SIGHT: Spatial Inattention Grasping Therapy for neglect post-stroke

Spatial Inattention Grasping Therapy (SIGHT) for rehabilitation of spatial neglect post-stroke: a randomised-controlled multicentre efficacy trial with embedded mechanistic study of determinants of therapy response

Version	1.0
Date	25/04/2025
Sponsor	University of East Anglia
Trial registration	[Trial registry name and identifier]
HRA/IRAS #	335220

Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:-

Deborah Clemitshaw	Sponsor's Representative	[insert signature]	[insert date]

Chief Investigator(s):-

Dr Stephanie Rossit	Chief Investigator	[insert signature]	[insert date]

Norwich Clinical Trials Unit:-

Matthew Hammond	CTU Director or Representative	[insert signature]	[insert date]
Allan Clark	Trial Statistician	[insert signature]	[insert date]

Table of Contents

1 Administrative information

This document was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol template Version 4.4. It describes the SIGHT trial, sponsored by University of East Anglia and co-ordinated by NCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to site investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at NCTU.

NCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials [1]. The SPIRIT Statement Explanation and Elaboration document [2] can be referred to, or a member of NCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act 2018, and the UK Policy Framework for Health and Social Care Research, the Mental Capacity Act 2005, Adults with Incapacity (Scotland) Act 2000, and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and NCTU.

Participating sites will inform NCTU as soon as they are aware of a possible serious breach of compliance, so that NCTU can fulfil its requirement to report the breach, if necessary, within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

1.2 Sponsor

University of East Anglia is the trial sponsor and has delegated responsibility for the overall management of the SIGHT trial to the Chief Investigator and NCTU. Queries relating to sponsorship of this trial should be addressed to the Chief Investigator or via the trial team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	ISRCTN tbc
Date of Registration in Primary Registry	Date when trial was officially registered in the primary registry.
Secondary Identifying Numbers	• Sponsor Identifier: R212454 • IRAS number 335220 • NIHR – NIHR159047
Source of Monetary or Material Support	NIHR Efficacy and Mechanism Evaluation (EME) Programme
Sponsor	University of East Anglia
Contact for Public Queries	sight@uea.ac.uk
Contact for Scientific Queries	Dr Stephanie Rossit Associate Professor School of Psychology University of East Anglia Norwich Research Park Norwich NR47TJ Email: S.Rossit@uea.ac.uk Tel: 01603 591674
Short Title or Acronym	SIGHT: Spatial Inattention Grasping Therapy for neglect post-stroke
Scientific Title	Spatial Inattention Grasping Therapy (SIGHT) for rehabilitation of spatial neglect post-stroke: a randomised-controlled multicentre efficacy trial with embedded mechanistic study of determinants of therapy response
Countries of Recruitment	United Kingdom
Health Condition(s) or Problem(s) Studied	Stroke patients experiencing spatial neglect or inattention
Intervention(s)	**Intervention Arm:** The SIGHT Intervention plus treatment as usual (TAU). The SIGHT intervention consists of 7 daily 30-minute sessions delivered by site trained staff over a 10-day period within acute or community hospitals. The patient will complete the SIGHT exercises with their less impaired arm using rods of varying lengths on a mat.

	Control Arm: Patients on the control arm will receive TAU.
Key Inclusion and Exclusion Criteria	Eligibility Criteria: • Aged at least 18 years at the time of consent • Stroke confirmed with clinical brain imaging (CT and/or MRI), not neck or brain vessel imaging (CTA, MRA, DSA) • Between 1-week and 60-days post-stroke • Signs of neglect on at least one of the following: o Star Cancellation ≤51, or o BIT Line Bisection score ≤7,or o Oxford Cognitive Screen cancellation accuracy score <42 and either Oxford Cognitive Screen Cancellation Object score >1 or < -1, or Oxford Cognitive Screen Cancellation Space score >3 or < -2 • Able to follow a one-stage command "*grasp this pencil/pen with your less affected arm*" as demonstrated by another • Able to sit with or without support in front of a table for 30 continuous minutes Exclusion Criteria: • Being discharged from in-patient hospital facility to home, or to an in-patient hospital facility that is not part of the regional participating hub, within the next 7 days • Enrolled on another interventional study targeting neglect • Limited life expectancy due to another illness or chronic condition making the 3-month follow-up difficult (e.g. widespread malignancy) • For mechanistic neuroimaging study only: Contraindications to taking part in MRI study as assessed by the local MRI safety questionnaire, e.g., non-MRI compatible pacemaker
Study Type	Phase II, multi-centre, 1:1 randomised, controlled, assessor-blind, 2-group (SIGHT+TAU and TAU alone) efficacy trial with an embedded mechanistic study to test determinants of therapy response
Date of First Enrolment	July 2025
Target Sample Size	206
Primary Outcome(s)	Difference between intervention and control group in change of neglect symptoms, measured with the Star Cancellation sub-test of the Behavioural Inattention Test (BIT) between baseline and immediately post-intervention.

