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Treatment of antipsychotic-associated obesity with a GLP-1 receptor agonist—protocol for an investigator-initiated prospective, randomised, placebo-controlled, double-blinded intervention study: the TAO study protocol

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ABSTRACT

Introduction: Antipsychotic medication is widely associated with dysmetabolism including obesity and type 2 diabetes, cardiovascular-related diseases and early death. Obesity is considered the single most important risk factor for cardiovascular morbidity and mortality. Interventions against antipsychotic-associated obesity are limited and insufficient. Glucagon-like peptide-1 (GLP-1) receptor agonists are approved for the treatment of type 2 diabetes, but their bodyweight-lowering effects have also been recognised in patients with non-diabetes. The primary endpoint of this trial is weight loss after 3 months of treatment with a GLP-1 receptor agonist (exenatide once weekly) in patients with non-diabetic schizophrenia with antipsychotic-associated obesity. Secondary endpoints include physiological and metabolic measurements, various psychopathological and cognitive measures, and structural and functional brain MRI.

Methods and analysis: 40 obese patients with schizophrenia or schizoaffective disorder treated with antipsychotic drugs will be randomised to subcutaneous injection of exenatide once weekly (2 mg) or placebo for 3 months, adjunctive to their antipsychotic treatment.

Ethics and dissemination: The trial has been approved by the Danish Health and Medicines Authority, the National Committee on Health Research Ethics and the Danish Data Protection Agency. Trial participation presupposes theoral and written patient informed consent. An external, independent monitoring committee (Good Clinical Practice Unit at Copenhagen University Hospital) will monitor the study according to the GCP Guidelines. Trial data, including positive, negative and inconclusive results, will be presented at national and international scientific meetings and conferences. Papers will be submitted to peer-reviewed journals.

Trial registration: ClinicalTrials.gov identifier: NCT01794429; National Committee on Health Research Ethics project number: 36378; EudraCT nr: 2012-005404-17; The Danish Data Protection Agency project number: RHP-2012-027.

Strengths and limitations of this study

- This is the first randomised, placebo-controlled, double-blinded trial investigating effects of a glucagon-like peptide-1 receptor agonist on bodyweight, metabolic, physiological, psychopathological and cognitive measures, as well as structural and functional brain MRI in patients with schizophrenia with antipsychotic-associated obesity.
- The study is statistically powered to conclude on the primary endpoint (bodyweight change), but it might be statistically underpowered to conclude on the secondary endpoints.
- Participants will be monitored and examined extensively with frequent trial visits.
- The length of the intervention is limited to up to 4 months and the potential long-term effects of the treatment may not be extrapolated from the study.

INTRODUCTION

Treatment of mental illness with antipsychotic medication is associated with the development of dysmetabolism, including obesity and type 2

diabetes, cardiovascular diseases and early death.[1–4] The effects of current interventions against antipsychotic-associated obesity are limited.[1 3 5–7] Obesity is considered as the single most important risk factor in the development of cardiovascular morbidity and mortality.[8 9] Effective and long-lasting interventions against antipsychotic-associated obesity are highly warranted.[10]

Glucagon-like peptide-1 (GLP-1) is a gut hormone synthesised in the intestinal mucosa. GLP-1 is secreted into circulation after food intake and acts both peripherally and centrally. In the pancreas GLP-1 plays an essential role in glucose homeostasis by stimulating insulin secretion and inhibiting glucagon secretion. The insulinotropic and glucagonostatic effects are glucose-dependent, that is, only exerted when plasma glucose levels are above 4–5 mM.[11] Furthermore, GLP-1 decelerates gastric emptying and inhibits appetite, hunger and food intake. These actions are most likely mediated through peripheral GLP-1 receptors and GLP-1 receptors in the brain.[11]

GLP-1 receptor agonists constitute a group of drugs that mimics the effect of native GLP-1 and they are used for the treatment of type 2 diabetes. In addition to the blood glucose-lowering effect of GLP-1 receptor agonists in patients with type 2 diabetes, growing evidence supports that they facilitate weight loss in obese patients with and without diabetes.[12 13]

