Clinical Trial Protocol

Trial Title:	A randomised phase II double-blinded placebo-controlled trial of intravenous immunoglobulins and rituximab in patients with antibody-associated psychosis (SINAPPS2)
Protocol Number:	CCTU 0145
EudraCT Number:	2016-000118-31
ISRCTN Number:	11177045
Investigational Product:	Intravenous immunoglobulin (IVIG) and rituximab
Protocol Version:	7.1
Version Date:	18.01.2024
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Funding:	Medical Research Council, Developmental Pathway Funding Scheme: MR/N019067/1 The Stanley Medical Research Institute: 22T-001

1 Protocol Signatures:

I give my approval for the attached protocol entitled "A randomised phase II double-blinded placebo-controlled trial of intravenous immunoglobulins and rituximab in patients with antibody-associated psychosis (SINAPPS2)" V7.1 18/01/2024

Chief Investigator

Name: Professor Alasdair Coles

Signature: Alasdair Coles

Date: 18.01.2024

Site Signatures

I have read the attached protocol entitled "A randomised phase II double-blinded placebo-controlled trial of intravenous immunoglobulins and rituximab in patients with antibody-associated psychosis (SINAPPS2)" V7.1 18/01/2024 and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and the GCP Directive 2005/28/EC.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Principal Investigator:

Name:

Signature: _____

Date: _____

2 Protocol and amendment history

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Summary of Changes made
Original protocol	1.0	26th Sept 2016		
Amendment 1	2.0	22nd Dec 2016	Alasdair Coles	To accommodate comments from MHRA
Amendment 2	3.0	08th March 2019	Alasdair Coles	Additional AARP questionnaires and MINI scale added (patient self-reported and clinician assessed measures) Clarified the primary and secondary outcome definitions Amendments to the inclusion criteria Amendments to the withdrawal criteria Additional exploratory outcome measure added. Addition of new minimisation factors Clarified dosage modifications Clarified screening, randomising and baseline order Updated Reference Safety Information section Updates to statistical methods and interim analyses
non-substantial, non-notifiable amendment	3.1	31st July 2019	Sponsor	Fax machine removal according to new Trust fax-free policy.
Amendment 3	4.0	28.07.2020	Alasdair Coles	Adjustments to inc/excl criteria and visit protocols in light of Covid 19 pandemic. Reduction in sample size, in light of low drop-out rate.
Amendment 4	4.1	01.09.2021	Alasdair Coles	Changes to inc/ex age limits back to pre-COVID levels.
Amendment 5	5.0	19.04.2022	Alasdair Coles	Update exclusion criteria related to live vaccines.
Amendment 6	6.0	19/08/2022	Alasdair Coles	Update inclusion criteria- include patients with a positive antibody results within 12 months of screening visit

Amendment 7	7.0	03/04/2023	Alasdair Coles	Provided flexibility with regards to IVIG treatment
Amendment 8	7.1	18/01/2024	Alasdair Coles	Removal of pneumococcal serology from the list of the Screening Blood tests

3 Trial Committees and Protocol Contributors

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4 Abbreviations

AARP	Abbreviated Acceptability Rating Profile
AE	Adverse Event
ANNSERS	Antipsychotic Non-Neurological Side-Effects Rating Scale
BACS App	Brief assessment cognition in schizophrenia
CA	Competent Authority
CCTU	Cambridge Clinical Trials Unit
CGI-SCH	Clinical Global Impression score in schizophrenia
CRF	Case Report Form
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CTIMP	Clinical Trial of Investigational Medicinal Products
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EEG	Electroencephalogram
ESR	Erythrocyte sedimentation rate
FBC	Full blood count
GABA(A)R	Gamma-Aminobutyric acid receptor subunit A
GAF	Global Assessment of Functioning
GP	General Practitioner
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IMP	Investigational Medicinal Product
IVIG	Intravenous immunoglobulin
LGI1	Leucine-rich glioma inactivated 1 antigen
MHRA	Medicines and Healthcare products Regulatory Agency
LFT	Liver function tests
MINI	Mini-International Neuropsychiatric Interview
MRI	Magnetic Resonance Image
NIMP	Non Investigational Medicinal Product
NMDAR	N-methyl D-aspartate receptor
PANSS	Positive and Negative Syndrome Scale
PeLR	Personal Legal Representative
PrLR	Professional Legal Representative
PLEX	Plasma exchange
PML	Progressive multifocal leucoencephalopathy
R&D	Research and Development
RA	Regulatory Agency
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
U&E	Urea and electrolytes
VGKC	Voltage gated potassium channel-complex
YMRS	Young Mania Rating Scale

5 Trial Synopsis

Title of clinical trial	A randomised phase II double-blinded placebo-controlled trial of intravenous immunoglobulins and rituximab in patients with antibody-associated psychosis (SINAPPS2)
Sponsor name	Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge
EudraCT number	2016-000118-31
Medical condition or disease under investigation	Acute psychosis associated with anti-neuronal membrane antibodies.
Purpose of clinical trial	To explore the utility of immunotherapy for patients with acute psychosis associated with anti-neuronal membrane antibodies.
Primary objective	To test the efficacy of immunotherapy (IVIG and rituximab) for patients with acute psychosis associated with anti-neuronal membrane antibodies.
Secondary objective (s)	To test safety of immunotherapy (IVIG and rituximab) for patients with acute psychosis associated with anti-neuronal membrane antibodies.
Trial Design	Phase II, multicentre, double blind, randomised, placebo-controlled trial.
Primary Outcome Measure	Time from start of treatment to symptomatic recovery i.e. symptomatic remission sustained for six months. Symptomatic remission is defined as PANSS score 3 or less on all PANSS items P1, P2, P3, N1, N4, N6, G5, G9.
Secondary Outcome Measures	• Time to first symptomatic remission (whether sustained or not) • Relapse • Number of adverse effects • Serious infections • Proportion of patients reaching 20%, 30% and 40% reduction in PANSS total score
Sample Size	Total n=70 [or to halt recruitment once 56 evaluable participants completed the trial]
Summary of eligibility criteria	Inclusion Criteria: • Acute psychosis >2 weeks. This may either be the first episode or relapse after remission (remission defined having mild or absent symptoms of psychosis for at least 6 months) • Aged 16-70 years* • Psychosis symptoms as defined by PANSS score 4 or more on at least one of the following items: P1, P2, P3, N1, N4, N6, G5, G9. • Patient or Legal representative is willing and able to provide informed consent • Have a positive Serum or CSF neuronal membrane autoantibodies at pathological levels

	(including NMDAR, LGI1 and other) within 12 months of screening. Key Exclusion Criteria (see section 10.2 for detailed list): • Current episode of psychosis greater than 24 months duration • Co-existing severe neurological disease • Evidence of current acute encephalopathy • Hepatitis or HIV infection, • Pregnancy • Concurrent enrolment in another CTIMP • Hypersensitivity or absolute contra-indication to any trial drug, murine proteins or excipients. • Risk factors associated with COVID 19 that in the opinion of the investigator would lead to unacceptable risks to trial participation. * Participants between 61-70 years of age and with both doses of COVID-19 vaccine can be included in the trial.
Investigational medicinal products and dosage	(a) One cycle of intravenous immunoglobulin (IVIG) 2g/kg over 2-4 days (days 1-4)[#] followed by (b) Two infusions of 1g rituximab (the first infusion starting between days 28-35, and the second infusion 14 days later). [#] If stocks are available, see 11.1.4
Comparator product(s)	Placebo to match IVIG and rituximab.
Route(s) of administration	Intravenous
NIMPs and Challenge Agents	Methylprednisolone 100mg IV prior to each rituximab dose. NaCl 0.9% IV prior to each placebo for rituximab dose (to maintain blinding). Best standard of care, including antipsychotic therapies.
Maximum duration of treatment of a participant	Approximately 50 days
Procedures: Screening & enrolment	Informed consent will be obtained from the patient, or patient's representative (if the patient lacks capacity) • Physician review • Physical examination • Pregnancy test (if appropriate) • Height and Weight • Collection of demographic data • Disease history and confirmation of the diagnosis of psychotic disorder by the Mini-International Neuropsychiatry Interview (MINI) for Psychotic Disorders studies • Screening blood tests[1] • Monitoring blood tests[2] • Research blood sample collection. • Anti-neuronal membrane antibody assays