Secondary Outcomes	The following **efficacy measures** will be captured at baseline, Day 11 and 12 weeks post-randomisation, unless stated otherwise:
	
	• Star Cancellation sub-test of the BIT
	• Oxford Cognitive Screen (OCS) cancellation task
	• Endpoint weightings line bisection task (LB)
	• Catherine Bergego Scale KF-NAP(CBS KF-NAP)
	• Stroke Impact Scale (SIS; only at 12-weeks post-randomisation)
	
	As part of embedded mechanistic sub-study and to determine if therapy response is modified by baseline behavioural and/or neuroimaging factors, the following **mechanistic measures** will be captured at baseline only:
	
	• NIH Stroke Scale/Score (NIHSS)
	• Perception-Grasping Dissociation task
	• Visual field assessment sub-test of the Vision Impairment Screening Assessment (VISA) tool
	• OCS
	• Gesture Recognition sub-test of the Birmingham Cognitive Screen (BCoS)
	• For sites that are able, the (optional) Computerised Extrapersonal neglect test (CENT)
	• Clinical brain imaging scans and reports (CT and/or MRI)
	• For those who are able and consent to MRI the following neuroimaging sequences will be acquired:
	  ○ Localisation/setup scans
	  ○ T1-weighted whole brain scan
	  ○ T2 FLAIR
	  ○ Diffusion weighted imaging scan (DTI)
	  ○ Resting-state functional MRI (rsfMRI)

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
Dr Stephanie Rossit	University of East Anglia	Chief Investigator
Prof Valerie Pomeroy	University of East Anglia	Stroke Physiotherapy Rehabilitation Trials/Co-Applicant
Dr Allan Clark	University of East Anglia	Senior Statistician, Co-Applicant
Prof Hugh Markus	Cambridge University	Stroke Medicine and Neuroimaging/Co-Applicant
Dr Davinia Fernandez-Espejo	University of Birmingham	Brain injury and Neuroimaging/Co-Applicant
Dr Kneale Metcalf	NNUH	Stroke Medicine/Co-Applicant
Prof Audrey Bowen	University of Manchester	PPI academic lead/Co-Applicant
Mrs Ann Bamford	University of Manchester	PPI stroke survivor lead/ Co-Applicant
Prof Fiona Rowe	University of Liverpool	Stroke Orthoptics Trials/ Co-Applicant
Dr Claire Howard	Northern Care Alliance NHS	Clinical Orthoptist/Co-Applicant
Prof Kate Radford	University of Nottingham	Stroke Occupational Therapy Rehabilitation Trials/Co-Applicant
Jennifer Crow	Imperial College London	Clinical Occupational Therapist/Co-Applicant
Prof Niall Broomfield	University of East Anglia	Clinical Psychology/Co-Applicant
Dr Daniel Tozer	University of Cambridge	MRI Physicist
Dr Erika Sims	NCTU	CTU Research Lead, Co-Applicant
Dr Gregory Howard	NCTU	SIGHT Trial Manager
Martin Pond	NCTU	Head of Data Management

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
Deborah Clemitshaw	University of East Anglia	Sponsor Representative
	NIHR EME	Funder: Research Manager

1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Dr Stephanie Rossit	University of East Anglia	Chief Investigator
Dr Erika Sims	NCTU	CTU Research Lead, Co-Applicant
Dr Gregory Howard	NCTU	SIGHT Trial Manager
Cecile Guillard	NCTU	Database Programmer
Hannah Clarke	University of East Anglia	SIGHT Research Associate
Martin Pond	NCTU	Head of Data Management

1.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
Dr Stephanie Rossit	University of East Anglia	Chief Investigator
Dr Erika Sims	NCTU	CTU Research Lead, Co-Applicant
Dr Gregory Howard	NCTU	SIGHT Trial Manager
Cecile Guillard	NCTU	Database Programmer
Hannah Clarke	University of East Anglia	SIGHT Research Associate
Prof Valerie Pomeroy	University of East Anglia	Stroke Physiotherapy Rehabilitation Trials/Co-Applicant
Dr Allan Clark	University of East Anglia	Senior Statistician, Co-Applicant
Prof Hugh Markus	Cambridge University	Stroke Medicine and Neuroimaging/Co-Applicant
Dr Davinia Fernandez-Espejo	University of Birmingham	Brain injury and Neuroimaging/Co-Applicant
Dr Kneale Metcalf	NNUH	Stroke Medicine/Co-Applicant
Prof Audrey Bowen	University of Manchester	PPI academic lead/Co-Applicant

Mrs Ann Bamford	University of Manchester	PPI stroke survivor lead/ Co-Applicant
Prof Fiona Rowe	University of Liverpool	Stroke Orthoptics Trials/ Co-Applicant
Dr Claire Howard	Northern Care Alliance NHS	Clinical Orthoptist/Co-Applicant
Prof Kate Radford	University of Nottingham	Stroke Occupational Therapy Rehabilitation Trials/Co-Applicant
Mrs Jennifer Crow	Imperial College London	Clinical Occupational Therapist/Co-Applicant
Prof Niall Broomfield	University of East Anglia	Clinical Psychology/Co-Applicant
Martin Pond	Norwich CTU	Head of Data Management