Recently, we suggested the GLP-1 receptor agonist therapy as a potential treatment strategy for patients with schizophrenia and obesity.[10] In a subsequent case report we provided the first clinical evidence in support of this idea.[14] In addition to beneficial metabolic effects, favourable central effects of GLP-1 receptor agonist treatment in patients with schizophrenia and obesity might be expected: preclinical data suggest potential procognitive effects of GLP-1 receptor agonist treatment on memory deficits.[15 16] Other preclinical studies have shown that GLP-1 receptor agonism has neuroprotective effects especially in the hippocampus.[17–19] Also, neuroprotective effects have been observed in dopaminergic areas of rodent brains and this may result in a reduction of extrapyramidal symptoms in patients treated with antipsychotic drugs. Finally, using single photon emission CT imaging the cerebral blood flow (CBF) in frontal cortex has been shown to be negatively associated with increased body weight in patients with non-psychiatric obesity.[20] Interestingly, the frontal CBF is also compromised in normal weight patients with schizophrenia. Therefore, we also aim to explore associations between the frontal CBF, GLP-1 receptor agonist treatment and changes in body weight.

This study protocol describes the first trial investigating effects of a GLP-1 receptor agonist (exenatide once weekly) on body weight in patients with schizophrenia and antipsychotic-associated obesity. Secondary endpoints comprise metabolic, physiological and cardiovascular effects and MRI of the brain, as well as psychopathological and cognitive measures.

METHODS AND ANALYSIS

Study design, inclusion, randomisation and blinding

The study will be conducted as an investigator-initiated prospective, randomised, placebo-controlled, double-blinded, parallel, 3-month intervention trial. Referred patients who meet the inclusion criteria will receive detailed oral and written information about the study according to the national ethical guidelines. A minimum reflection time of 24 h will be given before the written informed consent is obtained. After screening, enrolment and baseline examinations will be performed. Baseline examinations will be followed by an intervention period of 12 to maximum 16 weeks. Participants will be randomised to subcutaneous injections (once weekly) with either exenatide (2 mg) or placebo. A trained, impartial and unblinded researcher will be responsible for the computer-generated randomisation list and for subsequent allocation to treatment with either exenatide or placebo. The enrolment will continue until 20 participants in each arm have completed follow-up examinations. Owing to an expected attrition of 10–20% the enrolment will likely include up to 50 patients. Trial medication will be administered by unblinded research staff throughout the trial. The randomisation list, trial medication and medication documents will be safely concealed from the blinded principal investigator throughout the trial. Participants will be blinded throughout the entire trial. Data analysis will be performed after unblinding.

One week after the final dose of trial medication and on successfully completing the follow-up examinations, trial participation will be terminated. A flow chart of the study is provided in figure 1.

Study population

Patients are recruited from psychiatric outpatient and inpatient clinics in the Capital Region of Copenhagen, Denmark. The principal investigator reviews the patient referrals to secure that the inclusion and exclusion criteria are met (box 1). In case of doubt, the principal investigator involves the trial sponsor prior to final inclusion or exclusion. After screening, patients who meet the criteria for participation will be enrolled, examined (baseline examinations) and finally randomised. The individual patient data will be filed according to the progress made through the study of each participant and grouped into corresponding categories as shown in figure 1.

Trial visits and examinations

At baseline a complete medical history and a full physical examination will be performed. Questionnaires and various psychometric assessments will be collected. The participants' body weight (in fasting state) will be recorded. Blood sampling and whole-body dual-energy X-ray absorptiometry (DEXA) scan to measure the body composition (fat mass and fat distribution) will be performed (both in the fasting state). To investigate the