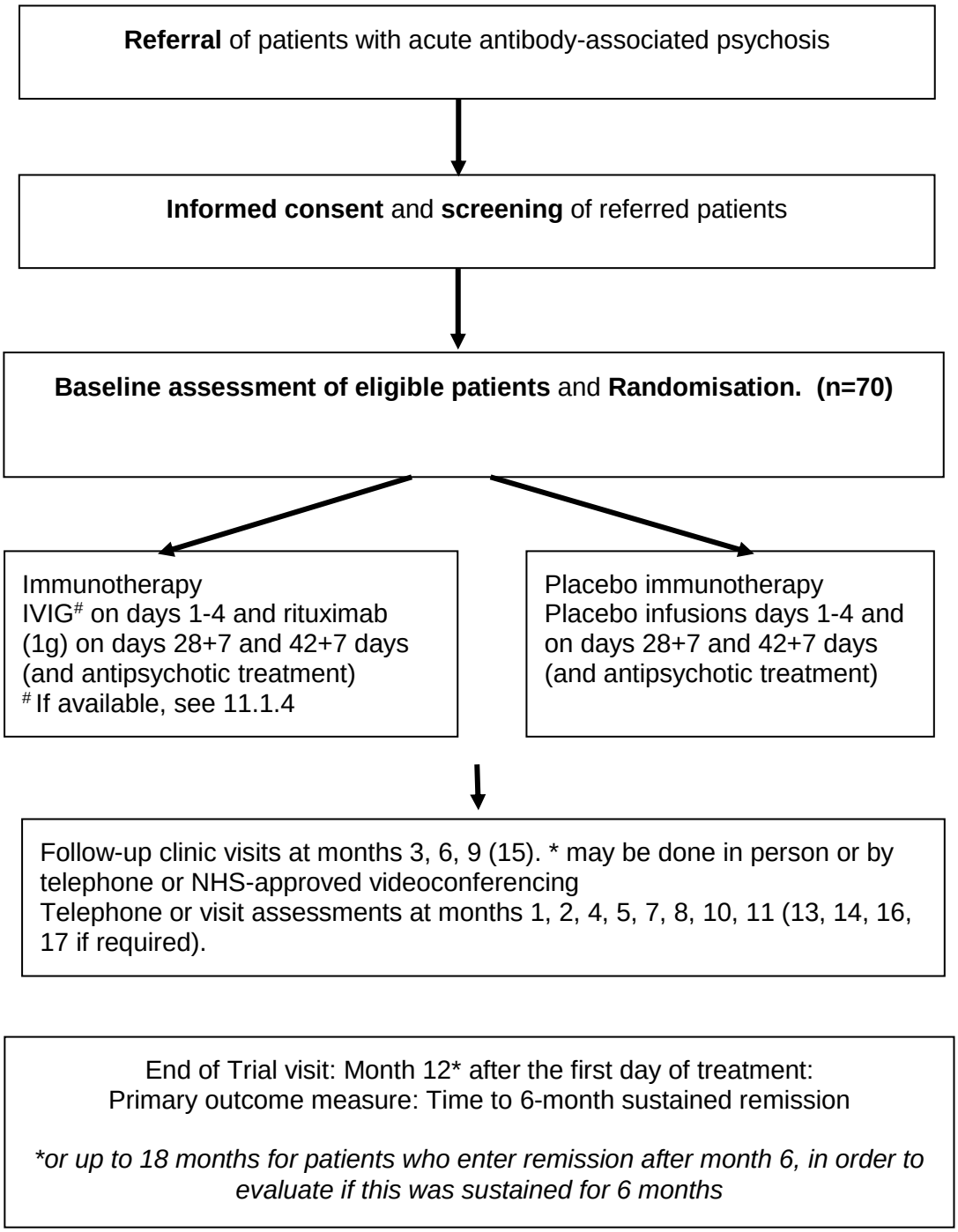
	• Severity of selected symptoms (Positive and Negative Syndrome Scale (PANSS) items P1, P2, P3, N1, N4, N6 G5, and G9 only) • Concomitant medications assessment • Recording of Adverse events (begins from the point of informed consent and they will be assessed at baseline).

Baseline	• Physician review (for period screening – baseline)
	• Pregnancy test (if appropriate)
	• Severity of symptoms (Positive and Negative Syndrome Scale (PANSS) all items)
	• Clinical and cognitive assessments
	  ○ Clinical Global Impression score in schizophrenia (CGI-SCH)
	  ○ Young Mania Rating Scale (YMRS)
	  ○ Antipsychotic Non-Neurological Side-Effects Rating Scale (ANNSERS)
	  ○ Brief assessment cognition in schizophrenia (BACS - App)
	  ○ Global Assessment of Functioning (GAF)
	• Adverse events assessment (for the time period consent date - baseline date)
	• Concomitant medications assessment
	• Any testing for SARS Cov2 advised by local or national guidance.
	
	The participants will be randomised following confirmation of eligibility and before Baseline.

Treatment period	Immunoglobulin or placebo for days 1-4, then first infusion of rituximab or placebo on day 28 (+ 7) days, and the second infusion or placebo 14 days later. Main assessments/procedures during treatment period: • Anti-neuronal membrane antibody assays (day 28 only) • Pregnancy test (up to 7 days before Rituximab or placebo 1st infusion) • Adverse event assessment • Concomitant medication assessment
Follow-up	Follow up visits (months 3, 6 and 9 (15)) for both (intervention and placebo) groups. These may be done in person or by telephone or NHS-approved videoconferencing, depending on the national and regional risk assessment of SARS-Cov2 infection. • Physician review • Physical examination [only at face to face visits]

	• Monitoring blood tests (at 6 monthly visits only or arranged locally to the participant, if possible, but may be omitted if the investigator judges the Covid19 risk of attending phlebotomy clinics is unacceptably high (6 & 12)[2] • Anti-neuronal membrane antibody assays (at 6 monthly visits (6 & 12) only) • Severity of symptoms (PANSS all items) • Clinical and cognitive assessments (CGI-SCH, YMRS, ANNSERS, BACS App, GAF) • Adverse events assessment • Concomitant medications assessment Monthly follow-ups (months 1, 2, 4, 5, 7, 8, 10, 11 (13, 14, 16, 17) • Severity of selected symptoms (PANSS items P1, P2, P3, N1, N4, N6, G5, G9, only) • Adverse events assessment • Concomitant medications assessment
End of Trial	The end of trial will be the date of the last patient's last visit, end of trial can occur at month 12, 15 or 18. This should be done in person, but could be done remotely at the discretion of the PI, with blood tests arranged at local healthcare settings, or omitted if investigator judges the Covid19 risk of attending phlebotomy clinics is unacceptably high. • Physician review • Physical examination [only at face to face visits] • Weight • Monitoring blood tests[2] • Anti-neuronal membrane antibody assays • Severity of symptoms (PANSS all items) • Clinical and cognitive assessments (CGI-SCH, YMRS, ANNSERS, BACS-App, GAF,) • Acceptability of treatment (Abbreviated Acceptability Rating Profile (AARP) • Adverse events assessment • Concomitant medication assessment.
Procedures for safety monitoring during trial	The safety of treatments will be assessed by physical examination findings, clinical laboratory tests, clinical observations and adverse event reporting. The DMC and TSC will review the safety data during the trial.
Criteria for withdrawal of patients	• Development of symptoms of an antibody-mediated encephalopathy (e.g. coma, seizures) • Patient choice • Pregnancy
[1]Screening blood tests – urea, electrolytes, calcium, HIV, Hepatitis B, Hepatitis C, syphilis, and varicella serology.	
[2]Monitoring blood tests are FBC, LFT and immunoglobulin levels.	

6 Trial Flow Chart



6.1 Schedule of Assessments

	Screening	**Randomisation**	**Day 0 (or day 1) Baseline**	**Days 1-4 IVIG** (2-4 Days)	**Day 28 - Rituximab**	**Day 42 - Rituximab**	**Monthly phone or visit follow-up**	**Month 3, 6, 9, 12 (15,18) clinic visit***
	Max 2 months from informed consent to eligibility confirmation	Occurs between screening & baseline visit	Up to a max of 4 weeks after eligibility confirmation	Up to a max of 7 days from baseline	4 weeks from IVIG (day 1)+7 days	2 weeks from 1st Rituximab +7days	Monthly from IVIG +/- 3 days	3 monthly from IVIG +/- 7 days
Informed consent	x							
Socio-demographic and clinical history data	x							
Physician review	x		x					x
Physical exam	x							x
Weight & height	x							x[1]
Pregnancy test	x		x		x			
Screening blood tests[2]	x							
Monitoring Bloods[3]	x							x[4]
Anti-neuronal membrane antibody assays	x				x			x[4]
Research blood sample collection	x							
Severity of selected symptoms (PANSS)	x						x	
Severity of symptoms PANSS (all items)			x					x

Clinical and cognitive assessments (GAF, CGI-SCH, YMRS, ANNSERS, BACS)			x					x
Abbreviated Acceptability Rating Profile (AARP)								x[5]
MINI (Mini Neuropsychiatric Interview)	x							
Adverse events			x	x	x	x	x	x
Eligibility Confirmation		x						
Randomisation		x						
Concomitant medication	x		x	x	x	x	x	x

IVIG 2-4 days (or placebo)				X[6]				
Rituximab (or placebo)					x	x		
Total time for visit	2 hrs		3 hours	up to max 6 hrs / day	up to max 4 hrs	up to max 4 hrs	15 mins	3 hrs

[1] Only Weight at End of study visit

[2] The required screening blood tests are urea, electrolytes, calcium, HIV, Hepatitis B, HbA1C, Hepatitis C, syphilis, and varicella serology

[3] FBC, LFT & immunoglobulins

[4] Only at month 6, 12 and End of trial visit

[5] End of study visit only

[6] If no stocks of IVIG are available, no treatment is given at this point, and the participant next attends for D28 Rituximab, see 11.1.4

* may be done in person or by telephone or NHS-approved videoconferencing

7 Introduction

7.1 Background

Psychosis and schizophrenia are caused by genetic and environmental factors, associated with excess mesolimbic and mesocortical dopamine and NMDAR hypofunction (Howes *et al*., 2015). A range of cell surface protein and immune genetic loci are associated with schizophrenia (Consortium, 2014; Howes *et al*., 2015) and there is increasing evidence for a role of inflammation in psychosis and schizophrenia (Needham and Zandi, 2014; Khandaker *et al*., 2014). We propose that one cause of psychosis may be antibodies binding to neuronal membrane targets, especially NMDA receptors, in the brain. Such antibodies were first described in 2007 causing an encephalopathy, with psychiatric features in over two thirds that responded to immunotherapy (Dalmau *et al*., 2007). In such patients, isolated psychotic episodes occur in 23/571 (4%), either at presentation (5/571) or relapse (18/571) (Kayser *et al*., 2013). The hypothesis underlying our trial is that these antibodies are pathogenic and may be responsible for isolated psychosis.