1.4.5 Trial Steering Committee

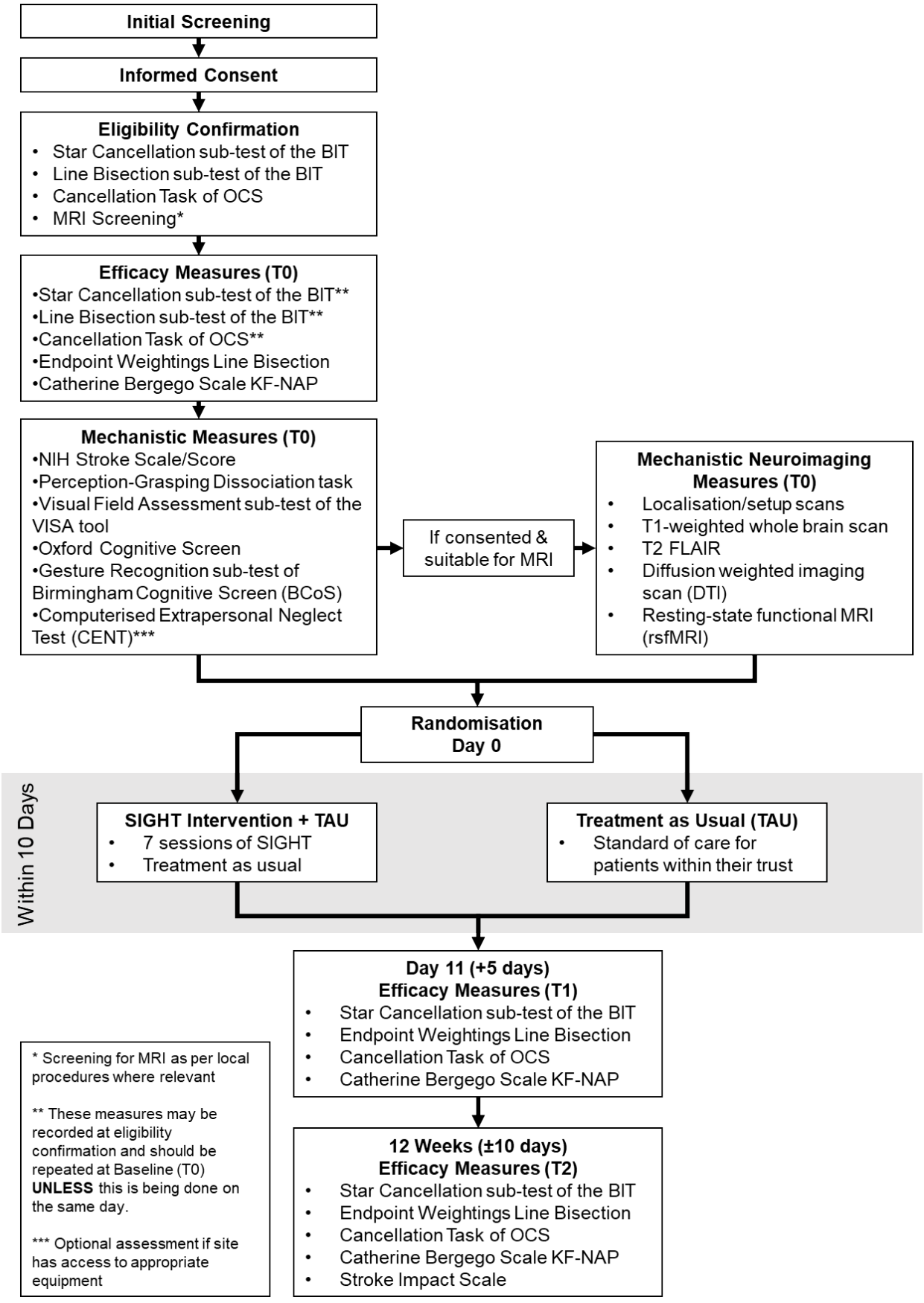
Name	Affiliation	Role and responsibilities
Prof. Keith Muir	University of Glasgow	Chair
Dr Stephanie Rossit	University of East Anglia	Chief Investigator
Prof. Amanda Farrin	University of Leeds	Independent Statistician
Prof. Nele Demeyere	University of Oxford	Independent Neuropsychology Expert
Mrs Sandra Ross	Norwich	Independent PPI partner
Mr Jim Waters	Norwich	Independent PPI partner

1.4.6 Data Monitoring Committee/Safety Committee

Name	Affiliation	Role and responsibilities
Prof. Rebecca Palmer	University of Sheffield	Independent Chair/Stroke Specialist Speech and Language Therapist
Dr. Charlie Welch	University of York	Independent Statistician
Prof. John Evans	University of Glasgow	Independent Neuropsychology Expert

2 Trial Diagram

SIGHT Patient Flow Diagram



3 Abbreviations

AE	Adverse Event
AR	Adverse Reaction
BIT	Behavioural Inattention Test
c-SIGHT	Computerised Spatial Inattention Grasping Therapy
CBS	Catherine Bergego Scale
CI	Chief Investigator
CM	Centimetres
CRF	Case Report Form
CT	Computerised tomography
CTA	Clinical Trial Authorisation
DMEC	Data Monitoring and Ethics Committee
DTI	Diffusion tensor imaging
EDI	Equality, diversity and inclusivity
EHR	Electronic Health Record
EME	Efficacy and mechanism
ESOC	European Stroke Organisation Conference
GCP	Good Clinical Practice
HRA	Health Research Authority
ICH	International Conference on Harmonisation
IPS	Intraparietal Sulcus
ITT	Intention to Treat
JLA	James Lind Alliance
KF-NAP	Kessler Foundation Neglect Assessment Process
LoS	Length of hospital stay
MRI	Magnetic resonance imaging
MRICROn	Open-source cross-platform medical image viewer
NAE	Notifiable Adverse Event
NCTU	Norwich Clinical Trials Unit
NHS	National Health Service
NICE	National Institute for Health and Care excellence
NSF	Norwich Science Festival
OCS	Oxford Cognitive Screen
PI	Principal Investigator
PID	Participant Identification Number
PIS	Participant Information Sheet
PPI	Patient and public involvement
PROMS	Patient Reported Outcome Measures
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
R&D	Research and Development
RCT	Randomised controlled trial
REC	Research Ethics Committee
ROI	Region of interest
rsfMRI	Resting state functional magnetic resonance imaging
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIGHT	Spatial Inattention Grasping Therapy
SIS	Stroke impact scale
SPM	Statistical parametric mapping
SSA	Site Specific Approval

SSNAP	Sentinel stroke national audit
T0	Timepoint for baseline measures
T1	Timepoint for measure immediately after intervention phase
T2	Timepoint for measures 12 weeks after end of intervention phase
TAU	Treatment as usual
TMF	Trial Master File
TMG	Trial Management Group
ToR	Terms of Reference
TSC	Trial Steering Committee
UEA	University of East Anglia
VISA	Visual impairment screening assessment

