global Impression Severity) (Guy, 1976);
- CGI-I (Clinical Global Impression Improvement) (Guy, 1976);
- CGI-Efficacy (Clinical Global Impression Efficacy) (Guy, 1976)
- GAPD (Global Assessment of Psychosocial Disability) (World Health Organization, 1993).

**Cognition**
- Cognition: BACS Global Score (Brief Assessment of Cognition in Schizophrenia) (Keefe et al., 2004);
- Cognitive daily functioning: Global functioning from SCoRS-DK (Schizophrenia Cognition Rating Scale, Danish version) (Keefe et al., 2006);
- Global executive functioning measured with BRIEF (Behavioural Rating Inventory of Executive Functions) (Gioia, G.A. 2005).
Other secondary outcomes are attention, executive functions and memory from BACS as well as specific sub-outcomes from SCoRS-DK and BRIEF.

Adverse reactions
- UKU side effect scale ('Udvalget for Kliniske Undersøgelser' Side Effect Rating Scale) (Lingjaerde et al., 1987);
- AIMS (Abnormal Involuntary Movement Scale) (Guy W., 1976);
- SAS (Simpson Angus Scale) (Simpson and Angus, 1970);
- BARS (Barens Akathisia Rating Scale) (Barnes T.R.E., 1989);
- Kinect™- based instrument
- Other adverse events, i.e., any untoward occurrences including:
  o cardiac adverse reactions effects such as prolonged QT- interval
  o somatic events (blood pressure, pulse, weight, height, BMI and abdominal circumference); and
  o abnormal laboratory test results (lipid status, metabolic changes, other general blood tests according to clinical guidelines for clinical practice, and ECG).

Suicidal ideation
- K-SADS-PL, specific questions for depressive disorders (current) recurring thought of death, suicidal thoughts, suicidal action level of serious, suicidal action level of life-threatening, non-suicidal physical self-inflicted harm.

Genetic and antipsychotic laboratory tests
- determination of serum concentration of antipsychotics;
- clinical genetic analysis, including analysis of genetic variants affecting metabolism of antipsychotics;
- offering of participation in the project "Arv og Miljø" for genetic analyses that is not included in the clinical genetic analysis.

Prognostic factors
- DUP (Duration of Untreated Psychosis) (see below for references);
- PAS (Premorbid Adjustment Scale) (see below for references).

Quality of life and stigma
- KIDSCREEN-52
- Semi structured, qualitative interview

4.2 Trial schedule for assessments
Eligibility assessment
Prior to inclusion of patients, a somatic examination, including a neurological screening, ECG, and routine blood tests are carried out in order to exclude serious somatic illness. Urine tests are carried out to detect pregnancy among female participants and severe substance abuse among male and female participants. The medical and somatic history is recorded for each patient. Psychiatric and important somatic illnesses among close biological relatives are recorded by interviewing parents, and the socioeconomic background of the participants’ parents is registered.
The presence of psychotic symptoms measured as a score of ≥4 on at least one of the following items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution) or G9 (unusual thought content); and a total PANSS score > 60 is verified, and current diagnoses are registered, using ICD-10 criteria (1993). Onset of psychosis is equated with the first appearance of positive psychotic symptoms, defined as the first week with symptoms retrospectively meeting the above-mentioned criteria (Melle et al., 2005). All available sources of information (the child/adolescent, parents, notes in medical records) will be used to ascertain the onset of psychosis according to a time-line, with major events of the patient’s life as anchor points (Jeppesen et al., 2008).

Healthy controls are assessed using the K-SADS-PL interview at inclusion in order to exclude the presence of previous psychotic disorder or current psychiatric disorder in the healthy control group. Urine tests are taken to trace substance abuse and pregnancy. Using the K-SADS-PL, healthy controls are reassessed in week 52 to exclude that psychiatric disorder has been developed since the first assessment. Healthy controls meeting the criteria for psychiatric disorder in week 52 will be excluded from the week 52 examination.

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<td><strong>Diagnostic verification</strong></td>
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<td>K-SADS-PL</td>
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<tr>
<td><strong>Cognition</strong></td>
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<tr>
<td>BACS and IQ (WISC-III, WISC-IV or WAIS-III, WAIS-IV)</td>
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<td><strong>Cognitive daily and executive function</strong></td>
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<td>SCoRS-DK and BRIEF</td>
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<td><strong>Somatic examination</strong></td>
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<td>Standard clinical examination, † blood pressure, pulse, weight, height, BMI, and abdominal circumference,</td>
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### Assessments

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<td>patients</td>
<td>patients &amp; healthy controls</td>
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<td>Stigmatization Interview</td>
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<td>Kinect™-examination Examination of motion disturbances with a newly developed Kinect-game</td>
<td>patients &amp; healthy controls</td>
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<td>patients</td>
<td>patients &amp; healthy controls</td>
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<tr>
<td>Sexual maturation Tanner scale</td>
<td>patients &amp; healthy controls</td>
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<td>patients &amp; healthy controls</td>
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<tr>
<td>Dispositions Psychiatric/somatic illness in close relatives</td>
<td>patients &amp; healthy controls</td>
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<td>patients &amp; healthy controls</td>
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<tr>
<td>Socioeconomic status</td>
<td>patients &amp; healthy controls</td>
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<td>patients &amp; healthy controls</td>
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* Inclusion (week 0) includes assessments done prior to inclusion (the eligibility assessments).
† IQ (WISC-III, WISC-IV or WAIS-III, WAIS-IV) is only assessed in week 0.
‡ Including the medical history.
§ Apart from assessment of serum values for antipsychotics.

### Laboratory tests

**Clinical standard laboratory tests (blood tests, urine tests, and ECG)**

The following tests are taken in the clinical setting as a routine treatment. Blood test are drawn from a peripheral arm vein and the test results from the blood tests and urine tests are send, in accordance with routine procedures, to the hospital department that ordered them, i.e., the hospital section the trial participant is connected to. The samples are taken at inclusion and after 4, 12, and 52 weeks, unless otherwise stated. The results of the laboratory test are obtained in TEA by the request to the participant to give informed consent to information being collected from their patient journals.
Total amount of blood collected per participant
- at inclusion: 30.5 millilitres;
- at week 4: 27 millilitres;
- at week 12: 28.5 millilitres;
- at week 52: 20.5 millilitres;
- in the entire trial period: 106.5 millilitres.

Total amount of blood collected per healthy control
- at inclusion: 20.5 milliliters;
- at week 12: 20.5 milliliters;
- at week 52: 20.5 milliliters;
- in the entire trial period: 61.5 milliliters.

