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PROTOCOL TITLE: TSPO PET as a measure of post-stroke brain inflammation: a natural history cohort

EUDRA CT NO: **NA**

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Version 3.1

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1. SPONSOR INFORMATION

The regulatory sponsor is Imperial College London.

2. LIST OF ABBREVIATIONS

AE	adverse event
BBB	Blood-brain barrier
BI	Barthel index
CRF	case report form
CRO	contract research organization
CNS	Central nervous system
CT	computed tomography
EC	ethics committee
EDC	electronic data capture
EU	European Union
LAR	legally authorized representative
LKN	Last known normal
ICF	informed consent form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
mRS	Modified Rankin scale
NIHSS	National Institutes of Health stroke scale
PET	Positron emission tomography
PHI	protected health information
RDC	remote data capture
SABR	Safety and Benefit-Risk
SAE	serious adverse event
SUSAR	suspected unexpected serious adverse reactions
TSPO	Translocator protein
UK	United Kingdom

3. SYNOPSIS

Tracking Number:	GBR-TYS-16-11060
Protocol Title:	TSPO PET as a measure of post-stroke brain inflammation: a natural history cohort
Version Number:	2.0
Name of Study Treatment:	Not applicable
Study Indication:	AIS
Phase of Development:	NA
Rationale for the Study:	Stroke is a leading cause of mortality and serious long-term disability. There is a substantial unmet medical need for new therapies that can improve outcomes in acute stroke. Experimental and pathologic data suggest that peri-infarct inflammation contributes to secondary injury after brain ischemia and that blocking inflammation could reduce the volume of brain infarction and improve clinical outcome. In a recently completed phase 2 placebo-controlled clinical trial, the administration of natalizumab (a potent inhibitor of leukocyte transmigration through the blood –brain barrier [BBB]) in the hyperacute phase of ischemic stroke was associated with beneficial effects in measures of functional outcome, but did not affect the rate of infarct volume growth during a 90-day assessment period. This apparent discrepancy between the lack of effect of anti-inflammatory therapy on lesion size and a substantial beneficial effect on functional outcome in ischemic stroke patients has raised further questions about the manifestation of neuroinflammation, its pathophysiological role and its relation to patients' functional outcome in stroke patients. The purpose of this imaging study is to characterize the subacute and longstanding extent of upregulation of the neuroinflammation marker TSPO on glial cells at two time points after stroke. The study will also explore the correlation of TSPO upregulation with measures of stroke severity and post-stroke functional outcomes.

Study Objectives and Endpoints:

The objectives of this study are:

- To characterize TSPO glial expression in specific regions of interest defined on correlative brain MRI (ROIs; infarct, peri-infarct, thalamus) in the subacute (day 15+7) and chronic (day 90+/-7) phases after an ischemic stroke;
- To determine the magnitude and variability of TSPO uptake at these ROIs during the assessment period;
- To describe changes in TSPO expression between 15 and 90 days
- To explore the relationship between TSPO uptake, blood and infarct volume, and measures of Wallerian degeneration,
- To characterize post-stroke TSPO glial expression in relation to measures of stroke severity (infarct size, volume and location; NIHSS) and functional outcome (mRS,BI, depression scale, MoCA)
- To characterize post-stroke TSPO glial expression in relation to systemic inflammatory markers in blood

The endpoints that relate to these objectives are:

- PET-derived measures of TSPO radiotracer uptake in the infarct and peri-infarct areas at day 15 and day 90 after a stroke
- PET-derived measures of TSPO radiotracer uptake in ROIs distant from the infarct area (e.g. thalamus, hippocampi, amygdalae and midbrain) at day 15 and day 90 after a stroke
- Correlation of PET-derived measures with clinical and imaging measures of stroke severity (stroke volume, size and NIHSS) and functional outcome (mRS Barthel index, MoCA, depression,) at day 15 and day 90
- Correlation of infarct volume and MRI measures of white matter tract injury determined from DTI MRI with measures of thalamic TSPO uptake (time-activity curve; measures of mean and max TSPO uptake on summed image sets fromTSPO PET
- Correlation of PET derived measures with inflammatory markers in the blood (e.g. cytokines)

Study Design:	This is an exploratory, prospective, natural history, imaging cohort study.
Study Location and Number of Sites:	The recruiting site will be Imperial College Healthcare NHS Trust. All study scans will be performed by Imanova, Hammersmith Hospital
Number of Planned Subjects:	Between 15 and 25 subjects, with recruitment ending when 15 participants have completed all study procedures.
Study Population:	Subjects aged 18-85 with a supratentorial ischemic stroke of moderate severity as measured by NIHSS >4 and evidence of infarction on clinical brain scan at time of stroke:
Duration of Treatment and Follow-up:	Subjects will participate in this study for approximately 90 days. No treatment will be started as part of the trial