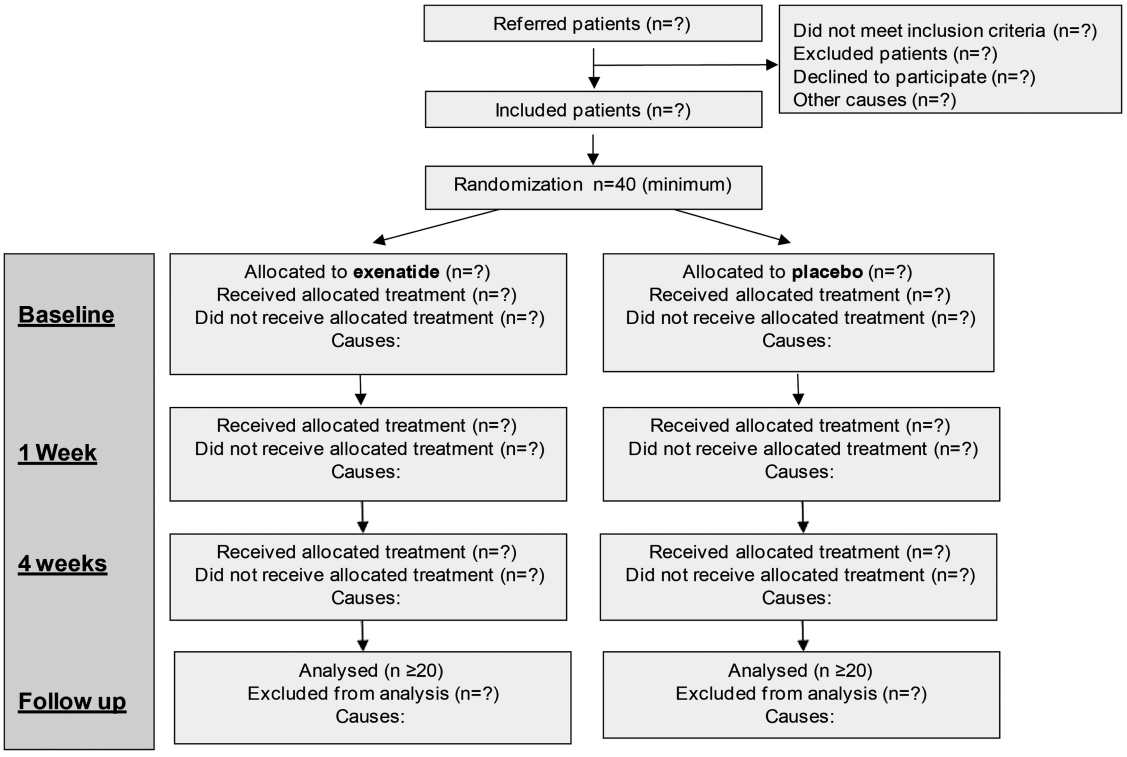

Figure 1 Flow chart of the TAO study. In each treatment arm 20 participants must complete follow-up examinations after 3 months of intervention. Adapted after the CONSORT statement.[37]

potential blood pressure-lowering effect of exenatide in patients with schizophrenia 24 h blood pressure monitoring including measurement of central blood pressure and augmentation index (Mobil-O-Graph 24-h PWA monitor, Stolberg, Germany) will be performed (approximately 80 measures in a 24 h period). All baseline examinations including MRI will be performed prior to randomisation and the first administration of trial medication. All the participants will attend four planned trial visits: 'Baseline' (week 0), '1 week' (7 days ±2 days), '4 weeks' (up to 6 weeks) and 'follow-up' (12–16 weeks). At each visit (except visit '1 week') blood sampling and ECG will be performed (table 1). Changes of any prescribed medication during the intervention period will be recorded.

Box 1

Inclusion criteria
- Age: 18–65 years
- Diagnosis in the schizophrenia spectrum (International Classification of Diseases (ICD)-10: F20.x, F25.x)
- Current and unchanged antipsychotic treatment for a minimum of 3 months
- Body mass index ≥30 kg/m^2
- Glycated haemoglobin (HbA1c) <6.5% (48 mmol/mol)

Exclusion criteria
- Substance dependence (ICD-10: F1x.2 (apart from nicotine addiction F17.2))
- Diabetes or HbA1c ≥6.5% (48 mmol/mol)
- Contraindications to MRI (eg, metal implants, pacemakers and severe claustrophobia)
- Previous head trauma with a loss of consciousness for more than 5 min
- Pregnancy (screened by urine human chorionic gonadotropin), lactation or no acceptance to use effective contraception during the intervention period
- Severe somatic disease, including inflammatory bowel disease and nephropathy
- Allergy to exenatide
- Coercive measures according to the Danish Mental Health Act
- Conditions that according to sponsor and/or investigators are not congruous with participation in the study
- Suicidal ideations

Intervention

Patients will be randomised after completion of the baseline examinations. All the participants will receive information about potential adverse effects prior to medicine administration. Trial medication, exenatide 2 mg once weekly (fixed dose) or placebo will be administered as subcutaneous injections by unblinded trial personnel throughout the trial. The first two doses will be given at the hospital (Psychiatric Center Glostrup). In order to maximise the trial adherence subsequent trial medication will be administered in the patient's home by trial personnel. On all trial visits a clinical examination and recording of any adverse events including hypoglycaemia will be performed. If a participant develops diabetes during the intervention, the participant will be excluded from the trial and referred to a diabetes outpatient clinic.