4 Introduction

4.1 Background and Rationale

Spatial neglect post-stroke: a world-wide problem with considerable unmet need. Stroke is the largest cause of adult disability worldwide. The latest estimate from the World Stroke Organization is that there are over 100 million people living with stroke, which affects 1 in 4 individuals, and its prevalence is estimated to double by 2035. Each year in the UK, 100,000 people suffer a stroke, and two thirds of survivors leave hospital with a disability [62]. There are 1.3 million stroke survivors in the UK and 300,000 people are living with stroke-related disability in England alone [4, 62]. The estimated annual cost of stroke is £26 billion, with £21 billion spent on rehabilitation and long-term care [63]. Thus, stroke rehabilitation is a research priority for stroke survivors, carers, the NHS, and UK government [3-6]. While physical and language impairments after stroke are seen easily, cognitive effects are often hidden and need further researching [5-6]. Consequently, rehabilitation and cognition were the key focus of the NHS Research Demand Signalling and the James Lind Alliance (JLA) Stroke Priority Setting in partnership with the Stroke Association [5-6].

This efficacy trial is directed at one of the most frequent and disabling cognitive impairments post-stroke: spatial neglect or inattention. Neglect affects 1 in 3 stroke survivors and is defined as an inability to orient and attend to stimuli, including own body parts, people, and objects, on the side of the body most affected by the stroke [7-8]. Neglect may improve within the first three months post-stroke, but for 40% of individuals it remains a persistent problem even one-year post-stroke [8-12]. People with neglect are usually unaware of their disorder, and therefore the condition differs from a visual field deficit (e.g., hemianopia) by which patients lose parts of their vision but are aware and thus more readily able to compensate for their blind field [42].

However, it is recognized that neglect is a heterogeneous condition with symptoms varying according to lesion location and co-morbidity with other post-stroke deficits such as in vision and cognitive abilities [57]. Neglect is now considered a syndrome with multiple sub-types, such as egocentric and allocentric neglect, now recognized in the NICE Guidelines as different presentations of the syndrome [42]. People with egocentric neglect miss objects located on the side of space opposite to their stroke (body-centred), whereas people with allocentric neglect miss one side within objects regardless of their location (object-centred) [42]. However, neglect interventions are prescribed based on presence of neglect and not according to sub-types of the condition – neglect is considered one disease and treated as a “one-size-fits-all" approach. Consequently, there has been no improvement in the outcomes of people with neglect. Compared to other stroke survivors, people with neglect present longer-lasting disability, poorer motor recovery, longer length of inpatient hospital stay, lower functional independence, decreased community mobility and are less likely to return to work [38-40]. Our patients tell us: “It’s terrifying, I bump into people”, and “there’s not enough support”. Their unpaid carers suffer long-term burden and stress [41]. Neglect has been consistently identified by stroke survivors, carers, and clinicians as one of the top unmet health needs and a research priority in stroke [13,34-38].

With an estimated 390,000 stroke survivors suffering from neglect in the UK, and 30 million worldwide, the condition poses an enormous challenge for healthcare. The recognition of neglect sub-types in clinical guidelines is a step-change in thinking that permits an

opportunity to identify and manage different presentations of the syndrome and better understand the mechanisms of its recovery so that targeted rehabilitation can be provided as part of patient-centred care.

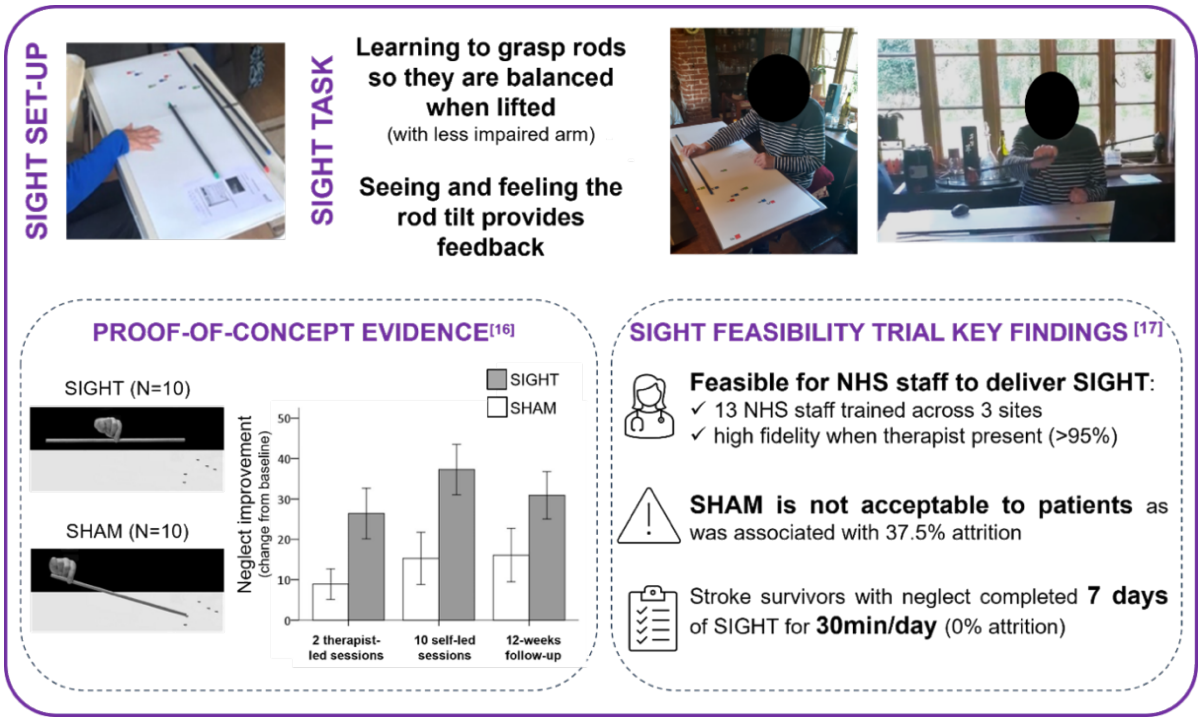
Current practice for spatial neglect rehabilitation is not evidence-based.
There is currently no clinically proven intervention for improving neglect post-stroke. In the last century, many approaches have been developed for its rehabilitation, but as concluded in the latest Cochrane review, most of the 65 trials conducted are small studies (average sample size=30, max=69) and there is a lack of well-designed efficacy RCTs [14-15]. Clinicians are encouraged to follow the National Institute for Health and Care Excellence (NICE) Guidelines for stroke [42] which recommend education, training in compensatory strategies, cueing to the impaired side and offering patients interventions aimed at reducing the functional impact of the reduced awareness (e.g., visual scanning training, limb activation, sensory stimulation, eye patching, prisms and prism adaptation, mirror therapy), ideally in the context of a clinical trial. Indeed, both the 2016 and 2023 NICE guidelines acknowledge the low-quality evidence available to guide clinical practice stating that there is some very limited evidence that cognitive rehabilitation may have an immediate beneficial effect on tests of neglect [14-15]. However, these guidelines conclude that there is insufficient high-quality evidence to recommend any specific interventions to increase independence and that larger RCTs with high quality research design and reporting are required [42].