Blood tests:
- measurement of lipids (in serum): triglycerides, total cholesterol, LDL, VLDL, and HDL (assessed after a minimum of eight hours of fasting);
- metabolic glucose and insulin values (assessed after a minimum of eight hours of fasting); (If a patient is predisposed with diabetes mellitus, glucose values are assessed more frequently according to individual estimation;
- determination of prolactin;
- determination of creatinphosphokinase;
- red and white blood cell status: haemoglobin, leukocyte cell count (and differential count), and thrombocyte cell count;
- electrolytes: sodium (Na), potassium (Ka), and creatinine;
- liver tests: ASAT, and alkaline phosphatases;
- metabolism: TSH;
- omega-3 fatty acids and vitamin D;
- genetic tests (only at inclusion) included in the clinical genetic analysis (can be supplied as saliva or as a mouth swab);

Urine tests:
- pregnancy test (only females at inclusion and at the 4, 12, and 52 weeks assessments if there is suspicion of pregnancy, e.g., if status is changed from not sexually active to sexually active);
- screening for medication and substance abuse (at inclusion and at week 4, 12, and 52 if there is a suspicion of substance abuse).

ECG:
- standard leads.

Serum values for antipsychotics (at 4 and 12 weeks after inclusion)
Blood samples will be sent to, and stored in freezers (minimum -20 degrees Celsius) at the Research Institute for Biological Psychiatry, Sct. Hans Hospital. The reason for storing these samples is to make a subsequent single-batch analysis, no sooner than after the last 12 week assessment of the last participant in order not to brake the blinding in the trial. Each trial participant will give 2 x 4 millilitre blood at 4 and 12 weeks follow-up for the analysis of
antipsychotics, thus 2 x 2 x 4 (16) millilitre blood (serum; see below), corresponding to the samples taken at the 4 and 12 weeks follow-up will be stored in the research bio bank.

1.5 millilitres of serum will be used for the analysis, i.e., the blood samples shall be drawn in tubes with no anti coagulant. Tubes with gel shall not be used, and the blood samples shall be protected from light. Serum is extracted and sent with regular post in ADR-approved packaging to the storage facility. The key for identification of the blood samples will be kept under lock and kept separate from the blood samples. When all samples are collected they will be analysed and thereafter the samples will be destroyed. The recruitment period is 2010 to 2013, and thus the blood samples are expected to be destroyed latest by the end of 2014. The biological material will not be subject to export to other countries.

Other genetic analyses
If the trial participant also has given specific informed consent to participate in the project ”Arv og Miljø“ (Ethics Committee of Capital Region, journal number: H-B-2009-026, Danish Data Protection Agency: Mental Health Services in the Capital Region of Denmark (Region Hovedstadens Psykiatri), ‘paraplyanmeldelse’ 2007-58-0015, serial nr: 00466, id nr: PSV-2009-07) will the remaining blood sample from the clinical genetic analysis be sent to storing and analysis at the Research Institute for Biological Psychiatry, Sct. Hans Hospital in accordance to the ”Arv og Miljø“ protocol.

Any new research on the stored biological material must be approved by a Regional Ethics Committee.

Prognostic factors
Two prognostic factors are measured: the premorbid functioning until six months prior to the onset of psychosis, and the time from the onset of psychosis until the start of adequate treatment, known as the duration of untreated psychosis (DUP). Premorbid functioning is measured by the Premorbid Adjustment Scale (PAS), using two indexes, the ‘premorbid school adaptation’ and the ‘pre-morbid social adaptation’ (Larsen et al., 2004; Cannon-Spoor et al., 1982). The inclusion into the trial and allocation to treatment marks the end of DUP.

Week 0: Inclusion (before start of antipsychotic medication)
Psychopathology is assessed using PANSS*, DIPI, CGI-S, and GAPD and adverse reactions are assessed using UKU, AIMS, SAS, and BARS. Motion patterns are registered with KinectTM. Assessment of suicidal behaviour using K-SADS-PL questions, depressive disorders. Cognitive functions are assessed using BACS and WISC-III, WISC-IV or WAIS-III, WAIS-IV (Weschler Intelligence Scale for Children - Third Edition / Fourth Edition (Wechsler, 1991) or (Weschler Adult Intelligence Scale - Third Edition/Fourth Edition (Wechsler, 1999)), and daily and executive functioning is measured using SCoRS-DK and BRIEF. Prognostic factors are assessed using DUP and PAS. Somatic examinations consists of standard clinical examination (including medical history)*, blood pressure, pulse, weight, height, BMI, and abdominal circumference. The phase of sexual maturation will be assessed using the Tanner scale (Marshall et al., 1969). All laboratory tests* are carried out (including the ECG* and urine tests*). Genetic dispositions and the socioeconomic status are registered. Health-related quality of life is measured with KIDSCREEN-52.
(* have already been conducted when assessing eligibility. The test results from will be transferred as the week 0 assessments.)
**Week 2: First follow-up (uptitration phase)**
After two weeks of antipsychotic treatment, psychopathology is assessed using PANSS, DIPI, CGI-S, CGI-I, CGI-efficacy, and GAPD, and adverse reactions are assessed using UKU, AIMS, SAS, and BARS. Motion patterns are registered with KinectTM. Assessment of suicidality by K-SADS-PL, specific questions for depressive disorders. Somatic examinations consist of standard clinical examination, blood pressure, pulse, weight, height, BMI, abdominal circumference.

**Week 4: Second follow-up**
After four weeks of antipsychotic treatment, psychopathology is assessed using PANSS, DIPI, CGI-S, CGI-I, CGI-efficacy and GAPD, and adverse reactions are assessed using UKU, AIMS, SAS and BARS. Motion patterns are registered with KinectTM. Assessment of suicidal behaviour using K-SADS-PL questions, depressive disorders. The diagnosis is verified with K-SADS-PL. Somatic examinations consist of standard clinical examination, blood pressure, pulse, weight, height, BMI, and abdominal circumference, and laboratory tests including ECG and serum-concentration tests.

**Week 12: Follow-up**
After 12 weeks of antipsychotic treatment, psychopathology is assessed using PANSS, DIPI, CGI-S, CGI-I, CGI-efficacy, and GAPD, and adverse reactions are assessed using UKU, AIMS, SAS, and BARS. Motion patterns are registered with KinectTM. Assessment of suicidal behaviour using K-SADS-PL questions, depressive disorders. Cognitive functions are assessed using BACS and daily functioning using SCoRS-DK and BRIEF. Somatic examinations consist of standard clinical examination blood pressure, pulse, weight, height, BMI, abdominal circumference, and laboratory tests including ECG are taken. Health-related quality of life is measured with KIDSCREEN-52.

**Week 52: Follow-up**
After 52 weeks, 36 weeks after completing the blinded part of the trial, psychopathology is assessed using PANSS, DIPI, CGI-S, CGI-I, CGI-efficacy and GAPD and adverse reactions are assessed using UKU, AIMS, SAS, and BARS. Motion patterns are registered with KinectTM. The diagnosis will be verified with K-SADS-PL, and assessment of suicidal behaviour using K-SADS-PL questions, depressive disorders. Cognitive functions are assessed using BACS and daily and executive function using SCoRS-DK and BRIEF. Somatic examinations consist of standard clinical examination blood pressure, pulse, weight, height, BMI, abdominal circumference, and laboratory tests including ECG are taken. The Tanner scale is used for assessment of phase of sexual maturation. Health-related quality of life is measured with KIDSCREEN-52. Perceived stigmatization is elucidated via a semi structured, qualitative interview.