Table 1 Summarises the examinations planned on the four trial visits: baseline, 1 week, 4 weeks and follow-up

	Baseline	1 week (±2 days)	4 weeks (up to 6 weeks)	Follow-up (12–16 weeks)
Clinical examinations	X	X	X	X
Paraclinical examinations				
MRI	X			X
DEXA	X			X
ECG	X		X	X
24 h blood pressure	X			X
Blood sample (fasting)	X		X	X
Psychometry and questionnaires				
PANSS	X		X	X
Cognitive tests	X			X
ESRS	X		X	X
UKU-S	X	X	X	X
SF-36 quality of life	X			X
GAF/PSP	X		X	X
IPAQ-S	X		X	X
FFQ	X		X	X

DEXA, dual-energy X-ray absorptiometry; ESRS, Extrapyramidal Symptom Rating Scale; FFQ, Food Frequency Questionnaire; GAF, global assessment of functioning; IPAQ-S, International Physical Activity Questionnaire; PANSS, Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale; UKU-S Udvalg af kliniske undersøgelser.

Risks, side effects and potential benefits

The risk associated with participating in the experimental procedures in the present trial is minimal. Blood samples will be taken under aseptic conditions. During the entire study approximately 250 mL of blood will be drawn and analysed (table 2). MRI is not associated with any known health risk. Mild-to-moderate gastrointestinal (nausea, vomiting and diarrhoea in 10–15%) side effects are common but transient during treatment with exenatide once weekly. Less often exenatide causes headaches. Patients may experience abdominal pain, decreased appetite, fatigue, fever, dizziness and upper respiratory tract infection, however, less frequently. Uncommon side effects include gout, thyroid adenoma and angioedema. The injection of exenatide may result in a small haematoma at the injection site and transient, regional redness or a nodule (a harmless infiltration of the skin which usually disappears within 4 weeks).

Outcome measures and analysis methods

Primary endpoint

The primary endpoint is weight loss after 3 months' treatment with exenatide once weekly. At the baseline 1-week, 1-month and 3-month trial visits, all adverse events will be registered and body weight will be recorded on authorised and calibrated weight scales (Cardinal Detecto 750, 203 East Daugherty, Webb City, Missouri, USA). Participants will be weighed without shoes and outerwear and in a fasting state. Body weight will be reported per protocol analysis, thus only including participants who complete a minimum of 12 weeks of intervention. All adverse events will be reported to the relevant authorities.

Secondary endpoints

Secondary endpoints will explore the effects of exenatide on various parameters including psychopathological, cognitive, behavioural, cardiovascular, biochemistry and imaging (DEXA and MRI; table 1). The Positive and Negative Syndrome Scale (PANSS) will be used to assess the severity of schizophrenia symptoms.[21] The brief assessment of cognition in schizophrenia will be employed to assess five domains of cognitive function: verbal memory, working memory, motor speed, verbal fluency and reasoning and problem-solving.[22] The REY complex figure test will be used to assess visuospatial memory.[23] The Danish adult reading test (DART, Danish version of NART) will be performed to estimate premorbid IQ.[24 25] The Extrapyramidal Symptom Rating Scale (ESRS) will be used to assess changes in antipsychotic-induced parkinsonism and dyskinesia and further information concerning side effects of antipsychotic treatment will be obtained using the questionnaire UKU-S (Udvalg af kliniske undersøgelser).[26 27] The IQOLA SF-36 (Danish V.1.1) will be used to evaluate patients' subjective perception of quality of life.[28] Global assessment of functioning and the Personal and Social Performance Scale (PSP) will be used to assess the patient's overall level of functioning.[29] The International Physical Activity Questionnaire will be employed to evaluate physical activity.[30] The Food Frequency Questionnaire will be used to assess food intake and habits.[31]

We will use a Lunar Prodigy whole-body scanner (GE Medical Systems, Madison, Wisconsin, USA) in conjunction with the Encore V.14.1 software to assess body composition (total fat mass and fat-free mass and their distribution in the trunk and upper and lower limbs).