Open-label experience from several hundred patients suggests that immunotherapy is effective in the full-blown syndrome of encephalopathy secondary to anti-NMDAR antibodies (Titulaer *et al*., 2013). The observation that underlies this protocol is that, in 2010, we discovered that 3 of 46 patients with first episode psychosis, without other signs of encephalitis, had autoantibodies to the N-methyl D-aspartate receptor (NMDAR) or the voltage gated potassium channel complex (Zandi *et al*., 2011). We have replicated this finding in an ongoing MRC-funded PPiP trial: 15 (6.6%; 7 NMDAR-antibodies, 8 VGKC-antibodies >400pM) of 227 patients with first episode psychosis also possess these autoantibodies (Palmer *et al*., 2015 [data updated]). We have recently reported on 18 such patients with NMDAR-antibodies in detail, nine of whom self-resolved or responded to antipsychotics. The remaining nine were resistant to up to 3 antipsychotics, so we treated them with corticosteroids combined with either plasma exchange (PLEX) or intravenous immunoglobulin (IVIG) to good effect (Zandi *et al*., 2014), with maintenance therapy for a few patients (mycophenolate or rituximab).

We have initiated a feasibility trial (SINAPPS One) that tests the referral pathway and acceptability of PLEX and IVIG with corticosteroids. Through discussion with our patient group representatives (The McPin Foundation) and through limited availability to deliver plasma exchange, which is an invasive procedure, we have redesigned our phase II double blind randomised clinical trial to test IVIG and rituximab versus placebo, added to best standard of care with antipsychotic medication if required, without corticosteroids. Methylprednisolone will be administered with Rituximab, but only as standard premedication to reduce the incidence and severity of infusion related reactions, not at a therapeutic level. IVIG has a direct immunomodulatory effect, probably through sialylated sugars, and may 'dilute' pathogenic antibodies. Rituximab is a monoclonal antibody directed towards CD20 on B cells, depletion of which results in immediate immunomodulatory effects and then reduction in pathogenic antibodies in the long term, associated with good clinical response in a range of immunological disorders (Faurschou and Jayne, 2014).

Reports vary from other groups on the prevalence of autoantibodies in psychosis and schizophrenia, which probably reflects differing assays systems. Our preferred system is Professor Angela Vincent's live cell-based assays (Irani *et al*., 2010). For instance, anti-NMDAR antibodies are detected by binding to HEK29 cells transfected with both the NR1 and NR2B subunits (Irani *et al*., 2010). Using similar methodology, another group has found autoantibodies in 8/43 (18.6%) cases of psychosis (Pathmanandavel *et al*.,

2015). A meta-analysis of 7 studies concluded that 115/1441 (7.98%, 95% confidence interval 6.69–9.50) of cases of psychosis or schizophrenia were anti-NMDA receptor antibody positive (Pollak *et al*., 2014). However, only in the subgroup of IgG antibodies, which were present in 1.5% cases, were in greater prevalence amongst patients than controls. Not only did this meta-analysis include patients with chronic schizophrenia, where we find very low prevalence of antibodies, but it also included studies using commercial antibody kits (Dahm *et al*., 2014) and including assays that detect IgA and IgM antibodies, which are of doubtful clinical significance (Lancaster *et al*., 2015). In the only published head to head study (albeit in neuromyelitis optica), live cell based assays were superior to fixed assays and importantly did not detect binding to intracellular epitopes, a cause of non-specific binding (Waters *et al*., 2012). A further complication is that there are clearly rare cases where anti-NMDAR and anti-VGKC complex antibodies are present but are clinically irrelevant; we have identified criteria to attempt to distinguish these from pathogenic antibodies (Paterson *et al*., 2014; Zandi *et al*., 2015) in a neurology setting.

7.2 Data from non-clinical studies

There is considerable evidence that anti-NMDAR antibodies are usually pathogenic, down-regulating NMDAR currents both in vitro and in vivo (Hughes *et al*., 2010; Moscato *et al*., 2014; Planaguma *et al*., 2015).

7.3 Clinical Data

7.3.1 Efficacy

IVIG has been used in NMDAR encephalitis extensively – in over 300 published cases (Titulaer *et al.*, 2013), and is effective and safe in other antibody-associated neuroimmunological disorders, including the Guillain-Barré Syndrome (GBS), in which equivalence to PLEX has been demonstrated (van der Meché and Schmitz, 1992; Raphaël *et al.*, 2012). Rituximab has also been used in NMDAR encephalitis (101 cases in Titulaer *et al.*, 2013), VGKC-antibody-associated psychosis (Brown *et al.,* 2014), and other immunological disorders (Faurschou and Jayne, 2014) with good effect and a good safety profile.

7.3.2 Safety and tolerability

IVIG is a blood product screened for known viral infections. No known case of prion disease has been transmitted in the history of its use, but this remains a theoretical risk. IVIG can cause headache, renal failure, transient lymphopaenia, ischaemic events, deep vein thrombosis and aseptic meningitis.

Rituximab use is associated with a risk of anaphylaxis, infusion reactions and serum sickness, raised risk of infections, hepatitis B reactivation and hypo-gammaglobulinaemia, which would be more severe and require long term IVIG replacement to prevent recurrent infections in around 4% of people receiving often more than one course of rituximab (Roberts, *et al.,* 2015). There is a very rare risk of the fatal brain infection by JC virus, progressive multifocal leukoencephalopathy (PML), seen in 1 in 25,000 patients treated for rheumatoid arthritis (Clifford *et al*.,2011).

A dose of corticosteroids (100 mg methylprednisolone) is given with rituximab to reduce the incidence and severity of infusion-related reactions. Corticosteroids can lead to mania, altered sleep, stomach ulceration, osteoporosis, hypertension, weight gain, but are unlikely to cause significant adverse effects with the proposed doses.

Clinical teams should follow local guidance of rituximab in relation to COVID vaccines.

7.3.3 Pharmacokinetics & pharmacodynamics

IVIG is recirculated through FcRn receptors and follows the same degradation pathway as host IgG; this is highly variable (range 22-100 days half-life, Vlam *et al*., 2014). Rituximab clearance is partly through internalisation by Cd20+ cells and otherwise unknown. Rituximab concentrations increase linearly with dosing, and there is a rapid decay (Maloney, *et al.* 1994), half-life approximately 19 days (Cartron *et al*., 2007), though the drug can still be detected at 6 months in some participants (Berinstein *et al*., 1998).

8 Rationale for Trial

We propose a randomised double-blinded placebo-controlled trial to test the hypothesis that immunotherapy is an effective treatment of antibody-associated psychosis, either first episode of psychosis or relapse following previous remission. Immunotherapy for the trial consists of one cycle of intravenous immunoglobulin (IVIG: 2g/kg over days 1-4) followed by two infusions of 1g rituximab (at day 28-35, and then 14 (+7) days after the first infusion). The rationale for this regime is that it combines a rapid-action treatment (IVIG) to induce remission with a longer-action therapy (rituximab) to maintain remission. It is based on a protocol where elimination of circulating antibodies is the treatment goal, namely "desensitisation" of potential transplant patients who have multiple anti-HLA antibodies capable of inducing hyperacute rejection (see (Kobashigawa *et al*., 2009) and also being tested in various trials on clinicaltrials.gov (NCT00642655, NCT01178216, and NCT01502267). Blinding is required to minimise placebo responses in a trial based on symptomatology.

During the course of the trial, we have experienced times when IVIG is not available, due to international shortages of IVIG. This has prevented us from recruiting participants with this rare form of psychosis. At the same time, there is growing recognition that rituximab alone may induce disease suppression in conditions like vasculitis, antiphospholipid syndrome and lupus[1]. Indeed ocrelizumab (the humanised form of rituximab) is now licensed for the first-line treatment of multiple sclerosis. Accordingly, in March 2023, the Trial Steering Group agreed that the primary endpoint (long term remission of psychosis, maintained over six months) is predominantly driven by rituximab and therefore would not be compromised by omitting IVIG. The Trial Steering Group therefore proposed that we should modify the protocol to allow participants to be recruited to the trial and receive only rituximab/placebo at times when IVIG is not available. We propose a sensitivity analysis of the efficacy and safety outcomes, by IVIG treatment receipt.

1 Li K, Comparative Effectiveness of Rituximab and Common Induction Therapies for Lupus Nephritis: A Systematic Review and Network Meta-Analysis. Front Immunol. 2022 Apr 4;13:859380. doi: 10.3389/fimmu.2022.859380. PMID: 35444666; PMCID: PMC9013779.

2: Gan Y, Low dose versus standard dose rituximab for the treatment of antiphospholipid syndrome: A pilot study from a tertiary medical center. Front Immunol. 2022 Nov 3;13:971366. doi: 10.3389/fimmu.2022.971366. PMID: 36405743; PMCID: PMC9670802.

3: Wallace ZS, The Comparative Effectiveness of Rituximab- vs Cyclophosphamide-Based Remission Induction Strategies in ANCA-Associated Vasculitis for the Risk of Kidney Failure and Mortality. Arthritis Rheumatol. 2023 Apr 3. doi: 10.1002/art.42515. Epub ahead of print. PMID: 37011036.

9 Trial Design

9.1 Statement of design

This is a phase II, double blind, randomised controlled trial, powered to show superiority of immunotherapy with IVIG and rituximab over conventional antipsychotic medication alone in patients with acute psychosis and CNS-membrane autoantibodies.

9.2 Number of Centres

SINAPPS2 will take place in a number of centres with suitable facilities to undertake the trial on this patient group. We anticipate that we will open at least 8 centres across England.

9.3 Number of Participants

We anticipate screening approximately 160 patients with antibody-associated psychosis to identify 70 eligible participants who consent to the trial. These will be randomised 1:1 (balancing antibody types, current smoking status and length of psychosis illness across arms) to intravenous immunoglobulin combined with rituximab versus placebo (infusions of 1% albumin and 0.9% sodium chloride, respectively) aiming for 56 or more patients to complete the trial, allowing for a drop-out of 12 participants per arm.