**Healthy controls**
The healthy control group will participate in the same examinations as patients, regarding cognition, PANSS (only N5: Difficulties in abstract thinking), adverse reactions (UKU, AIMS, SAS, and BARS) and health-related quality of life, cognitive daily and executive function, motion
patterns, somatic examinations, laboratory tests (see table 1), assessment of sexual maturation, dispositions and socioeconomic status at inclusion, and absence of previous psychotic disorder or current psychiatric disorder (multiaxial axis 1) psychosis is verified with K-SADS-PL. After 12 weeks assessments of cognition, daily and executive function, somatic measures, health-related quality of life, motion patterns and laboratory tests are repeated. After 52 weeks the somatic tests, laboratory tests and assessment of sexual maturation, motion patterns and health-related quality of life are repeated. Furthermore, the healthy controls are reassessed at week 52 with the K-SADS-PL, in week 52 to exclude that psychiatric disorder has been developed since the first assessment. Healthy controls meeting the criteria for psychiatric disorder in week 52 will be excluded from the week 52 examination.

Examination of motion disturbances at baseline may be carried out at both 0, 12 and 52 weeks. This means that the follow-up study at 12 weeks will be after additional 12 weeks after the 12 and 52 assessments and in these cases there will be an extra call. There will not be given any remuneration for this extra meeting (assessment time max. 20 min.), but transport compensation as required.

4.3 End of trial
The last follow-up of the last participant at week 52 is considered as end of trial.

For each individual participant, including healthy controls and patients, their participation in the trial (i.e., the trial period) is ending after his/her last assessment in week 52 after inclusion into the trial. However for the patients, after finishing the 16 weeks of blinded intervention treatment, s/he will continue in the trial period with any treatment of choice supervised by her/his psychiatrist or own general practitioner or equivalent.

4.4 Follow-up after two and five years
In preparation for a later separate long-term follow-up study, all trial participants are asked for permission to be contacted again two and five years.

5. Antipsychotic treatment
The two antipsychotic compounds investigated are quetiapine extended release and aripiprazole.

5.1 Choice of compounds
Aripiprazole is a newer atypical antipsychotic compound with high affinity for dopamine D2 receptors but with a partial agonist mode of action at dopamine D2 receptors, in contrast to all other used antipsychotics. This compound is used in treating psychotic symptoms in both children and adults. Quetiapine is dopamine D2 receptor antagonist which also is used in clinical practise for both adults and children. This compound has a less pronounced dopamine D2 receptor affinity. Both compounds are recommended as first choice for treatment in first episode psychosis in adults, according to guidelines from the American Psychiatric Association.
and The Danish Board of Health. Furthermore, aripiprazole has in July 2009 in Denmark obtained post-authorisation for extended use in adolescents from the age of 15 years (European Medicines Agency 2009).

In the present trial, aripiprazole and quetiapine have been selected since these compounds are frequently used in clinical practice and because it remains unclear whether their different receptor binding profiles can be related to differences in clinical efficacy and tolerability in children and adolescents with psychosis. Quetiapine is now available in an extended release formulation, which allows dosing only once daily and this formulation will be used in the present trial.

5.2 Quetiapine
According to case reports and open label studies, quetiapine has been shown to improve psychotic symptoms in children and adolescents aged 11–17 years, with daily doses ranging from 200–800 mg (for review see (Cheng-Shannon et al., 2004)). One of these studies used doses ranging from 300–800 mg/day, and an observation period of 88 weeks found favourable long-term safety and tolerability in 10 children and adolescents, aged 12–16 (McConville et al., 2003). In a recent trial, paediatric patients aged 10–17 years (n=27), quetiapine doses were titrated to 200 mg twice daily on days 5–7 and 400 mg twice daily on days 11–12. Quetiapine was well tolerated, with no serious adverse events and no unexpected events reported. In this trial, the paediatric population and a parallel adult population demonstrated similar pharmacokinetic, safety, and tolerability profiles for quetiapine by dose escalation. The predictability of quetiapine concentration profiles for children aged 10 years to adults suggested that no dosage adjustment might be required when treating patients of these ages (Winter et al., 2008). Since the launch of quetiapine in 1997, higher doses than those recommended by the compound producer have been widely used in clinical practice in adults, as the lower doses have not been found to be sufficiently effective (Citrome et al., 2005). It is generally assumed that younger patients require lower doses of antipsychotics than adults. However, according to Arango and colleagues (Arango et al., 2004), clinical experience suggests that in the case of quetiapine, this may be true for younger children with lower body weight, but adolescents typically require rapid titration to the same, or even higher, dose levels than adults for optimal clinical response. Effectiveness and safety of higher doses of quetiapine than those recommended by the compound producer have been reported in adolescents (Arango et al., 2004) and adults (Goodnick, 2005). An effectiveness and pharmacokinetic trial of children with conduct disorder (aged 6–12 years) investigated quetiapine administered twice-daily at doses escalated to approximately 3 mg/kg per day at the end of week one, to a median of 75 mg/day (range 50–150 mg) at week two, and to 150 mg (75–300 mg) at week eight. None of the patients (n=17) discontinued due to adverse events, during this eight-week trial (Findling et al., 2006).

Quetiapine extended release
Extended release quetiapine is a new formulation of quetiapine, which allows a once-daily dosing. Quetiapine extended release was approved in the USA for the treatment of acute schizophrenia in 2007 and in Denmark in 2008, and has been shown to be effective and well tolerated in schizophrenic adults in a randomized, double-blind, placebo-controlled trial (Kane et al., 2007).
We have chosen to use a 9-day titration phase with a final daily quetiapine extended release dose of 600 mg (equivalent to three blinded capsules per day). If needed for efficacy, the possible maximum dose can be titrated up to 800 mg if needed for efficacy, or titrated down to a lower dose level if not tolerated.

5.3 Aripiprazole
Documentation of the use of aripiprazole in children and adolescents has mainly focused on other disorders than psychosis, i.e., Tourette’s syndrome, or developmental disorders. These studies have shown safety for doses in the mean range of 5-17 mg/day in children from age 7, in open-label or naturalistic designs (Barzman et al., 2004;Bastiaens, 2008;Biederman et al., 2007;Gibson et al., 2007;Valicenti-McDermott and Demb, 2006;Yoo et al., 2007). A randomised, double blind multi-centre trial examined aripiprazole (30 mg/10 mg/placebo) in 302 adolescents (aged 13-17 years) with schizophrenia (Findling et al., 2008b). The trial concluded that treatment with aripiprazole lead to significant improvements in psychotic symptoms compared with placebo. The compound was generally well tolerated. A recent open-label trial with 21 children and adolescents aged 10-17 with bipolar or schizophrenia spectrum disorders, compared daily doses of 20, 25 or 30 mg aripiprazole in a 12 days titration phase, followed by a 14 days fixed dose phase (Findling et al., 2008a). The criteria for tolerability were met for all doses, and no adverse reactions met the regulatory criteria for serious adverse reactions. Effectiveness was found for all three doses.