4. SCHEDULE OF EVENTS

Tests and Assessments	Screening visit[9]	Day 15 (±3 days)	Day 90 (±7 days)
Eligibility confirmation[1]	X		
Sign Informed Consent Form[2]	X		
Demographics and medical history	X		
Physical and neurological examination	X	X	X
Vital signs[3]	X	X	X
Height (if available) and weight	X		
Urine (or serum) pregnancy test[4]	X	X	X
Medications	X		
NIHSS		X	X
mRS		X	X
BI		X	X
Beck Depression Inventory		X	X
Hematology and blood chemistry[5,6]	X		
Blood sample for systemic inflammatory profile	X	X	X
Blood sample for TSPO polymorphism genotyping[7]	X		
Confirmation of genotype eligibility criterion[8]		X	
PET and MRI scanning		X	X
Adverse Events reporting	throughout		

1. All but genotype exclusion criterion, see bullet point 8
2. Subjects will be consented prior to screening procedures
3. Vital signs include temperature, blood pressure, pulse or heart rate and respiratory rate
4. Women with childbearing potential only
5. Liver function, renal function and CBC will be performed at screening. Results of tests performed as part of standard of care can be accepted.
6. Renal function tests will be repeated before each PET MRI assessment in subjects older than 60 years of age or with known renal impairment
7. SNP genotype confirmation is required to determine eligibility. Blood samples for this assessment will be collected at screening only after other eligibility criteria have been met
8. Verification of the TSPO SNP genotype exclusion criterion will occur prior to or at the PET MRI acquisition day but will be confirmed before subjects undergo PET-MRI imaging acquisition.

9. Up to 10 days from stroke onset

5. INTRODUCTION

5.1. Background

Stroke is a leading cause of mortality and serious long-term disability. There is a substantial unmet medical need for new therapies that can improve outcomes in acute stroke. Experimental and pathologic data suggest that peri-infarct inflammation contributes to secondary injury after brain ischemia and that blocking inflammation reduces the volume of brain infarction and improves clinical outcomes.[1, 2] Hence, immunologic therapies have been investigated for treatment of ischemic stroke.[3] Nevertheless, there is substantial uncertainty about the time course and anatomic distribution of inflammation after stroke as well as its contribution to functional outcomes.

5.2. Rationale

TSPO, previously known as the peripheral benzodiazepine receptor (PBR), is a cholesterol transport protein that is present mainly in the mitochondrial compartment where it facilitates flow of cholesterol into mitochondria during steroid synthesis. [4] TSPO is overexpressed by microglia and monocyte-derived cells during inflammation and has been extensively used as a measure of inflammation.

In the brain, TSPO PET radioligands provide a measure of predominantly resident (activated) microglia and infiltrating monocyte-derived macrophages and, to a lesser extent, reactive astrocytes. [5]

Ischemic stroke is arguably one of the most robust examples of CNS inflammation following acute brain injury. As such, TSPO PET scans have been used to assess brain inflammation for over two decades. 11C-PK11195, a first generation radioligand, was used by several investigators to study the magnitude of inflammation after the occurrence of an acute ischemic stroke in humans. Table 1 below summarizes the key findings of these studies:

Table 1: Literature on 11C-PK11195 PET imaging in human ischemic stroke

Author/Date	Number of subjects studied	Key findings
Ramsay 1991	1	Uptake in infarct zone at 13d and 20d
Pappata 2000	7	All MCA stroke, imaged 2-24 months after stroke. Increased binding in ipsilateral thalamus and ipsilateral midbrain (not contralateral thalamus)
Gerhard 2000	5	Uptake at 5-33 days
Gerhard 2005	6	Early uptake in infarct zone

		Late uptake in thalamus/Wallerian degeneration
Price 2006	4 stroke, 4 control	Uptake in infarct, peri-infarct and contralateral brain increases from day 0-3, further at 7-14, and further at day 25-30
Radlinska 2009	21	Uptake along pyramidal tract as defined by DTI MRI within 2 weeks of acute ischemic stroke
Thiel 2010	18+ 6 controls	Uptake at 2 weeks, persisting to 6 months Persistent uptake correlates with a worse clinical outcome

As a summary, in these earlier TSPO PET studies there was an observable increase in PET radioligand uptake in the infarct zone at early time points, which increased up to 30 days after the stroke. [6, 7] In addition, development of an increased uptake at brain regions that are distant from the primary infarct area (i.e. thalamus and brainstem) was observable at later time points and seemed to be associated with areas of Wallerian degeneration, as demonstrated by concomitant acquisition of diffusion tensor imaging (DTI) on brain MRI. [8] Furthermore, the degree of microglial activation on 11C-PK11195 imaging appeared to be directly correlated with the degree of white matter fiber damage at MRI, which persisted in longitudinal TSPO PET assessments for up to six months after the index stroke. [5, 9]

Taken together, these findings provide scientific rationale to support that TSPO PET MRI is a valuable tool to assess dynamic changes in brain inflammation that occur after an event of acute ischemic brain injury, which could provide further insight on how brain inflammation relates to the natural history of the disease. Given the small size, variability in imaging time points, and cross sectional nature of the majority of these studies, larger cohorts that measure longitudinal changes and key determinants of TSPO signal changes after stroke are needed to better understand neuroinflammation after stroke in humans.

Rationale for radioligand selection

Second-generation TSPO radiotracers have been developed to overcome some of the shortcomings of 11C-PK11195, the first-generation tracer. Specifically, the on-target to off-target binding profile has been improved.

These second-generation tracers were validated in numerous types of human CNS inflammation, including multiple sclerosis, trauma, HIV encephalopathy, and chronic neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. A second-generation tracer, PBR28, has been shown to effectively identify a sub-acute ischemic stroke in a case report [10].