9.4 Participants Trial duration

The duration of screening is a maximum of two months (defined from obtaining informed consent to eligibility confirmation). There is a maximum 4-week interval from completion of the trial screening procedures (eligibility confirmation) to Baseline and a maximum 7 days interval from Baseline to treatment. Participants will be randomised following the eligibility confirmation and before Baseline. There is no other time limit for randomisation. The duration of the treatment period for individual participants will be approximately 50 days. Each patient is followed for 12 months minimum from the first day of treatment (with an additional maximum 6 months, if required to assess the primary outcome measure).

9.5 Trial objectives

9.5.1 Primary objective

To test the efficacy of immunotherapy (IVIG and rituximab[2]) of patients with acute psychosis associated with anti-neuronal membrane antibodies.

9.5.2 Secondary objective

To test the safety of immunotherapy (IVIG and rituximab) of patients with acute psychosis associated with anti-neuronal membrane antibodies.

9.6 Trial Outcome Measures

9.6.1 Primary outcome measure

The primary outcome is time from start of treatment to start of symptomatic recovery i.e. symptomatic remission sustained for 6 months. Symptomatic remission is defined

2 Or rituximab alone when IVIG is unavailable

according to Andreasen *et al*. (2005) as a score of 3 or less, on each of the following items from the Positive and Negative Syndrome Scale (PANSS; Kay *et al*., 1987): P1, delusions; P2, conceptual disorganization; P3, hallucinatory behaviour; N1, blunted affect; N4, social withdrawal; N6, lack of spontaneity; G5, mannerisms/posturing; G9, unusual thought content; (P1, P2, P3, N1, N4, N6, G5, G9).

9.6.2 Secondary outcome measures

The secondary outcomes are

- Time to first symptomatic remission. Symptomatic remission is defined as score of 3 or less on each of the following PANSS items: P1, P2, P3, N1, N4, N6, G5, G9 regardless of whether or not symptomatic remission is sustained for six months (i.e. symptomatic remission, but does not reach the duration criterion for symptomatic recovery).
- Relapse. Relapse is defined as a score 4 or more on at least one of the following PANSS items P1, P2, P3, N1, N4, N6, G5, G9 after a previous period of remission of any duration.
- Number of adverse effects
- Number of serious infections
- Proportion of patients reaching 20%, 30% and 40% reduction in PANSS total score

9.6.3 Exploratory outcomes

- Changes in the following clinical rating scales, from baseline to month 12
    - Clinical Global Impression Scale - Schizophrenia score for the Severity of Symptoms Rating (CGI-SCH; Haro *et al*., 2003)
    - Young Mania Rating Scale (YMRS; Young *et al*., 1978)
    - Antipsychotic Non-Neurological Side-Effects Rating Scale (ANNSERS; Ohlsen *et al*., 2008)
    - Brief Assessment of Cognition in Schizophrenia (BACS; Keefe *et al*., 2004)
    - Global Assessment of Functioning scale (GAF; Hall, 1995)

- Proportion of participants with grade 3 and 4 adverse effects
- Weight change
- Elimination or reduction of serum autoantibody levels
- Antipsychotic drug use
- Mental health hospitalisation
- Infections
- Hypogammaglobulinaenemia
- Acceptability of the treatment measured by the Abbreviated Acceptability Rating Profile (AARP; Tarnowski & Simonian, 1992) (adapted for use with adults)
- Serum stored for research may be used, at the request of the Trial Steering Committee, to assess SARS Cov2 antibody status of trial participants, in order to determine if Covid infection influences presentation with psychosis and/or response to treatment.

10 Selection and withdrawal of participants

10.1 Inclusion Criteria

To be included in the trial the patient must have all of:

- An episode of acute psychosis for at least 2 weeks (defined as symptomatic on the PANSS, at least one of item score 4 or more on P1, P2, P3, N1, N4, N6, G5, G9).

    - This may either be a first episode or relapse after remission (remission is defined as having mild or absent symptoms of psychosis for at least 6 months.
- Aged 16-70 years.*
- Patient or Legal representative is willing and able to provide informed consent

* Participants between 61-70 years of age and with both doses of COVID-19 vaccine can be included in the trial.

- Have a positive Serum or CSF neuronal membrane autoantibodies at pathological levels (including NMDAR, LGI1 and other) within 12 months of screening.

10.2 Exclusion Criteria

The presence of any of the following will preclude patient inclusion:

- Duration of current episode of psychosis greater than 24 months.
- Alternative co-existing severe neurological disease, including tumour, hippocampal sclerosis with refractory epilepsy, probable dementia with evidence of atrophy on brain imaging, moderate or severe learning disability.
- Any evidence of a current acute encephalopathy (for instance coma, seizures).
- Hepatitis B, Hepatitis C or HIV positivity.
- IgG level <3g/L.
- Previous malignancy (to be usually excluded unless agreed with CI).
- Pregnant, breast feeding or inadequate contraception if female.
- Hypersensitivity or absolute contra-indication to any trial drug, murine proteins or excipients.
- Previous treatment with rituximab in the past 12 months.
- Severe infection.
- Severe heart failure.
- Any other medical illness or disability that, in the opinion of the investigator, would compromise effective trial participation.
- Risk factors associated with COVID 19 that in the opinion of the investigator would lead to unacceptable risks to trial participation
- Concurrent enrolment in another CTIMP(s)

10.3 Treatment Assignment and Randomisation Number

Following informed consent and confirmation of eligibility and before Baseline, patients will be randomly assigned to either the IVIG/rituximab group or the placebo group, which will contain approximately 40 participants each. The randomisation will be performed using the minimisation technique of Pocock and Simon 1975, using NMDAR, LGI1, GABA-A, duration of psychosis illness and current smoking status as minimisation factors.

A web-based randomisation system will be used to randomise participants and allocate treatment to individual patients. This will be accessed by the PI and suitably trained site staff through a secure, person-specific log-in. Notification of the randomisation number and treatment allocation will be forwarded to the central trial coordinator, local investigator and local pharmacy by e-mail upon randomisation.

10.4 Method of Blinding

Trial participants and investigators will be blinded to treatment allocation. Site pharmacies and other authorised delegates as required will be unblinded.

Patients receiving intervention treatment will receive IVIG and rituximab infusions, plus 100mg methylprednisolone premedication prior to each rituximab dose. Patients receiving control treatment will receive matched placebo solutions for IVIG (human albumin solution 1%) and rituximab (NaCl 0.9%), with NaCl 0.9% being used in place of methylprednisolone premedication to maintain blinding within the trial. Each treatment product/premedication and its corresponding control will have identical presentations at the point of issue, in terms of product appearance, packaging and labelling. Further information will be available in the IMP Handling manual.

Albumin in glass bottles will give the same aesthetic appearance, in terms of colour and viscosity, as IVIG.

10.5 Emergency Unblinding

In the event of a clinical adverse event, where knowledge of the treatment allocation will alter management, the treating physician may unblind the patient using the web-based randomisation system (through a procedure documented in the trial manual/randomisation system manual). It is the responsibility of the treating physician to promptly document and explain any unblinding to the Sponsor.

10.6 Participant withdrawal criteria

Each patient has the right to discontinue their participation in the trial at any time. Incapacitated participants may also be withdrawn from the trial if the legal representative requests withdrawal. If a participant wishes to withdraw their consent to participate, any data and samples collected up until that point of consent withdrawal will continue to be used in the trial. However no further information will be collected or tests performed.

In addition, participants must be withdrawn from their allocated treatment arm if:

- The participant develops severe encephalopathy, e.g. typical of NMDAR encephalitis or LGI1-antibody encephalopathy, which would necessitate withdrawal to facilitate best standard of care of management for these conditions.

- The participant develops severe reactions to the IMPs, e.g. anaphylaxis to first rituximab infusion, aseptic meningitis to first dose of IVIG.

- A female participant becomes pregnant or will no longer use contraception.

Participants that have withdrawn from the allocated treatment will remain in the trial and be followed up as set out in the protocol, unless they withdraw their consent for this trial.

All discontinuations and withdrawals will be documented in the CRFs. Participants withdrawn between randomisation and completion of IMP visits will be replaced.

11 Trial Treatments

The Investigational Medicinal Products for this trial are:
Intravenous immunoglobulin (IVIG)
Placebo to match IVIG (1% human albumin solution)
Rituximab for intravenous infusion

Placebo to match rituximab infusion (0.9% sodium chloride)

11.1 Dosage schedules

a) IVIG

11.1.1 Route of Administration and Maximum dosage allowed

Intravenous infusion of 2g/kg (ideal body weight) as calculated at screening over 2-4 days as tolerated. Most young participants can tolerate a gram per kilogram a day, as limited by blood pressure changes or symptoms, including headache. Most participants are expected to receive the drug for two 2-6 hour periods.

11.1.2 Maximum duration of treatment of a participant

One course up to an expected maximum of 4 days.

11.1.3 Comparator products

Placebo, 1% albumin solution, to be given for 2-4 days.

11.1.4 Stock Availability

We have experienced disruptions to IVIG supply which have led to being unable to recruit participants to the trial. So, if stock of IVIG is not available at a trial site at time of planned infusion, then the participant may continue in the trial, omitting this visit, and attending site next for the D28 rituximab infusion. Rituximab doses should continue as per protocol.

b) Rituximab

11.1.5 Route of Administration and Maximum dosage allowed

Intravenous infusion of 1g over 2-4 hours as tolerated. The first infusion should commence at 50mg/hr; after the first 30 minutes, it can be escalated in 50mg/hr increments every 30 minutes, to a maximum of 400mg/hr. In the absence of serious previous infusion-related reactions, the second infusion can be infused at an initial rate of 100mg/hr and increased by 100mg/hr increments at 30 minute intervals, to a maximum of 400mg/hr.