In the TEA trial, we have chosen to use a 9-day titration phase with a final daily aripiprazole dose of 20 mg (equivalent to three blinded capsules per day). If needed for efficacy, the possible maximum dose can be titrated up to 30 mg. If final doses are not tolerated, patients can be titrated down to a lower dose level.

5.4 Dosing and titration schedule
Doses are initiated and titrated in accordance with the Danish guidelines for use of antipsychotics.

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Possible maximum titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5 (final)</td>
<td>6 (max)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole Daily dose, mg</td>
<td>2,5</td>
<td>2,5</td>
<td>5</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Quetiapine extended release Daily dose, mg</td>
<td>50</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>200</td>
<td>200</td>
<td>400</td>
<td>400</td>
<td>600</td>
<td>800</td>
</tr>
<tr>
<td>Blinded capsules Daily quantity, pieces</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
the amount of capsules containing active preparation (quetiapine extended release and aripiprazole) is complemented with capsules containing non-active preparation (see 9.2 Blinding)

5.5 Concomitant medication
Concomitant medication of any kind beyond trial medications will be recorded throughout the trial period in the CRF. In acute phases or situations, patients may be treated with sedating medications. Patients in the TEA trial will not be allowed any concomitant antipsychotic medication before all trial assessments up until week 12 have been conducted. As the sedative medication benzodiazepines (preferably oxazepam or lorazepam) or antihistamines will be the first choice. The use of long-lasting benzodiazepines in combination with antipsychotic drugs is generally not recommended. If the patient during the trial receive brief additional antipsychotic treatment anyway due to clinical indication (pro nescitare (pn)), the patient will not be excluded, but this deviation from the protocol will be noted in the CRF.

6. Safety
It is not anticipated that the trial will entail any particular risks or complications for participants. The two antipsychotic compounds investigated (quetiapine extended release and aripiprazole) have a market authorisation in Denmark and are frequently used in clinical practice in the intended age group. All blood sampling will be performed by accredited personnel. We do not expect any special circumstances that can lead to termination of the trial due to overall safety concerns. In addition, a Data Monitoring and Safety Board will monitor the trial (see section 6.3)

In case of adverse events, the antipsychotic treatment of the patient in question may be stopped (if considered severe and/or intolerable) or the dose may be reduced (if considered non-severe and/or tolerable); In the former case, please see section 9.3 and 9.4. In the latter case, the investigator chooses to step down one level in dose and the assessments of the next follow up are conducted as planned. If adverse events are judged by the treating physician to be intolerable, or if the participant requests it, the participant can be taken off the trial intervention before week 16. However, the participant will still be followed up at 52 weeks after the trial intervention started, unless s/he requests to be withdrawn from the trial altogether.

The treating physician can at all times decide to withdraw a participant from the trial altogether, according to current guidelines from the American Psychiatric Association and The Danish Board of Health. See section 9.4 and 9.4.

6.1 Known adverse reactions
It is currently recommended to use a second generation antipsychotics instead of first generation psychotics for children and adolescents with psychotic illnesses due to a more favourable adverse reaction profile.

Quetiapine (extended release) and aripiprazole are both second generation antipsychotics.

Generally, a slower titration is recommended for children and adolescents, a long with a more frequent monitoring of effects and adverse events than is normally recommended for adults.
This is because the number of adverse reactions is known to be more frequent and more severe in children and adolescents. This is especially the case for the two antipsychotic the when it comes to increased weight, metabolic adverse reactions, haematological adverse reactions, hormonal effects, and extrapyramidical adverse reactions.

**Rules of caution (for both antipsychotics)**

Caution with cardiovascular illnesses, increased risk of cerebrovascular illness, severely decreased liver function, earlier convulsions and illnesses associated with a risk of convulsions.

Severe hyperglycaemia has been known to appear with the use of second generation antipsychotics and the patient shall continuously be monitored. This is especially the case with patients with diabetes or a high risk of diabetes, and the blood glucose level shall be monitored frequently.

**QUETIAPIN (SEROQUEL® Prolong) (from product resume dated 19th of February 2013)**

The following are possible adverse reactions:

**Very common (>10%):** Increased appetite, weight gain, dry mouth, motorsystem symptoms, headache, somnolence, dizziness, hypercholesterolemia, hypertriglyceridemia, reduced haemoglobin, elevated prolactin, and increased blood pressure.

**Common (1-10%):** Asthenia (weakness), dyspepsia, constipation, orthostatic hypotension, peripheral oedema, rhinitis, tachycardia, abnormal dreams, suicidal ideation and suicidal behaviour, irritability, syncope, blurred vision, elevated liver transaminases, leukopenia, and hyperglycemia.

**Uncommon (0.1-1%):** Difficulty swallowing, increased risk of bleeding due to thrombocytopenia, seizures, restless legs, involuntary movements, hypersensitivity (including allergic skinreactions), sexual disturbances, disturbances in heafrhythm, reduced salt levels in blood.

**Rare (0.01-0.1%):** Jaundice, venous thromboembolism, galactorrhoea (swelling of breasts and production of breast milk), increased plasma creatine kinase (muscle enzyme), Neuroleptic malignant syndrome (NMS), priapism, menstruation disturbances.

**Very rare (<0.01%):** Hepatitis, Diabetes Mellitus, muscle tissue degradation, serious skinreaction, serious allergic reactions with low bloodpressure, breathingproblems, and possible seizures (anaphylactic reaction), angioedema, swelling, and raised lumps (weals) around the mouth, change in excretion of pituitary hormone (antidiuretic hormone).
Somnolence occurs usually transient during the first two weeks, and generally fades as medication is continued. Involuntary movements are most frequent during long term treatments. Normally, these declines as medication intake ceases, but are sustained occasionally. Very rarely do Neuroleptic malignant syndrome (NMS) – a serious condition with fever, unconsciousness, and several of the above adverse reactions - occur. This condition requires instant medical assistance.

The frequencies of following adverse reactions occurrence have not been possible to set. The frequency of following adverse reactions has not been possible to determine: toxic skin reaction (epidermisk nekrolyse), and acute inflammation of the skin (erythema multiforme).

ARIPRIPRAZOL (ABILIFY®) (from product resume dated 8th of October 2013)

The following adverse reactions are possible:
Very common (>10%): Fatigue, uncontrollable movements, motor restlessness

Common (1-10%): Stomachache, dry mouth, uncontrollable movements, nausea, vomiting, salivary hypersecrection, dyspepsia, constipation, increased heart rate, headache, dizziness, insomnia, somnolence, tremor, restlessness, anxiety, blurred vision, increased appetite, low blood pressure, weight gain and muscle twitches.