Despite the advantages of second-generation TSPO ligands in terms of image quality, a polymorphism (rs6971) in the gene encoding TSPO is responsible for existence of 3 classes of TSPO binders: Low-, Medium-, and High-affinity binders.[11, 12]

TSPO PET as a measure of post-stroke brain inflammation

Pharmacologic TSPO blockade in human studies has demonstrated that it is feasible to adjust image quantification to harmonize data between medium affinity binders (MAB's) and high affinity binders (HAB's).[13] Low-affinity binders, which comprise no more than 10% of the population are usually excluded from TSPO PET studies due to poor signal-to-noise ratios. Hence, low-affinity binders will also be excluded in the present study.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives and Endpoints

The objectives of this study are:

- To characterize TSPO glial expression in specific regions of interest defined on correlative brain MRI (ROIs; infarct, peri-infarct, thalamus) in the subacute (day 15±3) and chronic (day 90±7) phases after an ischemic stroke;
- To determine the magnitude and variability of TSPO uptake at these ROIs during the assessment period;
- To describe changes in TSPO expression between 15 and 90 days
- To explore the relationship between TSPO uptake, blood and infarct volume, and measures of Wallerian degeneration; and,
- To characterize post-stroke TSPO glial expression in relation to measures of stroke severity (infarct size, volume and location; NIHSS) and functional outcome (mRS, BI, MoCA, Beck depression inventory)
- To characterize post-stroke TSPO glial expression in relation to systemic inflammation in blood

Endpoints that correlate to these objectives are:

- PET-derived measures of TSPO radiotracer uptake in the infarct and peri-infarct areas at day 15 and day 90 after a stroke;
- PET-derived measures of TSPO radiotracer uptake in ROIs distinct from the infarct area (e.g., thalamus, hippocampi, amygdalae and midbrain) at day 15 and day 90 after a stroke;
- Correlation of PET-derived measures with clinical and imaging measures of stroke severity (stroke volume, size and NIHSS) and functional outcome (mRS and BI) at day 15 and day 90
- Correlation of infarct volume and MRI measures of white matter tract injury determined from DTI MRI with measures of thalamic TSPO uptake (time-activity curve; measures of mean and max TSPO uptake on summed image sets from TSPO PET.
- Correlation of PET derived measures with inflammatory markers in the blood (e.g. cytokines)

7. STUDY DESIGN

7.1. Study Overview

This is a natural history cohort study evaluating patterns of brain inflammation and its relationship to qualifiers of stroke severity, functional outcome and stroke location.

Patients participating in this study will be required to undergo physical examination, blood testing and PET-MRI imaging acquisition at distinct time points.

7.2. Participation in this study will not influence the patients' ability to receive standard of care treatment for stroke, as deemed necessary by the treating physician.Overall Study Duration and Follow-Up

The study period will consist of screening and two time point PET and MRI assessments during an approximately 90-day follow-up period. The end of study is defined as final collection of data.

7.3. Early Termination of Study

The Sponsor-Investigator, after consultation with Biogen, may terminate this study at any time.

7.4 Participant Identification and Recruitment

Study Investigators who are members of the direct care team looking after the patient on the stroke ward, will identify them as potentially eligible. They will be approached by the Investigator and will have the study explained to them and be given a participant information sheet to read and consider. If they decide to take part after having any questions answered, the Investigator will take written informed consent before the patient has their screening visit.

8. STUDY POPULATION

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following inclusion criteria at screening:

1. Able to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information in accordance with national and local subject privacy regulations in accordance with all local and national regulations OR according to the local institutional review board's (IRB's)/ethics committee's (EC's) guidelines OR by another process compliant with applicable national laws and regulations and IRB/EC requirement
2. Aged 18-85 years of age at the time of informed consent
3. Clinical diagnosis of supratentorial acute ischemic stroke within the previous 10 days. Note: An acute brain CT or MRI scan must be available from the patient's history to assess eligibility for the study and be consistent with the diagnosis of acute ischemic stroke.
4. Score of at least 5 points on the NIHSS at Screening.
5. Subjects of childbearing potential (male and female) must be willing and able to practice effective contraception during the study and for 4 weeks after their Day 90 appointment.
6. Negative serum/ urine pregnancy test on all females of childbearing potential within 2 days before each PET study.

8.2. Exclusion Criteria:

Candidates will be excluded if any of the following exclusion criteria exist at screening, or at the time point specified in the individual criterion listed:

1. Unable or unwilling to provide informed consent.
2. Presence of acute intracranial hemorrhage on acute brain CT or MRI
3. Inability to comply with study requirements (including implanted pacemaker).
4. Subject has contraindications to undergoing MRI examination (including, but not limited to metal foreign bodies incompatible with MRI exposure, cardiac pacemakers, renal impairment that contraindicates gadolinium etc.) or PET scan.
5. Subject has participated in a research and/or medical protocol involving nuclear medicine, PET or radiological investigations with radiation exposure that, when combined with the radiation exposure from the present study, would exceed 10 mSV in addition to the natural background radiation, in the previous 12 months.
6. Other unspecified reasons that, in the opinion of the Investigator make the subject unsuitable for enrollment.
7. Nursing or pregnant females or females planning to become pregnant during study participation.
8. Claustrophobic, unable to hold head continuously still for 90 minutes, or unwilling to undergo PET or MRI imaging and related procedures required for this study.