SIGHT shows promise at reducing spatial neglect: proof-of-concept and feasibility evidence.
Over the last decade we have worked with stroke survivors, their unpaid carers, and stroke clinicians to develop Spatial Inattention Grasping Therapy (SIGHT; Fig.1). SIGHT is a simple, low-cost, and portable therapy that aims to improve neglect via repeated exercises of grasping-to-balance rods with the less affected arm [16-17]. SIGHT equipment consists of 3 rods and a laminated mat placed on a table (Fig.1). Due to their neglect, patients initially grasp the rod off-centre causing it to tilt when lifted. Feeling and seeing the rod tilt provides feedback, cueing patients to self-correct their grasp until rod balancing is achieved, which in turn increases attention to the affected side. Patients learn to balance the rods themselves and no therapist feedback is provided.

Our published proof-of-concept study [16] showed that SIGHT was promising at reducing neglect. Twenty stroke survivors were randomly allocated to an experimental (who received SIGHT) or a SHAM group (N=10 each). The SHAM group was asked to grasp one end of the rod only (on their spared side) without balancing it. Training was delivered by a researcher in participants' own homes for two sessions and then participants self-administered for 10 sessions over two weeks. Significantly greater neglect improvements were found after SIGHT when compared to SHAM in neglect scores (p=0.018, η_p^2=0.27). In our just completed pilot c-SIGHT feasibility trial [17] we tested feasibility of an RCT of computerised versions of SIGHT vs. SHAM. Five clinical centres recruited neglect patients, and the interventions were delivered by a therapist in people's own homes. Blinded-assessors measured outcomes at baseline, post-intervention and at 1-month post-training. We trained 13 staff to successfully deliver c-SIGHT with high fidelity and blinding of participant and assessors was 100% successful. Eleven stroke survivors with neglect finished the trial, but the SHAM intervention proved to not be acceptable to patients as it was

associated with high attrition (37.5% patients dropped out due to dislike of SHAM). The SIGHT group completed 7 days of c-SIGHT (30min/day) on average over a 10-day period with high fidelity (>95%) and 0% attrition (all 6/6 allocated patients completed c-SIGHT) showing that c-SIGHT is feasible and acceptable to patients. This pilot feasibility study thus laid the foundation for the proposed efficacy trial.

Figure 1. SIGHT set-up, task, and evidence. For a short video demo of SIGHT please click here



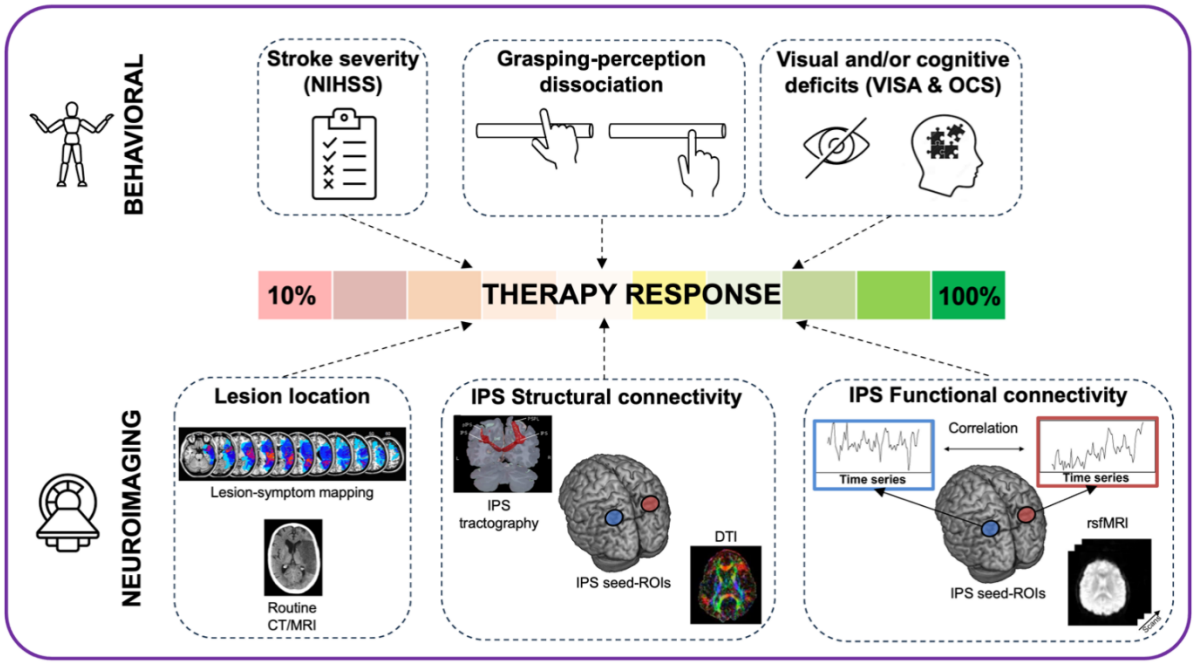
SIGHT and spatial neglect recovery: mechanistic evidence.
SIGHT is based on replicated findings that people with neglect are better in reaching and grasping actions than perceptual estimation tasks [18-24]. Specifically, they show a perception-grasping dissociation: when perceptually judging the middle of a rod they have larger errors than when grasping its middle [18-20]. It is thought that grasping and balancing the SIGHT rods gives neglect patients access to sensory information (e.g., visuomotor, proprioceptive) not available during perceptual tasks [16;18-20]. In other words, learning to balance the rods improves attention. This agrees with a neuroscientific model of vision that perception and action rely on visual processing by the ventral occipital-temporal and dorsal occipital-parietal streams respectively [25]. In fact, we and others have repeatedly shown that grasping involves the intraparietal sulcus (IPS) [24-27], a region that is structurally intact in most neglect cases [12;29;52] which may explain the spared grasping ability [21]. Based on our recent neuroimaging work showing that IPS represents how to correctly grasp objects for use [26], it is thus reasonable to assume that SIGHT may rely on the structural and functional integrity of this region, but this remains untested.