Not common (0.1 - 1%): Tachycardia, depression

Several other adverse reactions have been reported, but the frequency is unknown. These include: changes in laboratory blood work, arrhythmia, sudden unexplained death, cardiac arrest, allergic reactions, increased blood glucose levels, diabetes or deterioration of diabetes, ketoacidosis or coma, decreased concentration of salt (natrium) in the blood, weight gain, weight loss, loss of appetite, nervousness, agitation, anxiety, compulsive gambling, suicidal ideation and suicidal behaviour, suicide, speaking disturbances, convulsions, serotonin syndrome. Combination of fever, muscle rigidity, increased respiration, severe perspiration formation, reduced consciousness, sudden changes in blood pressure and cardiac rhythm, fainting, high blood pressure, thrombosis particularly in the legs, possibility that these migrate to the lungs causing chest pain and respiratory problems, convulsions in mouth/throat area, aspiration, difficulty swallowing, inflammation in the pancreas, liver failure, inflammation of the liver, yellowing of the skin and the whites of the eyes, effects on liver function, discomfort from abdomen or stomach, diarrhea, rash and lightsensitivity, unusual hairloss or thinning, rigidity or convulsions, muscular pain, weakening, urinary incontinence, urination problems, priapism, difficulties regulating body temperature (feeling too hot/cold), chest pain, swollen hands, ankles or feet.

In very rare cases, involuntary movements and Neuroleptic malignant syndrome (NMS) – a serious condition with fever, unconsciousness, and several of the above adverse reactions- occur. This condition requires instant medical assistance.
6.2 Reporting of adverse reactions and adverse events

All procedures for registering and reporting adverse reactions and adverse events will follow the regulations and guidelines from the Danish Health and Medicines Authority and the Ethics Committee of Capital Region.

Adverse events will be captured as an outcome measure during the trial intervention period, i.e., in the week 2, week 4, and week 12 assessments, and will further be registered, up to week 18, i.e., two weeks after the trial intervention period stops. If the participant is taken off the trial intervention before week 16, adverse events shall be registered during the following two weeks. Further, adverse events will be summed up in the assessment of outcomes in week 52. In accordance, adverse events will not be registered during the weeks of 19 to 52, but rather follow common clinical reporting of adverse events.

Table 3: Reporting of adverse reactions and adverse events

<table>
<thead>
<tr>
<th></th>
<th>Danish Health and Medicines Authority</th>
<th>Ethics Committee of Capital Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUSAR (suspected unexpected serious adverse reaction)</td>
<td>Immediately</td>
<td>Yes*</td>
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<tr>
<td></td>
<td>Yearly</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>End of trial</td>
<td>Yes</td>
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<tr>
<td>SAR (serious adverse reaction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immediately</td>
<td>No</td>
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<tr>
<td></td>
<td>Yearly</td>
<td>Yes</td>
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<tr>
<td></td>
<td>End of trial</td>
<td>Yes</td>
</tr>
<tr>
<td>AR (adverse reaction)</td>
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<td></td>
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<tr>
<td></td>
<td>Immediately</td>
<td>No</td>
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<td></td>
<td>Yearly</td>
<td>No</td>
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<tr>
<td></td>
<td>End of trial</td>
<td>Yes</td>
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<tr>
<td>SAE (serious adverse event)</td>
<td></td>
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<tr>
<td></td>
<td>Immediately</td>
<td>No</td>
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<tr>
<td></td>
<td>Yearly</td>
<td>No</td>
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<tr>
<td></td>
<td>End of trial</td>
<td>Yes</td>
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<tr>
<td>AE (adverse event)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Immediately</td>
<td>No</td>
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<td></td>
<td>Yearly</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>End of trial</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* will be reported immediately and no later than 7 days (if lethal and lifethreatening SUSAR) and no later than 15 days (if any other SUSAR) after sponsor has been made aware of the SUSAR.

The investigators will classify the adverse events for seriousness, causality, and expectedness, using the best clinical judgement and the knowledge of known adverse events for the investigated medical compounds. The current product resumé shall at all times be used, and can be found at http://www.produktresume.dk for Seroquel, and at http://www.ema.europa.eu for Abilify. In accordance with the GCP guidelines and the Directive 2001/20/EC, the following definitions will be used:

Suspected Unexpected Adverse Reaction (SUSAR): an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., summary of product characteristics for an authorised product).
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR): any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Adverse Reaction (AR): all untoward and unintended responses to an investigational medicinal product related to any dose administered.

Adverse Event (AE): any untoward medical occurrence to an investigational medicinal product and which does not necessarily have a causal relationship with this treatment.

6.3 Data Monitoring and Safety Committee
An independent Data Monitoring and Safety Committee will be established, and it will work according to the charter for the TEA trial (Appendix 1). The Data Monitoring and Safety Committee will monitor the primary outcome and adverse events occurring in the trial. The Data Monitoring and Safety Committee will advise the Steering Group to temporary halt or stop the trial prematurely, if there is convincing evidence that one of the interventions is superior in regards to benefits and harms, or if the level of adverse reactions is intolerable.

6.4 Contraception
Female participants, whom are fertile and sexually active, must use safe contraception when participating in the trial. Safe contraceptive is contraceptive coil or hormonal contraception, such as birth-control pill, implant, transdermal depot patch, vaginal ring, or depot injection. Sterile committed partner or use of double barrier (condom combined with occlusive cap, such as diaphragm or cervical/vault caps) can be accepted if it can be secured. The participant and the parent(s) are informed at the verbal information session that it is generally advised against pregnancy while in antipsychotic medical treatment, and that it must be secured in the trial period that the participant do not get pregnant whilst taking antipsychotic medical treatment.

The status of fertility (menarche has occurred) and sexual activity is evaluated by a physician based on conversation with the participant under the somatic assessment at screening. In addition, it will be assessed and secured at the follow-up visits in week 2, 4, and 12, if the status of fertility and sexual activity has changed from not present to present. Furthermore, it is strongly emphasized to the participant that if status of fertility and sexual activity is changed in between the follow-up assessments, the participant shall notify the treating physician of this, thus the need for anticonception will continuously be assessed.

If the participant is considered fertile and sexually active, the use of contraceptives shall be secured in the whole trial period, and after trial participation (or end of antipsychotic medical treatment along the way in the trial period) for a time period no less than 5 times the plasma half-life period for the interventions used. After the end of the intervention period, at week 16 according to the protocol, it will be secured by an agreement between the TEA investigator and the treating physician that the treating physician will regularly follow-up and secure the use of safe contraceptives in the remaining trial period, whilst the participant is in antipsychotic medical treatment.
7. **Statistical considerations**

7.1 **Sample size**

The power calculation is based on the primary outcome measure PANSS global positive symptoms. The average and standard deviation for PANSS global positive symptoms is based on Schimmelmann’s report on the prospective 12 week study in adolescents (Schimmelman et al., 2007) and on studies by Sikich et al and Arango et al (Sikich et al 2008; Arango et al 2009) as well as data from the project group’s previous trial of first-episode children and adolescents with psychosis (Fagerlund et al., 2006; Pagsberg et al., 2006).