9. Genetic polymorphism consistent with low TSPO binding affinity (expected in 10% of the population).

9. STUDY PROCEDURES

Once the investigational site has been activated for study participation, subjects may be enrolled if they have met the inclusion criteria in Section 8.1 and have not been excluded based on the exclusion criteria in Section 8.2.

9.1. Screening, Enrollment and Registration of Subjects

Subjects must provide informed consent before any screening tests or assessments are performed. When the subject signs the Informed Consent Form (ICF), the subject is considered to be enrolled in the study. Subjects will not be eligible for rescreening.

Subjects will be registered at screening visit after the eligibility criteria, with the exception of the TSPO genotype, have been determined.

Subjects will be registered and assigned a unique subject identification number after consent and before undergoing imaging acquisition. Any subject identification numbers that are assigned will not be reused even if the subject does not undergo imaging.

Subjects who withdraw from the study before completing Day 15 and Day 90 PET MRI scans may be replaced by discretion of the principal-investigator .

9.2. Follow-up

Subjects will be followed during a 90-day evaluation period during which time each participant is expected to undergo two visits where clinical assessment, blood sampling and PET-MRI scans will be conducted. Subjects will be called by study staff within 7 days after the 90 day study visit including the PET scan to inquire for potential adverse effects.

Withdrawal of Subjects from the Study

Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- The Physician withdraws the subject from the study for medical reasons.

The reason for the subject's withdrawal from the study should be recorded in the subject's case report form (CRF) if provided by the subject.

Participants who lose the capacity to consent during the trial will be withdrawn and have no further study procedures. The study team will retain the data and blood samples that are collected up until that point but no new data on the participant will be recorded.

10. DATA COLLECTION

10.1. Imaging Assessments

PET and MRI

10.1.1 Positron Emission Tomography (PET)

PET imaging involves the estimation of the availability of a specific molecular target via the evaluation of the tissue kinetics of a specific molecule administered at tracer amounts and labelled with a positron emitting radionuclide. PET imaging allows the accurate estimation of the availability of the molecular target of interest before and after an intervention or over time. Each PET scan session in this study, will include the administration of [11C]PBR28, a PET radioligand suitable for the quantification of TSPO availability in the human brain.

10.1.2 Magnetic Resonance Imaging (MRI)

MRI involves the use of an intense magnetic field to quantify tissue anatomical characteristics. In this study MRI will be used to define the volume of the stroke affected areas, and physiological characteristics of the brain tissue relevant to stroke physiology. In addition, a Gadolinium conjugated contrast agent will be used to assess the regional integrity (i.e. permeability) of the blood-brain-barrier. Each MRI scanning session will be up to 90 min in duration and will include the administration of a Gadolinium-conjugated contrast agent.

10.2 Summary of Risk Management for Imaging

10.2.1 [^{11}C]PBR28

10.2.1.1 Pre-clinical safety and toxicology
Safety and toxicity of PBR28 was studied in rodents and healthy human volunteers (n=10), at the National Institutes of Health (NIMH), USA. (National Institute of Health.html> February 2011). In an i.v. toxicity study in male and female Sprague-Dawley rats the NOAEL dose was determined to
be 445 µg/kg for a single dose, and 88µg/kg for repeat dose administration.

10.2.1.2 Clinical Safety
In humans, pharmacological effects of [^{11}C]PBR28 were monitored by performing vital signs and ECG monitoring, as well as blood tests (including full blood count, electrolytes, liver enzymes, creatinine) and standard urinalysis following i.v. injection of doses ≤10µg. No subject showed clinically
significant changes in vital signs after administration of [^{11}C]PBR28. Two subjects showed minor changes in laboratory tests, which could not be linked to administration of [^{11}C]PBR28 (Tracer Database Initiative).

10.2.2 Ionising Radiation Exposure

Radiation dosimetry studies were conducted in order to estimate the radiation exposure following the administration of [11C]PBR28. The dosimetry of [11C]PBR28 was estimated in 7 human volunteers (4 male, 3 female) (Brown et al., 2007). Based on these data, the effective dose (ED) of [11C]PBR28 was estimated at 0.0066 mSv/MBq. Each volunteer will receive a maximum dose of 300 MBq of [^{11}C]PBR28in each of their PET scans. The doses administered are adjusted to deliver the minimal radiation exposure compatible with a
good quality PET signal. In addition, a low-dose CT scan of the head will be acquired to estimate attenuation correction prior to each PET scan.The radiation exposure due to the 2 scans with [^{11}C]PBR28 will be 3.96 mSv, and 0.72 mSv from the 2 low-dose CT scans, yielding 4.68 mSv in total for the study. This exposure will place the study in category IIb of the International Commission on Radiological Protection (ICRP), an international workgroup on radiological protection.

10.2.3 Intravenous cannulae

Venous blood will be collected at screening to determine TSPO genotype and for routine safety tests. In addition a venous cannula will be inserted into a forearm or cubital vein for radiotracer administration and blood collection for pharmacokinetic analysis. Insertion of cannulae may lead to some transient pain and discomfort, and some bruising at the cannulation site.