11.1.6 Maximum duration of treatment of a participant

Up to 16 days: 2 day case admissions, 2 weeks apart (+ up to 7 days).

11.1.7 Comparator products

Placebo solution, sodium chloride 0.9%, in an equal volume to that used for rituximab infusion.

11.2 Presentation of the drug

11.2.1 IVIG and matching placebo

IVIG and corresponding placebo solutions are clear to slightly opalescent and colourless to pale yellow. IVIG will be presented as a 100g/L formulation, supplied in 50ml glass bottles (5g/bottle). The corresponding placebo formulation will be presented identically.

11.2.2 Rituximab and matching placebo

Rituximab solution for infusion and its corresponding placebo solution are clear and colourless. Rituximab is presented in vials as a concentrate for dilution prior to infusion.

11.3 Known drug reactions & interaction with other therapies

Infusion reactions are the most common side effect of Rituximab treatment, with an onset ranging from 30 minutes to 2 hours after starting the first intravenous Rituximab infusion. Symptoms include hives (red itchy welts) or rash, itching, swelling of the lips, tongue, throat, or face, shortness of breath, difficulty breathing or wheezing, weakness, dizziness or feeling faint, palpitations (feeling like the heart is racing or fluttering), and chest pain. These symptoms are usually reversible with interruption of Rituximab infusion and administration of an anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required.

11.4 Dosage modifications

No dosage modifications are permitted.

The IVIG dosage is weight determined (ideal body weight). Ideal body weight will be used unless this value exceeds a participant's actual body weight at screening, in which case actual body weight will be used to calculate dose. Patients below 152.4cm (5ft) will be treated using actual body weight. Please refer to Pharmacy Manual for further details.

IVIG dosing will be rounded down to the nearest 5g regardless of calculated dose i.e. if calculated dose is 39.9g, they will receive 35g.

Rituximab is given at 1g which will saturate CD20 binding and provide ideal B cell depletion, irrespective of patient's weight.

11.5 Legal status of the drug

While IVIG and rituximab are frequently used for autoimmune CNS disorders, the trial is being carried out under a Clinical Trial Authorisation. The IMPs are therefore only to be used by the named investigators, for the participants specified in this protocol, and within the trial.

11.6 Drug storage and supply

IVIG and matched placebo will be supplied to sites via Biotest UK, upon initial authorisation by the sponsor. IMP will be labelled in accordance with regulatory requirements (and be such that a blinded product is available at point of issue) and stored as per labelled instructions. All other medications associated with the trial will use standard hospital stock, stored and prepared as per licensed instructions.

IMPs will be supplied for treatment upon receipt by pharmacy of a suitably signed trial-specific prescription. Further details will be provided in the IMP handling manual.

11.7 Non Investigational Medicinal Products

For rituximab treatment, to reduce the incidence and severity of infusion-related reactions, premedication with an analgesic/antipyretic, e.g. 1g paracetamol, an antihistamine, e.g. 4mg chlorphenamine, and intravenous methylprednisolone 100mg should be administered. For patients receiving placebo treatment, an equivalent volume of sodium chloride 0.9% should be substituted for methylprednisolone, in order to maintain blinding.

Paracetamol - this drug is only potentially unsafe in overdose (e.g. 5g or more) particularly in low-weighted persons (<50kg). See https://www.medicines.org.uk/emc/medicine/31423 for details.

Chlorphenamine maleate (Piriton) - this antihistamine commonly causes drowsiness, headache, blurred vision, dry mouth, disturbed attention. See https://www.medicines.org.uk/emc/medicine/16103 for full details.

Methylprednisolone - an immune suppressive. This short-term use is unlikely to be associated with the full range of side effects associated with long term corticosteroids use (see https://www.medicines.org.uk/emc/medicine/25692 for a full list). Metallic taste sensation and/or disrupted sleep are likely, and require no medication steps to minimise. The risk of osteoporosis, diabetes, gastric ulceration, infection is far too low to warrant bone protection medication or a proton pump inhibitor.

Standard of care for people with psychosis may include the use of antipsychotic drugs. These may cause extrapyramidal symptoms, drowsiness, constipation, arrhythmias and hypertension.

11.8 Concomitant therapy

Participants will continue antipsychotic medications as standard of care, under the supervision of their local psychiatrist.

12 Procedures and assessments

Refer to section 6.1 for schedule of assessments and procedures.

For the protection of participants and trial team members, all staff will adhere to their local safety polices and guidelines to minimise exposure to the SARS Cov2 virus.

12.1.1 Identification of potential participants

The following avenues will be utilised for identification of potential participants: Participants will be identified by their direct care team through routine antibody testing in clinical practice or via the research team for the PPiP2 study (REC ref: 12/EE/0307). Any patient positive for antibodies of interest will be informed and referred to the local SINAPPS2 trial Neurologist who will provide further information on the trial.

12.1.2 Consent Process and Screening Assessments (Visit1)

Trial specific assessments will only be conducted after participants have given written informed consent. Potential participants will be approached by a member of the research team who will provide the patient information sheet and clarify any information the participant/relatives which may preclude recruitment.

Participants lacking capacity can still be enrolled in this trial providing that the conditions and principles listed in the Medicines for Human Use (Clinical Trials) Regulations are satisfied (See Appendix 3, 'Annex B' of the CT Regulations on informed consent). The process for obtaining consent in this situation is detailed below:

12.1.2.1 Personal Legal Representative

In the first instance, a Personal Legal Representative (PeLR) should be approached. The PeLR should be close to that incapacitated patient, aware of his/her wishes and independent of the research. If they decide that the patient is suitable for entry into the trial they will be asked to give the written consent on behalf of the incapacitated adult.

After consent is obtained, the patient will only enter the trial if they meet all the entry criteria. This will be explained to the patient's personal legal representative during the process of obtaining consent.

12.1.2.2 Professional Legal Representative

If this is not possible and there is no one sufficiently close to the potential participant who is willing or able to take on the role, then an independent clinician will be nominated to act as Professional Legal Representative (PrLR) to fulfil this role. The PrLR will be provided with sufficient information about the SINAPPS2 trial to ensure that they can make an informed decision to enter the incapacitated patient into the trial. In such a case we advocate enrolment would be possible with written agreement from the independent clinician.

For the purposes of the SINAPPS2 trial, the PrLR is defined as:

A person who is not connected with the conduct of the trial, specifically:

- NOT the Sponsor of the trial
- NOT a person employed or engaged by acting under the arrangements with the sponsor, and who undertakes activities connected with the management of the trial
- NOT an investigator of the trial and
- NOT a health care professional who is a member of the investigators' team for the purposes of the trial.

Participants who regain capacity will be informed of the clinical trial and consent to continue will be sought at that time as per the usual consenting process. The legal representative will be notified of this at the outset. If at any stage either the legal representative or the patient chose to withhold consent then the patient will be withdrawn from the trial.

If a participant consents to the trial but later becomes incapacitated, the original consent given remains valid after the loss of capacity, providing that the trial has not significantly altered.

12.1.2.3 Screening Assessments

Screening assessments will usually be performed at the local clinical research facility, but may also be performed at outpatient clinics. All screening assessments must be complete in maximum of two months from informed consent to eligibility confirmation.

1. Physician review.
2. Physical examination.
3. Weight and Height
4. Pregnancy test (urine sample) if appropriate.
5. Collection of demographic data.
6. Disease history and confirmation of psychosis illness by using Mini Neuropsychiatric Interview (MINI; Sheehan et al., 1998).
7. Screening blood tests: urea, electrolytes, calcium, HbA1C, HIV, Hepatitis B, Hepatitis C, syphilisand varicella serology
8. Monitoring blood tests: FBC, LFT and immunoglobulin levels.
9. Research blood sample collection.
10. Anti-neuronal membrane antibody assays.
11. Severity of selected symptoms assessments:
    - PANSS scale (items P1, P2, P3, N1, N4, N6, G5, G9) - a rating scale used for assessment of symptom severity of participants with schizophrenia, separated into positive, negative and general symptoms, usually taking

30-40 minutes to complete by an interviewer. At the Screening only items P1, P2, P3, N1, N4, N6, G5, G9, will be assessed and this will take 15 minutes to complete.

12. Concomitant medications assessment.

Adverse events recording begins from point of informed consent and they will be assessed continually throughout the trial.

12.2 Baseline assessments (Visit 2, Day 0 (or day 1) (up to 7 days before treatment)

Some visit elements may be done virtually. The BACS App and physician review should be done face to face. All participants will have a physician review. The following will be recorded:

1. Physician review for the period between the screening and the baseline date.
2. Clinical and cognitive assessments:
    - PANSS (all items, 30-40 min).
    - CGI-SCH – a 7-point a clinician-rated scale for a brief, stand-alone assessment of symptom severity and degree of change in treatment studies of participants with schizophrenia, usually taking 2 minutes to complete.
    - YMRS – an 11-item scale rated by a clinician/researcher used to assess symptoms of mania, usually taking 10 minutes to complete.
    - ANNSERS – a clinician/researcher-rated questionnaire for assessment of the side effects associated with both first- and second-generation antipsychotic drugs, usually taking 30 minutes to complete.
    - BACS App – a computerised battery of tests presented on an iPad App to a participant that assesses the aspects of cognition found to be most impaired and most strongly correlated with outcome in participants with schizophrenia (memory and executive function). It is designed to be completed by participants in 35 minutes.
    - GAF – a brief numeric scale (1 through 100) used by mental health clinicians, physicians and researchers to rate the social, occupational, and psychological functioning of adults, usually taking 3 minutes to complete.
3. Adverse event assessment for time period from the informed consent date and the baseline date.
4. Concomitant medication assessment.
5. Pregnancy test (to be done a maximum of 7 days before the first dose of IVIG).
6. Any testing for SARS Cov2 advised by local or national guidance.