As it is not previously reported, we estimate the minimal relevant difference expected on PANSS positive scale after 12 weeks between the two different interventions to be a score of 3.4 scores. This mean difference is less than half the standard deviation of 7.4 points, based on the data from Schimmelman et al. With a power of 90% and a two-sided alpha of 5%, the required sample size necessary to detect or reject this difference is n=100 in each of the intervention groups.

![Figure 1: Sample size according to the outcome PANSS positive scale *](image)

*The figure above illustrates the sample sizes required to maintain a power of 90% and an alpha of 5% according to changes in the population average on PANSS positive scale.*

The total number of trial participants will be 200: 100 patients in intervention arm A and 100 patients in intervention arm B.

In addition 100 healthy volunteering healthy controls will be assessed as reference population.

7.2 **Data analysis**

Data will be analysed by an independent statistician from Copenhagen Trial Unit, who will work according to a statistical analysis plan that will be developed at the latest before the last participant is randomised. Data will be blinded during the analyses, and the blinding will not be broken before a conclusion has been drawn.
Data will be analysed according to the intention to treat principle and missing data will be dealt with by multiple imputations. The data will be analysed with a two-sided statistical testing and P-values are assessed at the significance level of 5% with a correction for multiple testing according to Holm-Bonferroni (Holm S. 1979).

8. Recruitment of participants

8.1 Patients

The expected yearly intake of patients to the trial is based on the 2005 yearly report from the Danish BUP-Base (Danish National Child- and Adolescent Psychiatric Database) (Børne og Ungdomspsykiatrisk Selskab i Danmark (BUP-DK) and Kompetencecenter Syd (OUH), 2006) as well as data extracted from patient registrations from the Child- and Adolescent Psychiatric Department at Bispebjerg University Hospital in Copenhagen from recent years (2000 – 2005). When these data are extrapolated to the other child- and adolescent psychiatric departments in Denmark, the yearly number of first-time admissions with the relevant diagnoses is estimated to be approximately 200. Both inpatients and outpatients are included in the trial, and changes in hospitalisation status during the trial will not affect participation. If approximately 50% of these are expected to participate in the trial, the required 100 patients in each treatment arm are expected to be included within a two year period.

When patients first get in contact with one of the participating centres, s/he will be screened for eligibility with regards to age, diagnosis and previous treatment (antipsychotic-naïve). If the patient is potentially eligible, the investigator will initial ask the parent(s) and then the patient him/herself if they are interested to participate in a clinical trial. If both the parent(s) and the patient are interested they will be invited to an interview with the investigator. At this interview both the patient and the parent(s) will receive verbal information about the TEA trial to a level of his/her understanding by personnel with qualifications to work with the intended age group and that are well informed with the trial. All parents and patients, in the age of 15-17 years, will receive written information about the TEA trial. There will be an opportunity to ask questions about the trial at inclusion as well as any other time in the trial period. The potential trial participant and parent(s) will be informed of their right to take time to consider an eventual participation in the trial. The patients who agree to participate will be offered compensation for transportation costs for both the participant and the parent(s).

Approximately 4 weeks prior to the week 52 follow-up, a letter will be sent to the participant and his/her parent(s) notifying about the upcoming week 52 follow-up visit. This is done to assure that as many as possible participate in the follow-up assessment.

8.2 Healthy controls

Names and addresses of potential healthy controls will be extracted from the Danish Centralised Civil Register and will be applied for with the Danish Health and Medicines Authority (Sundhedsstyrelsen) according to age, sex, socioeconomic status, and previous psychotic diagnose. The potential healthy controls will be invited to participate in the study by a mailed letter addressed to the potential healthy controls parent(s). Both letter and envelope is labelled with the Capital region of Denmark’s (Region Hovedstadens) logo. In the envelope is an invitation to the parent(s) and one to the adolescent if he/she is of 15-17 of age. In addition to
that, the written participant information (to parent(s) and the adolescent if he/she is of 15-17 of age) is enclosed, along with a questionnaire. The questionnaire is asked to be filled in, by those who wish to participate and returned in an enclosed prepaid return envelope. If no reply is received from the potential participant, TEA personnel will make contact within 2-3 weeks. If the potential healthy control and the parent(s) are interested to participate in the study, they will be invited to an interview. At this interview both the healthy control and the parent(s) will receive verbal information about the TEA study to a level of his/her understanding by personnel with qualifications to work with the intended age group and that are well informed with the study. There will be an opportunity to ask questions during inclusion as well as any other time during the trial period. The potential participant and parent(s) will be informed of their right to take time to consider an eventual participation in the study.

9. Randomisation and blinding

9.1 Randomisation
Each consecutive participant will receive a patient number when assessed for eligibility at each clinical centre. Randomisation to either treatment arm A or treatment arm B is carried out centrally by the Capitol Region Pharmacy using a computer-generated allocation sequence with a block size unknown to investigators. To optimise the comparability between treatment groups, randomisation is stratified by the two factors: PANSS positive score (i.e., over 20 points or equal or under 20 points), and age (i.e., 12-14 years or 15-17 years). Allocation sequence lists will be prepared according to the stratification variables and the trial medication packages will be distributed accordingly. The corresponding randomisation code list will be sent electronically to the data manager at Copenhagen Trial Unit.

9.2 Blinding
The Capital Region’s Pharmacy will pack and distribute the two different medical compounds quetiapine extended release and aripiprazole. The compounds will be put into identical capsules. Both the filling material (lactose monohydrate) and the capsules are known not to interfere with the effectiveness or the pharmacological abilities of the active substances. The two administered intervention treatments will be alike regarding looks, size, taste, smell as well as number of capsules given at each phase of the titration schedule and in the following weeks (see Table 2: Dosing and titration schedule). In order to blind for the medical compounds given, the same number of capsules have to be given for both medical compounds at each level of the titration schedule. Thus, for the group taking the medical compound aripiprazole the number of blinded capsules will be completed by adding capsules containing a non-active preparation where necessary.

9.3 Breaking of the randomisation code
If a patient discontinues the assigned treatment, the investigator will, if at all possible, perform the next follow-up assessment and establish clean files for that particular patient regarding benefits and harms before breaking the randomisation code. If it is deemed a medical emergency the randomisation code can be broken immediately, and this is the ultimate choice of the investigator. Braking of the randomisation code will be done by telephone to the
Copenhagen Trial Unit, tel 3545 7171 (or in emergencies tel 40401181) and can be achieved 24 hours/7 days per week. When the randomisation code is broken for that participant and s/he will continue on any choice of treatment supervised by his/her physician.