10.2.4 PET

PET scans will be conducted according to GCP and GMP compliant procedures at the Imanova facility. Subjects will be screened for contraindications to PET scanning as per standard Imanova procedures. Before the start of each PET scan a venous cannula will be inserted into a forearm or cubital vein, for the administration of [11C]PBR28, and the subject will be positioned comfortably within the PET-CT scanner. A short low-dose CT of the brain will be conducted, and following this the PET emission data will be collected for approximately 90 minutes starting with the intravenous injection of [11C]PBR28. The primary discomfort arises from the need for subjects to lie supine during the scan. The scan will be stopped or abandoned if the subject is unable to complete the scan.

10.2.5 MRI

As a standard procedure, MR images will be evaluated by a radiologist. In the unlikely event of an unexpected and clinical significant finding on structural MRI which may require further investigation, participants and/or their General Practitioner will be informed, with the participant's consent. There are no known risks to subjects associated with MRI scanning, provided subjects have no contraindications to MRI as listed in the exclusion criteria. Some participants may find the PET and MRI scanning environments claustrophobic. Participants with severe anxiety in confined spaces will be excluded from the study. Furthermore, potential risks associated with metallic implants injury will be eliminated by screening during study enrolment and prior to the scan.

10.2. Clinical Assessments

After providing informed consent, the medical history will be documented in a CRF. Patients will also undergo a neurological examination. On the day of the PET and MRI examinations, the patients will be asked for the any events in the interim period since the screening examination. They will undergo a physical examination with a focus on neurological findings. Specifically, they will be assessed using the following tools: **mRS:** The mRS measures independence, rather than neurological function, with specific tasks pre- and post stroke [14-17]. The scale consists of 7 grades, from 0 to 6, with 0 corresponding to no symptoms and 6 corresponding to death. The premorbid mRS will be scored through interviews with the participant and/or family caregiver. Raters will be required to be certified in the use of the mRS. The mRS will be completed by a telephone interview for any subjects who fail to attend their Day 90 Follow-Up or Early Termination visit. The mRS takes less than 5 minutes to administer.

BI: The BI consists of 10 items that measure a person's daily functioning, specifically the activities of daily living and mobility [18-20]. The items include feeding, moving from wheelchair to bed and returning, grooming, transferring to and from a toilet, bathing, walking on a level surface, going up and down stairs, dressing, and maintaining continence of bowels and bladder. The assessment can be used to determine a baseline level of functioning and can be used to monitor change in activities of daily living over time. The items are weighted according to a scheme developed by the authors. The person receives a score based on whether they have received help while doing the task. The scores for each of the items are summed to create a total score up to a maximum of 100. The higher the score, the more "independent" the person is. The BI takes less than 5 minutes to administer.

NIHSS: The NIHSS is a reliable tool for rapidly evaluating the effects of acute cerebral infarction [21]. Raters will be required to be certified in the use of the NIHSS. A trained observer rates the subject's ability to answer questions and perform activities relating to level of consciousness, language, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, sensory loss, and extinction and inattention (formerly neglect). There are 15 items. Ratings for each item are scored with 3 to 5 grades, with 0 as normal and a maximum possible total severity score of 42 for all items. There is an allowance for untestable items. The test takes approximately 10 minutes to complete.

MoCA: The Montreal Cognitive Assessment (MoCA) is designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points. A score of 26 or above is considered normal.

Beck's Depression Inventory: The Beck Depression Inventory Second Edition (BDI-II) is a 21-item self-report instrument intended to assess the existence and severity of symptoms of depression. Each of the 21 items corresponding to a symptom of depression is summed to give a single score for the BDI. There is a four-point scale for each item ranging from 0 to 3. On two items (16 and 18) there are seven options to indicate either an increase or decrease of appetite and sleep. Cut score guidelines for the BDI are given with the recommendation that thresholds be adjusted based on the characteristics of the sample, and the purpose for use of the BDI. Total score of 0-13 is considered minimal range, 14-19 is mild, 20-28 is moderate, and 29-63 is severe.

Venous Blood Samples

Genetic Testing: At the screening visit, participants will have a blood sample of up to 15mls taken which will processed at Hammersmith Hospital for TSPO Polymorphism genotyping. The results will confirm whether the participants meet the full eligibility criteria of the trial. If the results show genetic polymorphism consistent with low TSPO binding affinity (expected in 10% of the population) those participants will be considered screen fails and will not be included in the trial. The test is purely to determine eligibility, the samples will be destroyed in accordance with local guidelines after testing is complete. **Haematology and Chemistry:** Participants will have a full blood count, renal and kidney function tests at screening if they have not had recent testing done as part of clinical care. It is expected that most participants will not require this.

Systemic Inflammatory Markers: To assess systemic inflammatory markers, venous blood samples of 15ml will be takenon both days of the PET und MRI examinations. Blood will be rapidly frozen and stored in -80 specimen freezers at Imperial College London.Cytokines in blood will be measured using Multiplex ELISA. Samples will be processed on site at Imperial College London and any remaining samples will be stored for future use by the research team but will not be transferred out of Imperial College London.