12.3 Randomisation

A web-based central randomisation system will allocate patient randomisation numbers sequentially in the order in which the participants are enrolled.

In order to enrol a patient, data will be entered onto the central randomisation system via an internet-based interface. The following data will be required in order to randomise a patient: screening number, initials, date of birth, antibody type (NMDAR or LGI1 or

GABA-A), duration of psychosis illness (greater than or equal to 3 months or less than 3 months) and current smoking status. The treatment arm will be assigned by the randomisation system. Participants' screening number will be used for the duration of the study and known as the trial number or TNO.

Randomisations can occur between the eligibility confirmation and the baseline visit. This has been allowed to ensure that IMP stock can be appropriately ordered prior to the participants baseline visit and not unnecessarily burden additional costs on to the NHS. The first treatment of IMP will follow the baseline visit.

12.4 Trial assessments during protocol treatment

Trial treatments will be infused at the local Trust approved facility.

12.4.1 Visit 3 (Day 1 (days 1-4))

1. Adverse events assessment.
2. Concomitant medications assessment.

12.4.2 Visit 4 (Day 28 (+ 7 days))

1. Pregnancy test (to be done a maximum of 7 days before the first dose of rituximab).
2. Anti-neuronal membrane antibody assays.
3. Adverse events assessment.

12.4.3 Visit 5 (Day 42 (+7 days))

1. Adverse events assessment.
2. Concomitant medications assessment.

12.5 Follow-up assessments

Following completion of the trial treatment each patient is followed for at least 12 months (with an additional maximum 6 months, if required to assess the primary outcome measure) from the day of first treatment. "Visits" take place at months 3, 6, 9, 12 (and 15, 18 for participants requiring longer follow up) with a window of one week either side of the designated visit. Monthly phone call or visit assessments occur at months 1 (at the Rituximab 1 visit), 2, 4, 5, 7, 8, 10, 11, (13, 14, 16, 17 if required) +/- 3 days.

Visits should be conducted face to face, but at the discretion of the PI these may be done by telephone or NHS-approved videoconferencing facility. Remote assessments may be preferable, for instance, when the risk of SARS Cov2 infection is considered high.

Blood tests may be collected at face to face visits, or at more local facilities, if possible. But, if the PI concludes that the risk of attending any healthcare setting is unacceptably high, blood tests may be omitted but should be done as soon as the risk level is reduced.

Physical exams and some elements of the BACS App cannot be collected at remote visits.

12.5.1 Visits 6-8 - Months 3, 6, 9, (12 & 15 if required)

1. Physician review
2. Physical examination
3. Monitoring blood tests: FBC, LFT and immunoglobulin levels. (to be collected at 6 monthly visits only (6 & 12))
4. Anti-neuronal membrane antibody assays (at 6 monthly visits only (6 & 12))
5. Severity of symptoms (PANSS all items).
6. Clinical and cognitive assessments (CGI-SCH, YMRS, ANNSERS, BACS App, GAF).
7. Adverse events assessment.
8. Concomitant medications assessment.

12.5.2 Monthly telephone call or visit assessments (Months 1, 2, 4, 5, 7, 8, 10, 11/+6 months (13, 14, 16, 17 if required)) +/- 3 days.

1. Severity of selected symptoms (PANSS items P1, P2, P3, G5, N1, N4, N6, G9 only).
2. Adverse events assessment.
3. Concomitant medications assessment.

12.6 End of Trial Visit - Month 12 (or month 15 or 18 if required)

1. Physician review.
2. Physical examination
3. Weight.
4. Monitoring blood tests: FBC, LFT and immunoglobulin levels.
5. Anti-neuronal membrane antibody assays.
6. Severity of symptoms (PANSS all items).
7. Clinical and cognitive assessments (CGI-SCH, YMRS, ANNSERS, BACS App, GAF).
8. Acceptability of treatment (Abbreviated Acceptability Rating Scale (AARS)
9. Adverse events assessment.
10. Concomitant medications assessment.

12.7 Psychiatry Follow-up

Participants may continue to be seen in their local psychiatry clinic for review of symptoms and antipsychotic medication as required.

12.8 End of Trial Participation

Participation will end 12 months after first day of treatment, or up to 18 months if the participant enters clinical remission after month 6 (to include follow up for 6 further months from the point of entering clinical remission). Participants will return to normal standard of care after participation in the trial, which is likely to be local psychiatry review, with neurologist input and review if antibodies and symptoms return.

12.9 Trial restrictions

Women of childbearing potential are required to use adequate contraception for the duration of the trial and for 12 months after the last treatment. This includes:

- Intrauterine Device (IUD)
- Hormonal based contraception (pill, contraceptive injection or implant etc.)
- Barrier contraception (condom and occlusive cap e.g. diaphragm or cervical cap with spermicide)

- True abstinence (where this is in accordance with the participants preferred and usual lifestyle)

Men are required to use adequate contraception for the entire duration of the trial and for 90 days after the completion of the last treatment. This includes:

- Barrier contraception (condom and spermicide) even if female partner(s) are using another method of contraception or are already pregnant (also to protect male partners from exposure to the trial IMPs etc.)
- True abstinence (where this is in accordance with the participants preferred and usual lifestyle)

Male participants should refrain from donating sperm for the duration of the trial and for 12 months thereafter.

Vaccinations

Most live vaccines are ineffective if given within three months after taking IVIG.

Live vaccinations are not recommended after rituximab for about 12 months [or for as long as the blood immune cells are still low]. Non-live vaccinations, such as most Covid19 vaccines, are safe after rituximab but may not be as effective as usual. Clinical teams should follow local guidance for rituximab in relation to COVID vaccines.

Live vaccines may be given up to 4 weeks before receiving rituximab.

13 Assessment of Safety

13.1 Definitions

13.1.1 Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Please note: Recording of all adverse events must start from the point of Informed Consent regardless of whether a patient has yet received a medicinal product.

13.1.2 Adverse reaction to an investigational medicinal product (AR)

All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

13.1.3 Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the applicable reference safety information (RSI) (summary of product characteristics for IVIG and rituximab)

When the outcome of the adverse reaction is not consistent with the applicable RSI this adverse reaction should be considered as unexpected.

The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as "serious," which is based on patient/event outcome or action criteria.

13.1.4 Serious adverse event or serious adverse reaction (SAE / SAR)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect.
- is an important medical event - Some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/ consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious'.

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

13.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information set out in the Reference Safety Information

13.1.6 Reference Safety Information (RSI)

The information used for assessing whether an adverse reaction is expected. The RSI is contained in a clearly identified section of the Investigator's Brochure (IB) or the Summary of Product Characteristics (SmPC)

For this trial the Reference Safety Information is section 4.8 of the:

SmPC for Intratect 100g/litre for intravenous immunoglobulin (Biotest Pharma GmbH); updated 14-Jul-2016, Table based on 100g/L of Intratec.

SmPC for Mabthera 100mg and 500mg concentrate for solution for infusion (Roche Registration Ltd); updated 08-Jun-2016, Table 2.

13.2 Expected Adverse Reactions/Serious Adverse Reactions (AR /SARs)

All expected Adverse Reactions are listed in the latest MHRA approved version of the reference safety information as specified in section 13.1.6. This must be used when making a determination as to the expectedness of the adverse reaction. If the adverse reaction meets the criteria for seriousness, this must be reported as per section 13.5 and 13.6.

13.3 Expected Standard of care related adverse reactions

Expected adverse reactions and serious adverse reactions due to use of antipsychotic medication include extrapyramidal symptoms, drowsiness, constipation, arrhythmias and hypertension.

13.4 Evaluation of adverse events

The Sponsor expects that adverse events are recorded from the point of Informed Consent regardless of whether a patient has yet received a medicinal product. Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, expectedness and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event.

13.4.1 Assessment of seriousness

Seriousness is assessed against the criteria in section 13.1.4. This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction.

13.4.2 Assessment of causality

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**
Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product and there is a reasonable response on withdrawal. **This is therefore an Adverse Reaction.**
Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational medicinal product. **This is therefore an Adverse Reaction.**
Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**
Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unlikely and Unrelated causalities are considered NOT to be trial drug related
Definitely, Probable and Possible causalities are considered to be trial drug related

A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in the appropriate section of the CRF.

13.4.3 Clinical assessment of severity

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated
Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity
Severe: Significant impairment of functioning; the participant is unable to carry out usual activities and / or the participant's life is at risk from the event.

13.4.4 Recording of adverse events

Adverse events and adverse reactions should be recorded in the medical notes and the appropriate section of the CRF and/or AE/AR log. Serious Adverse Events and Serious Adverse Reactions should be reported to the sponsor as detailed in Section 13.5 and 13.6.

13.5 Reporting serious adverse events

Each Principal Investigator needs to record all adverse events and report serious adverse events to the Chief Investigator using the trial specific SAE form within 24 hours of their awareness of the event.

The Chief Investigator is responsible for ensuring the assessment of all SAEs for expectedness and relatedness is completed and the onward notification of all SAEs to the Sponsor immediately but not more than 24 hours of first notification and to the IMP manufacturers within the timelines defined in the contracts. The sponsor has to keep detailed records of all SAEs reported to them by the trial team.