9.4 Discontinuation of the intervention and/or exclusion from the trial
A trial participant does not continue in the randomised part of the, if s/he stop taking the allocated antipsychotic medication before the end of week 12 due to lack of effect, an unacceptable level of adverse reactions, suspected unexpected serious adverse reactions (SUSARs) or if the patient wishes to withdraw of the blinded treatment. At the time of treatment discontinuation, the next scheduled follow-up assessment shall be performed in order to perform statistical imputation of data from patients who are withdrawn from the blinded part of the trial before week 12, and thus these assessments may be moved forward from the original timetable. Effect assessments (cognitive tests and/or laboratory tests including ECG), which are planned to be conducted at later assessment (not the first assessment coming up) shall likewise be moved forward for the ‘discontinuation assessment. However, the diagnostic interview (K-SADS) shall in any case be maintained as part of the 4-week follow-up assessment, as this is not a ‘proper’ dynamic outcome measure, but a diagnostic assessment through a longer period in time, which initially assess the presence or absence of specific symptoms, which can best describe the patient's symptomatology at the time of enrolment. When the possible follow-up assessments have been conducted, the randomisation code and the blinding will be broken (see section 9.3). Patients who are withdrawn from the blinded part of the trial before week 12, - to the extent it is possible, and if they consent to this (i.e., do not withdraw their original consent) – shall be followed in all the remaining follow-up assessments according to the initial schedule (yet with the immediate follow-up assessment brought forward before unblinding, see also above), so their data can be included in the intention-to-treat analyses. If a patient withdraws his or her initial consent, the patient is excluded from the trial and no further contact will be taken with him or her.

9.5 Deviations from the protocol
If the trial protocol is deviated for a participant, this will be registererd as ‘protocol deviation’ in the participant’s CRF.

10. Quality control
Reliability of collected data will be optimised by using co-rating of interviews and tests. Data entry from the paper case record forms into database will be centralised and quality controlled. Further, the trial will be monitored by the GCP-units in Denmark. The investigators will allow direct access to source data and documents (including medical records) for audit, inspection, and monitoring by the relevant authorities. The trial participants are informed of this and will provide specific written informed consent for this purpose.
10.1 Regulatory compliance and approvals
The present clinical trial follows the Helsinki Declaration and current guidelines for ICH-GCP and EU’s directive for clinical drug trials. Approval from the Danish Data Protection Agency, the Danish Health and Medicines Authority, as well as the Ethics Committee of Capital Region is required before inclusion into the trial will be initiated. The trial will be registered in EudraCT (the European Union’s database of clinical research before application to the Danish Health and Medicines Authority). All procedures for registering and reporting severe adverse reactions and adverse events will follow the existing above mentioned guidelines. The trial will be registered at www.clinicaltrials.gov, which is an American system of registration of international clinical intervention studies.

11. Ethical considerations
The TEA trial involves minors with psychosis, i.e., a vulnerable population. The antipsychotic medications used today in children and adolescents are not sufficiently studied in this patient group. The TEA trial will improve the understanding of the benefits and harms in children and adolescents with psychosis and psychotic symptoms.

Both investigational compounds used in the trial (quetiapine and aripiprazole) have already obtained approval for treatment of psychosis among adults in Denmark. They are both commonly used in clinical practise in the children and adolescent psychiatry, and aripiprazole have in July 2009 achieved post-authorisation for use in adolescents from 15 years and older with schizophrenia (European Medicines Agency 2009).

Since the trial is on a medicinal product and the participants are under 18 years of age (children and adolescents), an informed consent is required from the holders of custody. Trial participants will only be enrolled into the trial after the proper informed consent has been obtained. A participation in the trial based on a consent cannot be initiated or continued if the trial participant him/her self objects to it. Adolescents whom will turn 18 years in the trial period, will upon up on turning 18, receive new written and verbal information as an adult (the participant information for adolescent patients (15-17 years) contains all the requirements for adult participant information). Prior to any further trial participation new informed consent shall be obtained by the participant him/her self. A copy of the new informed consent is given to the participant and the original is filed in the investigator site file.

All parents and the participants in the age of 15-17 years will receive oral as well as written information about the trial prior to inclusion and will be well informed of their rights to withdraw from the trial without it affecting the patient’s current or future treatment. Participants in the age of 12-14 will receive oral information at a level of the participants understanding. The giving of the verbal information shall be planned carefully, and it shall be scheduled in advance with the child or adolescent. The information shall be delivered with no interruptions, and the information shall be understandable and neutral and be given by a person, who is knowledgeable in the area (medical treatment of psychosis), and also has pedagogical qualifications in order to communicate the information adapted to the age group. The written participant information shall be given at the time of verbal information. Informed consent will be sought after the verbal and the written information is given.
The written participant information will state the risks and advantages of the trial in clear and understandable terms. The trial participants and their parents are informed of their right to take time to consider an eventual participation in the trial. Participants are informed of the right to bring an assessor when receiving oral information. Prior to the inclusion into the trial, informed consent must be documented in writing on the informed consent form, to be kept by the investigators and supplied in copy to the parent(s). The signed informed consent forms are to be kept in the investigator site file. All trial participants are informed that all person-related information is encompassed by confidentiality. Patients are informed of their right to access to documents and their right to file complaints according to existing laws. All trial participants and parent(s) are informed that participation is voluntary and that they are allowed to withdraw from the trial without explanation and without this affecting their subsequent treatment. In case of withdrawal from the trial, either by the participant’s own choice or the treating physician’s choice, the investigator will ask permission from the participant to use the so far collected data.

After patients have completed the intervention period (16 weeks), feedback about their own results in terms of psychopathology and cognition will be offered. All participants and parents participating in the trial will receive information, if they wish so, about the results of the TEA trial approximately one-two years after inclusion of the last participant.

Healthy controls will be offered feedback about their trial results, if they wish so. The healthy controls and their parents are contacted and informed of their results according to existing guidelines.

Any new research in the stored biological material will require the approval from the Research Ethics committee.

Compensation for patients
To assure high participation at the week 52 follow-up, the participant and his/her parent(s) are informed at the time of unblinding in week 16, about the importance of the last follow-up. At the same time, they are informed that the participant will receive four cinema tickets with popcorn (worth 420 DKK) for the participation in this last follow-up. This remuneration shall be seen as compensation to be given to the participant after the completion of the trial, to underline that the week 52 follow-up is an essential part for the TEA trials results. As the initial assessments, at week 0, 2, 4 and 12, encompass medicinal treatment, we do not see it ethically to inform of this remuneration prior to week 16 (unblinding), as this information might influence the patients willingness to participate in the intervention part of the trial. The remuneration shall thus only be seen as compensation, to boost the number of participants that will participate in the TEA trials full follow-up period.

Compensation for healthy controls
The healthy controls, who agree to participate in the trial, will be compensated for their effort with two cinema tickets with popcorn (worth 210 DKK) per visit, as well as offered compensation for transportation costs for both the participant and his/her parent(s).
12. Data handling and record keeping

Copenhagen Trial Unit will arrange for retention of the patient identification code list for at least 15 years after completion or discontinuation of the trial. Identification lists for the healthy controls will be kept by the sponsor. The sponsor is responsible for upholding the trial master file and the principal investigators will uphold their respective investigator site files during the trial period. Essential documents will be filed and archived according to the good clinical practice guidelines, and the sponsor has the overall responsibility for making sure the trial master file and investigator site files are complete and archived under safe conditions throughout the archiving period.