11. SAFETY DEFINITIONS, MONITORING, AND REPORTING

Throughout the course of the study, every effort must be made to remain alert to possible adverse events (AEs). If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention will be provided. At the signing of the ICF, each subject or his/her legally authorized representative and/or main caregiver must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

11.1. Definitions

11.1.1. Adverse Event (AE)

The present study is observational. No drugs will be given as a therapeutic intervention.

Therefore, only adverse reactions related to study procedures including PET and MRI scanning, blood sampling and clinical examination will be recorded.

11.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that

- results in death
- in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- results in a congenital anomaly/birth defect.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

11.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized; the study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the

Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.

- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.

If a subject is hospitalized due to local requirements for administration of standard of care, the hospitalization should not be considered an SAE unless one of the requirements in Section 11.1.2 is met.

11.2. Safety Classifications

11.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria of an SAE as defined in Section 11.1.2
- The relationship of the event to study intervention as defined in Section 11.2.1
- The severity of the event as defined in Section 11.2.2

11.2.2. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptom(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptom(s) but may be given because of personality of subject.
Moderate	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) may be given and/or subject hospitalized.

11.3. Monitoring and Recording Events

11.3.1. Adverse Events

Adverse events will be collected during the period between informed consent and 7 days after the second follow-up visit (about 90+7 days after the index stroke). :

-

11.3.2. Serious Adverse Events

Any SAE experienced by a subject after the subject signs the informed consent form (ICF) and before the final follow-up visit is to be recorded on an SAE Form. For reporting timelines and procedures, see Section 11.3.3.

Subjects will be followed for all SAEs until 7 days after the second MRI and PET scan (i.e. 90days after the index stroke)

Any SAE ongoing when the subject completes the study or discontinues from the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

11.3.3. Immediate Reporting of Serious Adverse Events

The Investigator will notify the local ethics committee per local requirements and report applicable events to Heath Authorities as required by local legislation.

The study site must formally notify Biogen SABR within 24hours of the study site staff becoming aware of the SAE. It is the Sponsor-Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately. Site Principal Investigators must report SAE to the Sponsor-Investigator within 24 hours of becoming aware of the event.

11.3.4. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the appropriate CRF. All causes of death must be reported as SAEs. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen SABR.

11.4. Procedures for Handling Special Situations

11.4.1. Reporting Pregnancy

The Investigator should refer to the approved local label for guidance if female subjects become pregnant.

11.4.2. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care.

11.5. Chief Investigator Responsibilities

The Sponsor- Investigator's responsibilities include the following (refer to Section 11.3.1for details):

- Review all AEs to determine seriousness and fulfillment of collection criteria
- Monitor and record all SAEs
- Determine the onset and resolution dates of each SAE
- Record all pregnancies.
- Complete the appropriate form for each SAE and fax or email it to Biogen SABR within 24 hours of the study site staff becoming aware of the event.

- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen SABR within 24 hours of the study site staff becoming aware of new information.
- Ensure all SAE reports are supported by documentation in the subjects' medical records.
- Report SAEs Biogen, local ethics committees, Health Authorities, other Investigators and entities as required by local law.

12. STATISTICAL CONSIDERATIONS

12.1. Sample Size Justification

This is a natural disease progression study. Quantitative data on the uptake in and around infarcts and changes over time are not available to base a power calculation on. Therefore, sample size has been determined pragmatically, based on feasibility. The main purpose is to pilot characterization of the magnitude and variability of the change in a normalized measure of the TSPO radioligand uptake in the target regions between baseline (14 days) and 90 days post infarction in untreated patients. We chose to use a pseudo-reference region quantification as it avoids the need for radial artery cannulation in these patients. In addition, this method has a significantly better test-retest variability than the fully quantitative methods using metabolite corrected arterial plasma input function (~4-5% vs ~20%)..[22] . While such an approach may lead to an underestimation of any changes seen,[23] due to potential changes in signal in the pseudo-reference region, we believe it is justified in this situation where a focal change in signal is expected, and will be compensated for by reduced signal variability.

The magnitude of the signal change between days 14 and 90 is unknown but it is expected that changes above 10% will be detectable given the small test/retest variability of [11C]PBR28.

12.2. Analysis Population

All eligible subjects who have completed at least one PET-MRI scan will be included in the analysis

12.3. Methods of Analysis

In general, summary statistics will be presented. Continuous variables will be summarized using descriptive statistics, and categorical variables will be presented using frequency distributions.

12.4. Endpoints Analysis

PET-derived measures including SUVR in the infarct and peri-infarct area, and ROIs distant from the infarct area at Day 15 and Day 90 will be summarized by visit. Various aspects of change over time including magnitude, variability and pattern will be assessed. The relationship between PET-derived measures and stroke severity (including stroke volume, size, NIHSS) will be examined using methods including linear correlation and regression. Also, the relationship between PET-derived measures and functional outcomes , markers of systemic inflammation and relationship between measures of white matter tract injury and measures of thalamic uptake will be explored.

A detailed statistical analysis plan will be established before the beginning of the analysis.

13. ETHICAL REQUIREMENTS

The Sponsor-Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Conference on Harmonisation (ICH) guidelines and conduct the study according to local regulations. The subject's privacy; physical, mental, and social integrity; and the confidentiality of his or her personal information will be strictly respected in accordance with the World Medical Association Declaration of Helsinki.