The Chief Investigator is also responsible for prompt reporting of all serious adverse event findings to the competent authority (e.g. MHRA) of each concerned Member State if they could:

- adversely affect the health of participants
- impact on the conduct of the trial
- alter the risk to benefit ratio of the trial
- alter the competent authority's authorisation to continue the trial in accordance with Directive 2001/20/EC.

The completed SAE form can be emailed. Details of where to report the SAEs can be found on the 'A randomised phase II double-blinded placebo-controlled trial of intravenous immunoglobulins and rituximab in participants with antibody-associated psychosis (SINAPPS2)' SAE form and the front cover of the protocol.

All SAEs (that are related to the trial IMPs) still present at the end of the trial, must be followed up at least until the final outcome is determined, even if it implies that the follow-up continues after the patient leaves the trial or after the end of the planned period of follow-up.

13.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an investigational medicinal product (the tested IMP and comparators) which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting. Please see section 13.1.6 for the Reference Safety Information to be used in this trial.

13.6.1 Who should report and whom to report to?

The Sponsor delegates the responsibility of notification of SUSARs to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described, to the:

- Sponsor,
- Competent authorities in the concerned member states (e.g. MHRA)
- Ethics Committee in the concerned member states
- The IMP Manufacturers

The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

13.6.2 When to report?

13.6.2.1 Fatal or life-threatening SUSARs

All parties listed in 13.6.1 must be notified as soon as possible but no later than **7 calendar days** after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting.

In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional **8 calendar days**.

13.6.2.2 Non-fatal and non-life-threatening SUSARs

All other SUSARs and safety issues must be reported to all parties listed in 13.6.1 as soon as possible but no later than **15 calendar days** after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

13.6.3 How to report?

13.6.3.1 *Minimum criteria for initial expedited reporting of SUSARs*

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:
a) a suspected investigational medicinal product,
b) an identifiable participant (e.g. trial participant code number),
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship,
d) an identifiable reporting source,

and, when available and applicable:
- an unique clinical trial identification (EudraCT number or in case of non- European Community trials the sponsor's trial protocol code number)
- an unique case identification (i.e. sponsor's case identification number).

13.6.3.2 *Follow-up reports of SUSARs*

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.
In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

13.6.3.3 *Format of the SUSARs reports*

Electronic reporting is the expected method for expedited reporting of SUSARs to the competent authority. The format and content as defined by the competent authority should be adhered to.

13.7 Pregnancy Reporting

All pregnancies within the trial (either the trial participant or the participant's partner) should be reported to the Chief Investigator and the Sponsor using the relevant Pregnancy Reporting Form within 24 hours of notification, for up to 2 years after trial enrolment.

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

14 Toxicity – Emergency Procedures

Anaphylaxis: intravenous chlorphenamine (Piriton), hydrocortisone, and rarely adrenaline, will be given in line with local procedures for anaphylaxis.

Paracetamol may be given for mild headaches and infusion reactions.

15 Evaluation of Results (Definitions and response/evaluation of outcome measures)

PANSS and safety measures will be recorded at the clinic visits outlined in section 12.

15.1 Response criteria

Symptomatic recovery i.e. symptomatic remission sustained for six months. Symptomatic remission is defined as PANSS≤3 on all PANSS items P1, P2, P3, N1, N4, N6, G5, G9.

16 Storage and Analysis of Samples

Once collected, both research samples and serum samples for antibody testing will be labelled with trial number and date of collection and sent directly (in serum separator tubes) to the Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford. Samples for Antibody testing will be analysed and any leftover material will be destroyed. Serum samples for future research will be periodically transported to the NIHR National Biosample Centre in Milton Keynes or the PPiP2 study designated laboratories at the University of Oxford where they will be stored at approximately -80^{o}C indefinitely for use in future research. Full instructions for the collection, labelling, storage and shipment of samples are provided in the Laboratory Manual.

17 Statistics

17.1 Statistical methods

The final analysis will use a Cox proportional hazards model with fixed effects for minimisation covariates. The primary analysis will be per-protocol rather than intention-to treat, although both will be done. Secondary and exploratory outcomes will be analysed with Cox models (time to any remission), logistic regression models (relapse rate, proportion of participants with serious adverse events) and Poisson models (number of adverse events). The per-protocol population is defined as all participants who have received all protocol defined IMPs and have no major protocol violation as defined prior to analysis. A full detailed analysis plan will be prepared by a statistician who is independent from the study. We will undertake a sensitivity analysis of the trial efficacy outcomes, based on the presence or absence of anti-neuronal antibodies at the time of screening and whether or not participants received IVIG/placebo.

17.2 Interim analyses

There will be no interim analyses of efficacy. Data on trial progress such as recruitment and participant drop-out at months 12, 24, 36 of the trial (after activation of the first site) and quality of data will be reported to both Trial Steering Committee and to the Data Monitoring Committee. Target recruitment rates at these times are a minimum of 15, 36, 64 participants. If recruitment falls below these rates, the Trial Steering Committee will consider opening additional sites and / or modifying eligibility criteria.

Full details of the role and responsibility of the Data Monitoring Committee and Trial Steering Committees will be specified in the corresponding charters.

In addition, the overall rate of participants entering symptomatic recovery at month 24, as defined by the selected PANSS items criteria, will be communicated to the Trial Steering Committee, to assess whether the primary outcome event rate was occurring as expected. If not, the Trial Steering Committee would consider opening additional sites and / or modifying eligibility criteria to increase the power of the trial.

The interim analyses will also consider the safety data from the trial (e.g. rate of Severe Adverse Events/Severe Adverse Reactions).

17.3 Number of Participants to be enrolled

To estimate the control rate for the primary outcome efficacy measure, we have re-analysed the raw data of the national EDEN study (Birchwood et al., 2014). This study consisted of 1000 patients with psychosis (antibody associations not known); 19% of those, who were symptomatic at entry, experienced sustained remission as per the Andreasen criteria (Andreasen *et al*., 2005) on standard antipsychotic therapy at one year. The 50% remission rate on immunotherapy that we have selected is a conservative estimate; in anti- NMDAR encephalopathy, remission may be as high as 85% at one year following IVIG and rituximab (Titulaer et al., 2013). We agreed on 50% as a clinically meaningful and important remission rate that from a patient perspective would make participation in the trial acceptable. The Trial Steering Committee and statistician will analyse recruitment and dropout rates at month 12 and 24 of the trial, and consider altering the recruitment strategy. We have chosen a sample size to target a time-to-remission hazard ratio of 0.322 with a one sided type I error rate of 5% and a power of 80%, standard for a stage II clinical trial. This target hazard ratio comes from assuming a one year remission probability of 0.2 in the control arm and 0.5 in the experimental arm and assuming the time-to-remission distribution is exponential with proportional hazards. With all participants followed up for a year, a sample size of 56 participants, equally randomised between the control and experimental arms is required. We intend to recruit about 70 participants, allowing drop out of 7 participants per arm, and will halt recruitment when 56 evaluable participants have completed the trial. This level of drop out is a cautious estimate because, although a high dropout is often seen in drug trials in psychosis, we are not requiring continued compliance with medication regimes after the infusions of IVIG and rituximab.

17.4 Criteria for the premature termination of the trial

The trial will be terminated in the event that significant safety concerns are raised that may be attributable to the IMPs.

This decision will be made by the TSC following discussions with the CI.

17.5 Procedure to account for missing or spurious data

Since there is likely to be a high proportion of participants who are lost to follow up, we will use a suitable missing data technique for the logistic regression and Poisson models such as multiple imputation. The Cox regression analysis will use censoring for loss to follow-up which assumes the censoring is non-informative. We will use a suitable sensitivity analysis (e.g. Jackson *et al*., 2014) to investigate the impact of deviating from this assumption.

17.6 Definition of the end of the trial

The trial will end when the last patient has completed their last visit.

18 Data handling and record keeping

18.1 CRF

All data will be transferred into a Case Report Form (CRF) which will be anonymised. All trial data in the CRF must be extracted from and be consistent with the relevant source documents. The CRFs must be completed, dated and signed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness, legibility and accuracy of the CRF pages. The CRF will be accessible to trial coordinators, data managers, the investigators, Clinical Trial Monitors, Auditors and Inspectors as required.

All CRFs should be completed in the manner, and within the timelines, detailed in the CRF-completion guidelines and sent to the trial coordinator at the CCTU by email.

The investigator will retain a copy of each completed CRF page at site in the relevant sections of their Investigator Site File with any required anonymised background information from the medical records as required.
The investigator will also supply the trial coordination centre with any required, anonymised background information from the medical records as required.

The investigators must ensure that the CRFs and other trial-related documentation is sent to the trial coordination centre containing no patient identifiable data.

Completed CRF data should be entered into the database within 6 months of the patient involvement being completed.

All CRF pages must be clear, legible and completed in black ink. Any errors should be crossed with a single stroke so that the original entry can still be seen. Corrections should be inserted and the change dated and initialled by the investigator or designee. If it is not clear why the change has been made, an explanation should be written next to the change. Typing correction fluid must not be used.

A trial specific data management plan will describe in detail the data management processes.

18.2 Source Data

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating participants (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed informed consent forms and copies of the CRF pages.
In this trial source data include, but are not limited to:

Patient Medical records,
Informed Consent Forms,
Screening Logs,
Results of cognitive tests,
Results of clinical tests, including EEG, MRI, CSF, viral studies,
Paper or electronic forms of questionnaires,

Worksheets for sample collection, processing, storage and shipment.

18.3 Data Protection & Patient Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the General Data Protection Regulation 2018, Data Protection Act 2018 and Trust Policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

The PI at each site must ensure that only data labelled with the trial identifiers is received by the trial coordination team.

18.4 Data storage

All trial data will be entered and stored in a MACRO database.