Stroke lesion locations associated with poor neglect recovery include damage to right superior and middle temporal gyri, basal ganglia, inferior occipitofrontal fasciculus/extreme capsule, or uncinate fasciculus [12]. Examining structural connectivity with diffusion tensor imaging (DTI) tractography has also highlighted that damage within white matter long-range and projection pathways, for example in the right superior longitudinal fasciculus (SLF) and

superior fronto-occipital fasciculus (SFO), is also relevant as it is significantly associated with severity of both egocentric and allocentric neglect [54]. In addition, resting-state functional magnetic resonance imaging (rsfMRI) studies in neglect have repeatedly shown that the connectivity of the structurally intact IPS to other brain regions within the damaged hemisphere seems key [28-30;58]. Specifically, interhemispheric (left-right) functional connectivity between the IPS and the rest of the brain is the most robust correlate of neglect deficits at 2 weeks post-stroke (r=0.55; p<0.001, N=25 neglect patients [28]). In fact, interhemispheric (left-right) functional connectivity between the IPS and the rest of the brain even predicts neglect improvement at 12-weeks post-stroke (r=0.58; p<0.001, N=25 neglect patients [28]).

Thus, the mechanistic study embedded into the proposed efficacy trial aims to test if both behavioural and neuroimaging measures can be used as determinants of therapy response (Fig.2). Our testable hypothesis, based on the neuroimaging studies reviewed above, is that neglect patients with structural or functional damage to IPS and/or its projections will benefit less from SIGHT [16]. Notably, it is important to acknowledge, as highlighted above, that the neglect syndrome does not occur in isolation, but is often accompanied by other post-stroke visual and cognitive deficits (e.g., hemianopia and executive functioning) which also further impede stroke recovery and functional outcome [57]. Thus, to carefully examine the impact of these factors, our mechanistic study will combine innovative neuroscience and clinical expertise to characterize each patient's residual IPS structure and function, perception-grasping dissociation, cognitive and visual profile and stroke severity, and test if these measures can determine response to SIGHT, following MRC and American Society of Neurorehabilitation guidelines [31-33].

Figure 2. Mechanistic study of determinants of response to therapy.



4.1.1 Explanation for choice of comparators

Currently there are no established interventions for neurorehabilitation of spatial neglect. Having established proof-of-concept and feasibility of SIGHT [16-17], we will now test its efficacy in reducing neglect in a robust adequately powered RCT in tightly controlled conditions of secondary care acute stroke units with a therapist present delivering the intervention in a highly standardised way. NICE guidelines recommend that stroke rehabilitation should be started early after stroke, be provided daily with the aiming to deliver 45 minutes per day of occupational therapy (OT) to all patients in the acute setting [42].

Stroke neurorehabilitation, including for spatial neglect, is not standardised and can vary dependent upon the preferences of the individual therapist. In our previous pilot, we attempted to control for therapist preferences for treatment of spatial neglect by using a sham control as the comparator. However, a high attrition rate was observed in the sham arm indicating poor acceptability. For this trial we will therefore use usual care as the comparator and will record daily rehabilitation therapy received in both arms between baseline and first outcome measures. Differences in duration and type (motor, psychological including cognitive, vision, scanning, communication/speech and language) of rehabilitation may be adjusted for in the analysis.

Most of the intervention trials for neglect in the WHO clinical trial register are proof-of-concept or feasibility studies with small sample sizes (average=32). Only two large RCTs are currently active: one in Spain with a target of 102 testing the effects of optokinetic stimulation using virtual reality and one in Germany with a target of 120 investigating galvanic vestibular stimulation which both use a sham control which does not reflect usual care. In contrast to these and other neglect therapies, SIGHT is one of the very few therapies designed with input from people with neglect, is simple and easy to administer, low cost (SIGHT rods and mat=£50) and portable, so if shown effective has the potential to transform neglect therapy worldwide.

4.2 Objectives

This multicentre RCT aims to investigate the clinical efficacy of SIGHT on post-stroke neglect when delivered by a therapist in tightly controlled within-hospital settings, whilst simultaneously determining the causes of differing responses to therapy between individuals. Our primary research aims are to:

(1) determine whether SIGHT in addition to TAU produces greater reduction in neglect than TAU alone (i.e., standard occupational therapy for neglect).