Data are collected by the investigators in case record forms (CRFs), and kept and handled as confidential material according to current guidelines from the Danish Data Protection Agency. In addition to this raw material (in paper form), data from each participating department is typed into a database. The database will be developed by the Copenhagen Trial Unit in collaboration with the coordinating investigators. The database will be set up according to the abovementioned guidelines for data protection. All data will be stored in locked facilities and only authorised personnel will have access to it. An application for collecting CRFs and setting up the database will be made to the Danish Data Protection Agency.

The registration of raw data and motion logfiles from the KinectTM-examinations will be collected via an integrated depth-measuring sensor card and video. The KinectTM-generated data/exposures will be connected with the serial numbers of the participants and stored with strong encryption on TrueCrypt harddisc on the laptops for subsequent data processing at DTU Compute. When the KinectTM-instrument and the connected laptop are not in use they will be stored behind double lock. Under the data processing the raw data/exposures will be stored on a secure computernetwork at DTU Compute. Approval of data collection and processing is handled by the coordinator of information security of the Capital Region. An application on the linkage of data has been reported to the Danish Data Protectionency.

13. Publication policy

The trial investigators will prepare manuscripts for publication according to the Vancouver Guidelines, which will determine co-authorship. We will strive to publish the results of the TEA trial in the best international journals irrespective of the findings are positive, neutral, or negative.

One or two appointed investigators from each participating department will be included in the trial's collaborative work group "TEA" (Tolerance and Effect of Antipsychotics). This group will be mentioned in all trial publications under acknowledgements. One or both of these investigators from each department will be included as co-author(s) in at least one publication from the trial, depending on contribution.
14. Practicalities
Each participating psychiatric department, and the staff involved with the trial there, will receive training in administration of the trial materials, i.e., ratings of psychopathology and daily functioning scales, and cognitive assessments.

The trial materials (i.e., CRFs, the cognitive test battery, and psychopathology and daily functioning rating scales and questionnaires), will be provided by the principal investigator at Bispebjerg Centre for Child and Adolescent Psychiatry. Participating departments will keep the materials after completion of the trial, with stipulation of adherence to the rights of copyright holders.

14.1 Participant Insurance
Participants in the TEA trial are covered by the Danish patient insurance system ('Patient forsikringen')

14.2 Time schedule
2009
- Applications to the Danish Data Protection Agency, the Danish Health and Medicines Authority, and the Regional Ethics Committee (conducted by the Copenhagen Trial Unit on behalf of the coordinating investigators).
- Continuing applications for funding.
- Hiring of trial employees and staff.
- Teaching about the trial program and material used of participating departments.

2010-2013
- Recruitment of patients and healthy controls starting in the middle of 2010.
- Continuous teaching and supervision of participating departments.
- Hiring of trial personnel.

2014-2015
- Recruitment and inclusion of patients and healthy controls is completed by June 30th 2014
- Data analysis, presentation of results from the randomised blinded trial.

2015-16
- Data analysis, presentation of results from the randomised blinded trial, presentation of results from the follow-up assessments.

14.3 Funding
Funding obtained
The TEA trial has obtained the following funding:
- The Research Council for Health and Disease in 2007 (Forskningsrådet for Sundhed og sygdom). Post Doc scholarship for Birgitte Fagerlund for three years. Appointed DKK
1,953,745, where only DKK 293,722 is spend as Birgitte Fagerlund discontinued her position.

- Allocated inheritance from Elizabeth Stevn and Niels Rindom, Landsforeningen SIND (the Danish Association for Mental Health). **DKK 50,000, 2008**
- Rosalie Petersen Foundation **DKK 60,000, 2008**
- The Psychiatric Centre for Children and Adolescents in Bispebjerg (Børne- og Ungdomspsykiatrisk Center Bispebjerg). A half-time clinical assistant for three years, beginning when the TEA trial begins in late 2009.
- The Capitol Region Psychiatry (Region Hovedstadens Psykiatri) 2009. A Ph.D. scholarship, **DKK 1,530,000**, and general grant, **DKK 880,000**.
- A.P. Møller foundation. Amounts sought are: statistician DKK 420,000; web editor 150,000; software and psychiatric test material DKK 125,000; Laboratory tests 60,000 – in total DKK 755,000. Funding obtained: **DKK 50,000, 2008**.
- Research Institute for Biological Psychiatry, Sct. Hans Hospital 2009. Funding of genetic analyses **DKK 3,000,000**.
- Tryg Fonden. Amounts sought are: **DKK 4,000,000**. Funding obtained: **DKK 2,000,000, 2010**
- Region Hovedstadens Forskningsfond. Funding obtained: **DKK 2,475,000, 2010**.
- Tryg Fonden. Amounts sought 2011: **DKK 12,000,000**. Funding obtained 2011: **DKK 2,000,000**.
- Psykiatris Forskningsfond i Region Syddanmark. Amounts sought **DKK 2,515,922**. Funding obtained 2011: **DKK 67,700**.
- PsykiatriFonden. Amounts sought **DKK 1,534,077**. Funding obtained: **DKK 1,000,000, 2012**
- Tryg Fonden. Amounts sought 2012: **DKK 2,779,953**. Funding obtained 2012: **DKK 1,000,000**
- Fund of 17-12-1981. Amounts sought: **DKK 2,145,000**. Funding obtained: **DKK 600,000, 2012**
- Capital Region Psychiatry Research Fund. Amounts sought: **DKK 67,000**. Funding obtained: **DKK 67,000 DKK, 2012**
- Capital Region Strategic Research Fund. Amounts sought: **DKK 2,999,280**. Funding obtained: **DKK 800,000, 2012**
- Knud and Dagny Andresens Fund. Amounts sought: **DKK 206,066**. Funding obtained: **DKK 100,000, 2012**
- Psychiatry Research Fund of 1967. Amounts sought: **DKK 40,000**. Funding obtained: **DKK 30,000, 2012**
- Capital Region Psychiatry Reseach Fund. Amounts sought: **DKK 60,000**. Funding obtained: **DKK 60,000, 2012**
- Capital Region Psychiatry Reseach Fund. Amounts sought: **DKK 60,000**. Funding obtained: **DKK 60,000, 2012**
- Danish Psychiatry Researcher Development Programme. Amounts sought DKK 120,000. Funding obtained: **DKK 30,000, 2013**
- Jacob Madsen and wife Olga Madsens. Amounts sought DKK 32,561. Funding obtained: **DKK 10,000, 2013**
- Timber trade Johannes Fogs Fund. Amounts sought DKK 511,000. Funding obtained: **DKK 25,000, 2013**
- The Brothers Hartmanns Fund. Amounts sought: DKK 581,000. Funding obtained: DKK 150,000, 2013
- Aase and Ejnar Danielsens Fund. Amounts sought: DKK 200,000. Funding obtained: DKK 100,000, 2013

There will continuously be sought funding for the TEA trial from various foundations. Sponsor, steering group and investigators have no economic association to funding bodies.
Literature


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