19 Data Monitoring Committee/Trial Steering Committee

Members of these committees are listed in Section 3.

The ethical and safety aspects of the trial will be overseen by the DMC. The DMC will meet (virtually if necessary) at least annually to consider the safety data emerging from the trial. They may request unblinded data and more frequent listings if necessary. They report to the CI and the Trial Steering Committee. Full details of the DMC membership and remit can be found in the DMC Charter.

The TSC will provide overall supervision with respect to the conduct of the trial. Full details of the TSC membership and remit can be found in the TSC Charter.

20 Ethical & Regulatory considerations

20.1 Consent

The Informed Consent form must be approved by the REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator must ensure that each trial participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with their participation. A mental health advocate may assist the participant in understanding their rights in relation to taking part in the research, if requested.

The investigator or designee will obtain written informed consent from each patient or the patient's legally acceptable representative before any trial-specific activity is performed as outlined in section 12.1.2 of the protocol.

The informed consent form used for this trial and any change made during the course of this trial, must be prospectively approved by the REC. The investigator will retain the original of each patient's signed informed consent form.

Should a patient require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators.

If the trial requires documentation in a different language (other than English) the translation and back translation documents need to be reviewed and approved by the

Sponsor prior to use. All sections of the approved documents must appear in the translation. The translated version must be appropriately dated and include version controlled.

Any new information which becomes available, which might affect the patient's willingness to continue participating in the trial will be communicated to the patient as soon as possible.

20.2 Ethical committee review

Before the start of the trial or implementation of any amendment we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g., advertisements and GP information letters if applicable from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

20.3 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Development Safety Update Reports (DSURs) will be submitted to the MHRA in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

20.4 Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the REC and/or MHRA.

The only circumstance in which an amendment may be initiated prior to REC and/or MHRA approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the REC and/or MHRA approval has been obtained.

20.5 Peer Review

This trial design and protocol were reviewed by independent scientific reviewers of the Medical Research Council, the funders of the trial.

20.6 Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

20.7 GCP Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with your Trust's policy.

21 Sponsorship, Financial and Insurance

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust and University of Cambridge.

The trial will be funded by the Medical Research Council, Developmental Pathway Funding Scheme: MR/N019067/1.

The trial is also funded by The Stanley Medical Research Institute: 22T-001

Biotest will provide IVIG and placebo preparations, including packaging.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

Patient travel expenses will be covered through the Cambridge University Department of Clinical Neurosciences, or via a delegate as appropriate.

22 Monitoring, Audit & Inspection

The investigator must make all trial documentation and related records available should an MHRA Inspection occur. Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the Sponsor's representative. All patient data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed and the monitoring frequency adjusted as necessary.

Remote monitoring will be conducted for all participating sites. The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the trial.

23 Protocol Compliance and Breaches of GCP

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used. Substantial protocol amendments would be sought from the MHRA and REC in the event of planned changes to eligibility criteria or restrictions.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time, but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay.

24 Publications policy

Ownership of the data arising from this trial resides with the trial team. On completion of the trial the data will be analysed and tabulated and a Final Trial Report prepared. The funders of the trial will be acknowledged. Participants will be informed of the outcome of the trial through our trial website.

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26 Appendices

26.1 Appendix 1 - Trial Management / Responsibilities

26.1.1 Patient registration/ Randomisation procedure

Following informed consent and confirmation of eligibility patients will be randomised into either the IVIG or placebo group of the trial via a web- based randomisation system. This will be done by the CI/PI and suitably trained site staff through a secure log-in. The CCTU coordinator and data manager will receive notifications of randomisations.

26.1.2 CRF Completion & Data management

All CRFs should be completed in the manner and timelines detailed in the CRF completion guidelines and sent to the CCTU coordinator by email. The local Principal Investigator will be responsible for overseeing the collection of accurate data at each participating site. The completed CRFs will be signed by either the PI or a suitably qualified and delegated member of their trial team. The Data management team at the CCTU will be responsible for checking CRFs, entering data into a trial specific database and issuing queries according to the trial Data Management Plan. Queries will be sent to participating sites for resolution.

26.1.3 Preparation & submission of amendments

The trial coordinator will be responsible for the preparation and submission of amendment documentation to the appropriate authorities. Approvals of these amendments will be disseminated by the trial coordinator to all participating sites for implementation.

26.1.4 Preparation and submission of Annual Safety Report/Annual Progress Reports

In collaboration with the CI, the trial coordinator will prepare the annual progress report (APR), DSUR and funder reports, and submit these within the appropriate timelines.

26.1.5 Trial Monitoring

The frequency, scope and method of monitoring will be determined by the Sponsor's trial level risk assessment and will be detailed in the trial monitoring plan. All participating sites will be monitored in accordance with the Sponsor's SOP.

26.1.6 Data protection/ confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the General Data Protection Regulation 2018, Data Protection Act 2018 and Trust policy with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

26.1.7 Trial documentation & archiving

All trial documentation will be retained in a secure location during the conduct of the trial and following end of trial, archived in accordance with the Sponsor's SOPs. Each participating site will be responsible for archiving the Investigator Site File and associated trial documentation.

26.2 Appendix 2 – Authorisation of Participating Sites

26.2.1 Required Documentation

Prior to initiating a participating site the following documentation is required:

- Principal Investigator and other key trial team staff CVs (signed and dated) and GCP certificates
- REC/HRA approval
- Competent Authority approval (e.g. MHRA)
- Local R & D approval or equivalent
- Participating Site Agreement executed, including pharmacy participating site agreement
- Patient Information Sheets and Informed Consent Forms on local headed paper
- Protocol signed and dated by PI
- Delegation of authority Log
- Confirmation of randomisation system training
- Trial-specific prescription

26.2.2 Procedure for initiating/opening a new site

When all the required approvals for the site are in place, prior to site opening, an initiation meeting will take place, either face to face or via a teleconference. This will be led by a member of the Trial Coordinating team with as many of the local team present as is practicable. This initiation meeting constitutes training for the trial and it is therefore imperative that all members of the trial team who will be involved in the trial are represented at the meeting. A log of attendees will be completed during the meeting. The presentation slides will be provided to the site in advance of the meeting. A trial initiation form will be completed for each site initiation meeting. Copies of all initiation documentation must be retained in the Investigator Site File.

The sponsor's regulatory green light procedure will be followed. Following the green light, the initial supply of IMP will be ordered for shipment to the site on the authorisation of the coordinating centre coordinator. Following confirmation of receipt of the IMP at site, the site will be opened for recruitment and the randomisation system opened to that site.

26.2.3 Principal Investigator Responsibilities

The Principal Investigator has overall responsibility for the conduct of the trial at the participating site.

In particular, the PI has responsibilities which include (but are not limited to):

- Ensuring the appropriate approvals are sought and obtained
- Continuing oversight of the trial
- Ensuring the trial is conducted according to the protocol
- Ensuring consent is obtained in accordance with the protocol and national requirements
- Ensuring that the ISF is accurately maintained
- Delegation of activities to appropriately trained staff (this must be documented on the signature and delegation of responsibility log)
- Providing protocol or specialised training to new members of the trial team and ensuring that if tasks are delegated, the member of staff is appropriately trained and qualified

- Appropriate attendance at the initiation meeting
- Ensuring appropriate attendance at the TSC/DMC meetings if required and ensuring appropriate safety information is made available to the coordinating centre team in advance of the meetings
- Dissemination of important safety or trial related information to all stakeholders at the participating site
- Safety reporting within the timelines and assessment of causality and expectedness of all SAEs

26.3 Appendix 3 – Annex B of CT Regulations – informed consent (version 3, 01 May 2008)

Conditions and principles which apply to the inclusion of an incapacitated adult in a clinical trial.

The following conditions and principles are listed in Part 5 of Schedule 1 to the Regulations and implement Article 5 of the EU Directive.

1. The legal representative has had an interview with the investigator, or another member of the investigating team, in which opportunity has been given to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted.

2. The legal representative has been provided with a contact point where further information about the trial may be obtained.

3. The legal representative has been informed of the right to withdraw the participant from the trial at any time.

4. The legal representative has given informed consent to the participant taking part in the trial.

5. The legal representative may, without the participant being participant to any resulting detriment, withdraw the participant from the trial at any time by revoking the informed consent.

> *[Note: Paragraphs 1-5 do not apply where treatment is being, or is about to be provided for a participant who is an incapacitated adult as a matter of urgency and, having regard to the nature of the clinical trial and of the particular circumstances of the case:*
>
> *(d) It is also necessary to take action for the purposes of the trial as a matter of urgency, but*
> *(e) It is not reasonably practicable to meet the conditions set out in paragraph 1-5, and*
> *(f) The action taken is carried out in accordance with a procedure approved by the ethics committee.]*

6. The participant has received information, according to his or her capacity of understanding, about the trial and its risks and benefits.

7. The investigator must consider the explicit wish of a participant capable of forming an opinion and assessing the information provided. This applies both to the wish of a participant to refuse to take part, or to withdraw from the trial at any time.

8. No incentives or financial inducements are given either to the participant or to the legal representative, except the provision of compensation for injury or loss.

9. There are grounds for expecting that administering the medicinal product to be tested in the trial will produce a benefit.

10. The trial is essential to validate data obtained (a) in other clinical trials involving persons able to give informed consent, or (b) by other research methods.

11. The clinical trial relates directly to a life-threatening or debilitating clinical condition from which the participant suffers.

Principles

12. Informed consent given by a legal representative shall represent the presumed will of an incapacitated adult.

13. The trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and the cognitive abilities of the patient.

14. The risk threshold and the degree of distress have to be specially defined and constantly monitored.

15. The interests of the patient always prevail over those of science and society.

26.4 Safety Reporting Flow Chart