(2) determine whether benefits from SIGHT are still evident at the 12-week follow-up after the intervention ends.

(3) determine if therapy response is modified by: (a) lesion location; (b) left and right IPS functional connectivity; (c) left and right IPS structural connectivity; (d) perception-grasping dissociation; (e) stroke severity, (f) visual and/or (g) cognitive deficits.

Our testable hypotheses, generated by our early phase work and neuroimaging studies [16,19-20,26-27], are that:

(1) when added to treatment as usual (TAU), 30 minutes/day of SIGHT for 7 days (over a 10-day period) will produce greater reduction in neglect than TAU alone.

(2) patients with impaired IPS structure or function will benefit less from SIGHT.

4.3 Trial Design

This is a multi-centre randomised, controlled, assessor-blind, 2-group (TAU alone and SIGHT+TAU) efficacy trial with an embedded mechanistic study to test determinants of therapy response.

Participants will complete efficacy and mechanistic measures at baseline (T0). Where NHS trusts have the capacity and participants are able and consent to an MRI, they will complete mechanistic neuroimaging measures at baseline (T0) as well. Participants will be randomised, considered Day 0, to one of the two groups after baseline measures are completed. The intervention group will receive seven 30-minute SIGHT sessions over a 10-day period. Both groups will receive usual care (TAU). The efficacy outcomes taken at baseline will be repeated at Day 11 (T1) and 12 weeks (T2) post-randomisation.

Randomisation will be implemented by a secure web-based service provided by the NCTU after T0 measures are collected. Randomisation sequence will be stratified by clinical centre and will balance the following evidence-based factors across groups: age (<65 or ≥65), neglect severity (0-25 very severe or 26-51 less severe on Star Cancellation Test [17]) and preservation of the IPS (yes or no) assessed with routine clinical imaging. Age and neglect severity are included as these have been shown to significantly impact stroke recovery [59;38-39]. IPS lesion is included to balance our groups for the mechanistic analysis. Time after stroke was not included as our inclusion criteria of participants being ‘less than 60-days post stroke’ will ensure that all participants will complete intervention within the first 90-days post-stroke (i.e., early subacute phase [32]), which is the recommended period for all stroke recovery trials as it is a critical time for neural plasticity [31-33]. In a similar vein, participants will also be ‘at least 1-week post-stroke’ thus avoiding the inclusion of the 30% of patients that show rapid neglect recovery in the first week post-stroke [86].

The research staff delivering therapy at each site will be notified of group allocation via the NCTU secure web-based service. Group allocation will be withheld from other members of the Trial Team, the recruiting staff in each stroke service and the blinded assessors. To reduce the risk of contamination, SIGHT will be delivered in a separate treatment room and onsite monitoring of intervention delivery will review trial progress and discuss the importance of this risk.

5 Methods

5.1 Site Selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to the CI and NCTU.

5.1.1 Study Setting

Participant recruitment will be from stroke centres in NHS trusts, within wards and community hospitals across the UK.

The trial has been designed to allow T1 and T2 assessments to be delivered where the patients are discharged to (e.g., own homes) avoiding additional travel to hospital settings and thus reducing the burden on participants. Baseline assessments and interventions are delivered while the patient is within hospital settings to maximise controlled conditions and avoid additional travel to hospitals or transfer by ambulance for MRI.

Both sites with and without MRI can participate as only a subsample of patients (80) are required to meet the target for the MRI mechanistic sub study.

5.1.2 Site/Investigator Eligibility Criteria

To participate in the SIGHT trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the SIGHT Trial Management Group (TMG) and that are defined below.

Trial sites meeting eligibility criteria will be issued with the SIGHT local information pack needed by the Research and Development Department (R&D) of their Trust to enable the Trust to provide confirmation of capacity and capability to undertake the study.

Some sites for this study have been preselected based on their ability to recruit sufficient participants to the trial and/or having an interested principal investigator. The following sites will be included: Norfolk and Norwich University Hospital; Cambridge University Hospital; Imperial College Healthcare Trust; Salford Royal Hospital; Nottingham University Hospital; and Birmingham Community Healthcare Trust. To achieve our target, we will need at least 8 acute and 8 community centres and as such additional sites will need to be opened.

5.1.2.1 Principal Investigator's (PI) Qualifications and Agreements

The investigator(s) must be willing to sign an investigator statement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, familiarity with the appropriate use of any investigational products, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

5.1.2.2 Resourcing at site

The investigator(s) should be able to demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period (i.e., the investigator(s) regularly treat(s) the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to

conduct the trial properly and safely including separate staff for delivery of assessments and intervention. The minimum expected per site:

- Demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period (i.e., the investigator(s) regularly treat(s) the target population)
- A named clinician is willing and appropriate to take Principal Investigator responsibility
- Suitably experienced and trained staff are available to recruit participants, enter data and undertake trial procedures as detailed in this protocol:
    - Trained staff who can deliver the baseline assessments and intervention
    - Trained staff who can deliver the blinded assessments at T1 and T2 (including outside of recruiting hospital, e.g., patients' own homes)
- The site should have a separate room to deliver the SIGHT intervention
- The site should have space to store the assessment and therapy materials
- Site team willing and able to take steps to avoid unintentional unblinding on patient files or Electronic Health Records (EHR) system (e.g., not record SIGHT intervention delivery on patient notes)
- The site should have sufficient data management resources to allow prompt data return to NCTU

Optional

- Sites able to deliver the (optional) CENT measure should have access to a 40inch TV screen and be able to have patients approximately 170cm away from this to complete the test. Additionally, sites should have access to a laptop to run the CENT application on, a HDMI cable to connect the laptop to the screen, and a mouse for the participant to use. UEA will provide the CENT measure free of charge.