Table 2 Biochemistry (fasting blood samples) collected on the trial visits: baseline, 4 weeks and follow-up.

Potassium	Total cholesterol
Sodium	VLDL cholesterol
Haemoglobin	Triglyceride
Leucocytes	Proinsulin C-peptide
Lymphocytes	Insulin
Atypical cells	Proinsulin
Basophilocytes	Glucagon
Eosinophilocytes	Thyrotropin
Monocytes	Tri-iodothyronine (free T3)
Neutrophilocytes	Thyroxine (free T4)
Thrombocytes	Lactate dehydrogenase
Bilirubin	Amylase
Aspartate aminotransferase	γ-Glutamyltransferase
Alanine aminotransferase	Calcium
Alkaline phosphatase (liver)	Magnesium
Albumin	Carbamid
Creatinine	Alkaline phosphatase (bone)
Glucose	Osteocalcin
HbA1c	Procollagen type I *N*-propeptide
Ferritin	β-C-telopeptides of type I collagen (CTX)
Transferrin	C reactive protein
Iron	Adiponectin
LDL cholesterol	TNF-α
HDL cholesterol	Interleukin 1
	Interleukin 6

HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TNFα, tumour necrosis factor α; VLDL, very low-density lipoprotein.

We will use a Philips Achieva 3.0 T whole-body MRI scanner (Philips Healthcare, Best, The Netherlands) with a 32 channel SENSE Head Coil (Invivo, Orlando, Florida, USA). During MRI-specific structural sequences (T1 and T2 weighted) and fluid attenuated inversion recovery will be performed and assessed by a radiologist regarding potential pathology. In addition, diffusion tensor imaging, Quantitative STAR labelling of Arterial Regions (QUASAR) and pseudo-continuous arterial spin labelling measurements will be performed in order to measure the integrity of white matter tracts and CBF, respectively.

By means of these physiological data, potential neuroprotective effects and changes in CBF will be explored. These changes will be correlated to potential improvements in the global cognitive performance, with mainly the hippocampus, prefrontal cortex and hypothalamus as regions of interests. The relation between potential volumetric changes in striatum and a reduction of extrapyramidal symptoms will be explored. Duration of MRI will be approximately 50 min.

Finally, associations between potential weight loss and any improvements in secondary metabolic parameters (induced by exenatide) will be related to possible improvements in, for example, the patients' subjective quality of life and/or psychopathology.

Data analysis

Demographic variables and clinical characteristics will be measured by frequency (percentage) for categorical data, mean values (with SDs) for normally distributed, continuous variables and medians (range) for other continuous variables. Changes from baseline to follow-up will be analysed for all participants and for the exenatide and placebo arms separately. The primary outcome is bodyweight change in the exenatide group compared to the placebo group after 3 months of treatment. Weight changes will be correlated to various variables, for example, age, gender, baseline body weight, duration of obesity, type of antipsychotic drug and changes in the brain structure. Changes in CBF will be correlated to changes in, for example, cognition, subjective quality of life and to extrapyramidal side effects of antipsychotic medication.

Power calculation

We hypothesise a weight loss of 2.5 kg (±2.5 kg) in the exenatide arm versus 0 kg (±2.5 kg) in the placebo arm, which results in an observed effect size (Cohen's d) of 1.2 SDs based on Drucker *et al*.[32] In a priori Student t test (two-sided) with significance level α of 0.05 and a desired power (1−α) of 80% shows that 16 patients in each arm is adequate to test this hypothesis. We will include a minimum of 20 patients in each arm to ensure the power of the primary endpoint (>80%) and to increase the power of the secondary analyses. Homogeneity of variance between the two groups will be assessed using the Levene's test. Parametric data will be evaluated using parametric testing. Non-normally distributed data or data that exhibit unequal variances will be preferred. Fisher's or χ^2 exact tests will be used for group comparisons between categorical data. The Benjamini-Hochberg procedure will be used to control the type I error rate.