13.1. Ethics Committee

The Sponsor-Investigator will obtain ethics committee and HRA approval of the protocol, ICF, and other required study documents prior to starting the study.

The Sponsor-Investigator will ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

Biogen must receive a letter documenting ethics committee approval, which specifically identifies the protocol, tracking number, and ICF version, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually. At the completion or termination of the study, the investigational site must submit a close-out letter to the ethics committee.

13.2. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative, as applicable, in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

In addition, subjects who have the capacity should provide their consent to participate in the study. The level of information provided to subjects should match their level of understanding as determined by the Investigator and in accordance with applicable regulations and guidelines.

A copy of the signed and dated ICF must be given to the subject. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including screening tests and assessments.

The signed ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

13.3. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law.

The subject will not be identified by name in the CRF or in any study reports, and these reports will be used for research purposes only. Ethics committees and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

Participants will be assigned a subject number by their recruiting physician and all data collected about them during the study will only be recorded under this subject number. A log of the subject numbers and the identities of the participants will be securely stored on an NHS Trust computer with password protection and will only be accessible by the members of the research team who also direct care team members. This will ensure that all participants cannot be identified by the research data collected.

All physical documents will be stored anonymized at Charing Cross Hospital in locked filing cabinets with only the research team having access to them. Consent forms will be stored separately from the research data. After the end of the study, data will be archived in accordance with Imperial College London procedures and it will be stored for a minimum of 10 years.

The clinical team (Including: study coordinators, Dr's, PET and MRI technicians) will have access to patient details for the scanning procedures. They will enter the demographics of participants into the Imanova database. All scans taken will be anonymized at source and transferred electronically for storage on NHS Trust computers. Imanova keeps all archived data for 30 years.
Selected individuals at Biogen will have access to anonymized data, such as brain scans. They will be securely stored on private company computers in line with the data protection act and Biogens own data security protocols. Biogen staff will not see any patient identifiable information and will not have the patient identity log to be able to identify patients from their study identification numbers.

13.4. Compensation for Injury

The Sponsor-Investigator must maintain appropriate insurance coverage for clinical trials and follow applicable local compensation laws.

13.5. Conflict of Interest

Investigators should address any potential conflicts of interest with the subject before the subject makes a decision to participate in the study.

13.6. Registration of Study and Disclosure of Study Results

The Sponsor-Investigator will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

14. ADMINISTRATIVE PROCEDURES

14.1. Study Site Initiation

Investigators must not screen or enroll any subjects into the study prior to all prerequisite study document completion and agreement by the Sponsor-Investigator and Biogen.

14.2. Study Funding

Biogen will financially support the work of the Sponsor-Investigator as it pertains to the conduct of this study. All financial details are provided in the separate contract(s) between the institution, Sponsor-Investigator, and Biogen.

14.3. Study Completion

The ethics committee must be notified of completion or termination of the protocol. Within 3 months of protocol completion or termination, the investigator must provide a final clinical summary report to the ethics committee. The Sponsor-Investigator will maintain an accurate and complete record of all submissions made to the ethics committee, including a list of all reports and documents submitted.

14.4. Publications

Details are included in the clinical trial agreement for this study.

15. FURTHER REQUIREMENTS AND GENERAL INFORMATION

15.1. External Contract Organizations

Imanova next to the Hammersmith Hospital of Imperial College in London has been selected to perform all study PET and MRI imaging acquisitions for this study.

15.2. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and Regulatory Authorities as required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

In the event of a protocol modification, the subject consent form may require similar modifications (see Sections 13.1 and 13.2).

It is the responsibility of the Chief Investigator to agree all revisions to the protocol with Biogen. Proposed amendments will be submitted for approval to the sponsor before being submitting to the Research Ethics Committee.

15.3. Ethics Committee Notification of Study Completion or Termination

Where required, the Health Authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

15.4. Retention of Study Data

The minimum retention time for study records will be 10 years, which is Imperial College London policy.

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17. INVESTIGATORS SIGNED AGREEMENT OF STUDY PROTOCOL

I have read the foregoing protocol, "TSPO PET as a measure of post-stroke brain inflammation: a natural history cohort" and agree to conduct the study according to the protocol and the applicable ICH guidelines and local regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

31.07.2017

Sponsor-Investigator's Signature Date

(Rocan) Veerapen

Sponsor-Investigator's Name (Print)

Imperial College Healthcare NHS Trust

Study Site (Print)

APPENDIX

Modified Rankin Scale (MRS)	
0	No symptoms
1	No significant disability, despite symptoms; able to perform all usual duties and activities
2	Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability; requires some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requires constant nursing care and attention
6	Death

National Institutes of Health Stroke Scale (maximum = 42)