ETHICS AND DISSEMINATION

This investigator-initiated randomised placebo-controlled trial will explore the effect of exenatide once weekly on various metabolic parameters of importance in the schizophrenia population. All patients will receive oral and written information about the study prior to participation and oral and written informed consent of participation will be required. All female participants of childbearing potential will be tested for pregnancy (measurement of human chorionic gonadotropin in urine) and assurance of anticonceptive treatment will be obligatory throughout the study period. Personal integrity and privacy concerning participants will be protected by the Danish Law of Health. The study will be conducted in accordance with the Helsinki Declaration II and according to the current GCP principles (ICH-GCP).

Antipsychotic-associated obesity is a major and unresolved clinical problem due to its strong association to increased cardiovascular morbidity and premature death among patients with schizophrenia and other mental illnesses.[2 4 33 34] Moreover, obesity is associated with accelerated brain deterioration, cognitive decline and poor quality of life.[1 35] Today's interventions against antipsychotic-associated obesity do not facilitate a satisfying and lasting weight loss.[7 36]

The TAO study may provide evidence of the potential weight reducing properties of the GLP-1 receptor agonist treatment in patients with antipsychotic-associated obesity. In addition, we may also unravel neuroprotective and pro-cognitive effects, which may benefit and improve the global level of functioning in patients with schizophrenia. Thus, the outcome of our study may well have direct clinical implications for the future management of antipsychotic-associated obesity.

The positive, negative and inconclusive results of the trial will be presented at national and international scientific meetings. Scientific manuscripts will be written in accordance with the CONSORT 2010 Statement and submitted to peer-reviewed journals.[37]

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Contributors PLI, FKK, BVB, LB, BF, NRJ, UBA, ER, BYG and BHE have been involved in writing and designing the protocol. BHE and FKK conceived the idea and promoted the concept. BHE sponsors the trial. PLI is the principal investigator at Center for Neuropsychiatric Schizophrenia Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, Psychiatric Center Glostrup, Glostrup Hospital, University of Copenhagen, Glostrup, Denmark. All the authors have read and approved the final version of the manuscript.

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Competing interests FKK has received lecture fees from AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Company, Gilead Sciences, Merck Sharp & Dohme, Novo Nordisk, Ono Pharmaceuticals, Sanofi and Zealand Pharma, is part of the Advisory Boards of Eli Lilly Danmark, Bristol-Myers Squibb/AstraZeneca and Zealand Pharma, and has consulted for AstraZeneca, Gilead Sciences, Ono Pharmaceuticals and Zealand Pharma. BHE has received lecture fees from Bristol-Myers Squibb, Otsuka Pharma Scandinavia AB, and Eli Lilly and Company and is part of the Advisory Board of Eli Lilly Danmark A/S and Takeda Pharmaceutical Company Ltd.

Patient consent Obtained.

Ethics approval The trial is approved by the Danish Health and Medicines Authority, the National Committee on Health Research Ethics project number: 36378 and the Danish Data Protection Agency and registered on clinicaltrials.gov.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The TAO study will record datasets of up to 50 patients with schizophrenia recruited from clinical facilities in the Capital Region of Copenhagen. The dataset will include demographic data from interviews, self-reported behavioural data from questionnaires, imaging data (dual-energy X-ray absorptiometry and MRI) and laboratory (biochemical) data. The final dataset will be stripped of identifiers after analysis according to the law of The Danish Data Protection Agency. We applied the Danish Data Protection Agency concerning the data conceived in TAO study and the application was approved. All research data and associated documentation is available to other researchers and official institutions (Ethical Committee, The National Board of Health and the Good Clinical Practice Unit) affiliated to the TAO study during the intervention. However, only under a data-sharing agreement that provides for: (1) a commitment in using the data only for research purposes and not to identify any individual participant; (2) a commitment in securing the data using appropriate computer technology and (3) a commitment in destroying or returning the data after analyses are completed. New analysis of the data might necessitate new application for relevant authorities. All data will be stored for 10 years after completing the primary analysis and hereafter destroyed.

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