Response	(Score)	Response	(Score)
Level of consciousness		Motor arm (left and right)	
alert	(0)	no drift	(0)
drowsy	(1)	drift before 10 seconds	(1)
stuporous	(2)	falls before 10 seconds	(2)
coma	(3)	no effort against gravity	(3)
		no movement	(4)
Response to level of consciousness questions*		Motor leg (left and right)	
answers both correctly	(0)	no drift	(0)
answers one correctly	(1)	drift before 5-10 seconds	(1)
answers neither correctly	(2)	falls before 5-10 seconds	(2)
		no effort against gravity	(3)
		no movement	(4)
Response to level of consciousness commands†		Ataxia	
obeys both correctly	(0)	absent	(0)
obeys one correctly	(1)	one limb	(1)
obeys neither	(2)	two limbs	(2)
Pupillary response		Sensory	
both reactive	(0)	normal	(0)
one reactive	(1)	mild	(1)
neither reactive	(2)	severe loss	(2)
Gaze		Language	
normal	(0)	normal	(0)
partial gaze palsy	(1)	mild aphasia	(1)
total gaze palsy	(2)	severe aphasia	(2)
		mute or global aphasia	(3)
Visual fields		Facial palsy	
no visual loss	(0)	normal	(0)
partial hemianopsia	(1)	minor paralysis	(1)
complete hemianopsia	(2)	partial paralysis	(2)
bilateral hemianopsia	(3)	complete paralysis	(3)
Dysarthria		Extinction/inattention	
normal	(0)	normal	(0)
mild	(1)	mild	(1)
severe	(2)	severe	(2)

* Level of consciousness questions: "How old are you?" "What month is this?"

† Level of consciousness commands: "Squeeze my hand" (using nonparetic hand), "Close your eyes."

<4 = Good prognosis -- No tPA 4-20 = mild to moderate - ideal tPA >20 = severe defiicit --No tPA

THE BARTHEL INDEX

Patient Name: _____

Rater Name: _____

Date: _____

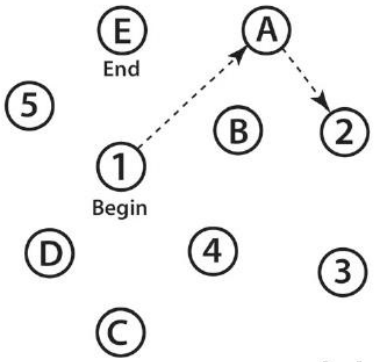
Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	_____
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____
TOTAL (0–100):	_____

TSPO PET as a measure of post-stroke brain inflammation

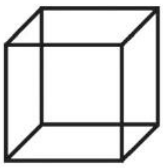
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



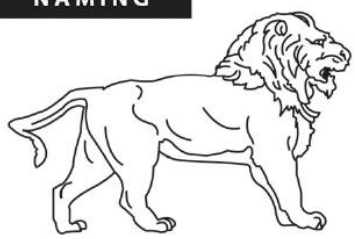
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING



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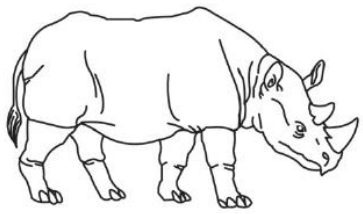

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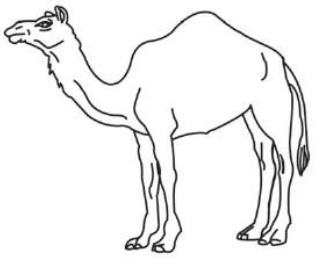

[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2
__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B
__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**
__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]
__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)
__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler
__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City
__/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the questionnaire.

1.

0	I do not feel sad.
1	I feel sad
2	I am sad all the time and I can't snap out of it.
3	I am so sad and unhappy that I can't stand it.

2.

0	I am not particularly discouraged about the future.
1	I feel discouraged about the future.
2	I feel I have nothing to look forward to.
3	I feel the future is hopeless and that things cannot improve.

3.

0	I do not feel like a failure.
1	I feel I have failed more than the average person.
2	As I look back on my life, all I can see is a lot of failures.
3	I feel I am a complete failure as a person.

4.

0	I get as much satisfaction out of things as I used to.
1	I don't enjoy things the way I used to.
2	I don't get real satisfaction out of anything anymore.
3	I am dissatisfied or bored with everything.

5.

0	I don't feel particularly guilty
1	I feel guilty a good part of the time.
2	I feel quite guilty most of the time.
3	I feel guilty all of the time.

6.

0	I don't feel I am being punished.
1	I feel I may be punished.
2	I expect to be punished.
3	I feel I am being punished.

7.

0	I don't feel disappointed in myself.
1	I am disappointed in myself.
2	I am disgusted with myself.
3	I hate myself.

8.

0	I don't feel I am any worse than anybody else.
1	I am critical of myself for my weaknesses or mistakes.
2	I blame myself all the time for my faults.
3	I blame myself for everything bad that happens.

9.

0	I don't have any thoughts of killing myself.
1	I have thoughts of killing myself, but I would not carry them out.
2	I would like to kill myself.
3	I would kill myself if I had the chance.

10.

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11.

0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.

12.

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13.

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions more than I used to.
3 I can't make decisions at all anymore.

14.

0 I don't feel that I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly.

15.

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16.

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18.

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19.

0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate your depression according to the Table below.

Total Score_____Levels of Depression

1-10_____These ups and downs are considered normal
11-16_____ Mild mood disturbance
17-20_____Borderline clinical depression
21-30_____Moderate depression
31-40_____Severe depression
over 40_____Extreme depression