For sites participating in mechanistic MRI sub study only:

- the site should have sufficient access to a 3T MRI scanner and be able to deliver the sequences listed in this protocol (T1, T2-Flair, DTI and rsfMRI)

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details. The local site team should communicate changes in staff, delegated to undertake activities for the SIGHT trial, to the trial team. Further trial specific training of local site staff will be provided by NCTU as necessary.

The site should have sufficient data management resources to allow prompt data return to NCTU.

5.1.2.3 Training for staff on recruitment and baseline and follow-up assessments

Training for recruitment will be provided by the NCTU and members of the research team. Initial training will be provided during the start-up phase of the trial and staff undertaking recruitment will be required to maintain a current Good Clinical Practice certificate. Online videos and textual resources will be available to recruiting staff throughout the trial.

Research staff will be trained in delivering the baseline and outcome assessments. Blinding of assessors for complex interventions such as the SIGHT intervention can be challenging due to site resources and unintended feedback from patients. Where possible, baseline measures and randomisation will be undertaken by staff separate to those staff in

undertaking the outcome measures at T1 and T2 timepoints. For T1 and T2, assessors will be requested to indicate whether they have been unblinded to the treatment arm prior to starting the measures.

5.1.2.4 Training for Staff delivering the SIGHT Intervention

Site staff will be trained to deliver the intervention. This training will comprise of a therapy manual and video supported by online/in person training. The intervention may be delivered by staff undertaking baseline measures and randomisation, but not outcome measures at T1 and T2 timepoints. We will follow a 'train-the-trainer approach' with one lead therapist at each site being trained to be able to train new staff coming into the trial.

Following training, site staff will be asked to demonstrate competency in applying SIGHT. Catch-up meetings with site intervention delivery teams will help to address any issues with delivery and discuss the importance of reducing risk of contamination. A fidelity checklist will be completed at the first and last session and will be monitored by the central team, and intervention delivery teams will be contacted about deviations. No formal education in stroke care is required to deliver SIGHT, as the intervention is easy to administer. The lead therapist at each site will be asked to randomly check throughout the trial if the intervention is being delivered as per protocol by SIGHT therapists.

5.1.2.5 MRI site set-up

MRI set-up support will be provided to sites by the MRI physicist. Local MRI support at each site will work with the central support to modify/develop the required sequences, which will be matched as closely as possible to other sites accepting that there will be differences based of scanner manufacturer/model. Set-up scans on healthy volunteers (same person at each site, where possible) will be performed and analysed to determine that a) scans are of acceptable quality and b) the quantitative results are consistent with other sites. Once this process is completed, approval of the MRI protocol will be given by the central MRI physicist.

At sites with ethical approval for imaging healthy volunteers for the purpose of technical development, the site PI will be responsible for seeking local approval for set-up scans on healthy volunteers. Where a site does not have such approval, sites can be provided with the SIGHT healthy volunteer PIS and consent form to provide to healthy volunteer(s). Where a healthy volunteer has provided informed consent for a setup scan at one site, should this volunteer undergo a scan at one or more other sites for setup purposes, a copy of the consent form can be provided to other sites.

Consent will be sought for the MRI set-up scan and for the arising data to be shared with the research teams at the Universities of East Anglia, Cambridge and Birmingham.

5.1.2.5.1 Incidental findings during set-up scans

Heathy volunteers will be made aware that the setup scans will not be reviewed by radiologist although there is the possibility for incidental findings to be identified. The volunteer will be asked to provide consent to be advised of any incidental findings, and ideally to provide GPs details, although this will be optional. Volunteers will be advised that their GP will only be contacted in the event of an incidental finding.

5.2 Site approval and activation

On receipt of the signed investigator statement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial manager or delegate will notify the PI in writing of the plans for site initiation. Sites will not be permitted to recruit any participants until a letter for activation has been issued. The Trial Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor, HRA, by the regulatory authorities (as appropriate), and which was given favourable opinion by the Research Ethics Committee (REC). The PI or delegate must document and explain any deviation from the approved protocol and communicate this to the trial team at NCTU.

A list of active sites may be obtained from the SIGHT Trial team.

5.3 Participants

5.3.1 Eligibility Criteria

206 participants will be recruited from NHS stroke units by RDN staff or clinicians in the stroke service from either acute or community hospital settings. The eligibility criteria have been informed by our pilot c-SIGHT feasibility trial and are designed to be as inclusive as possible to match our trial sample to the 'real' clinical population for whom SIGHT would be suitable if it were available as part of NHS routine stroke rehabilitation.

Patient information sheets and informed consent forms are adapted for people with aphasia post-stroke and those without capacity. We will use aphasia friendly documents as they facilitate maximum engagement of participants with visual, cognitive and/or communication impairments which has proved to be most efficient for both patients and staff as seen in our previous work [17]. We will also implement consent by personal consultee for those without mental capacity to consent. This will be implemented in response to feedback from PPI representatives in our c-SIGHT feasibility trial and follows other stroke trials (such as SPATIAL - the largest RCT on spatial neglect in the UK to date [56]). Consenting patients will be asked to identify a partner, relative or friend who is in regular contact with the participant. If the patient loses capacity, consultee assent will be sought from the partner, relative or friend for the remaining outcome measures.

Patients who lack capacity were included in our c-SIGHT and SPATIAL feasibility trials and we did not find specific compliance issues in relation to the intervention or to OT in general. Including stroke survivors without capacity will increase recruitment of people with spatial neglect who tend to have more significant cognitive issues than other stroke survivors and have so far been excluded from taking part in rehabilitation trials. In addition, our budget also includes the cost of translation services for people who cannot communicate in the English language. Finally, SIGHT intervention will be delivered either in acute or community hospital settings. Together, these procedures will ensure that our trial is directed at all stroke survivors regardless of level of stroke severity, disability and communication ability. Some attrition is anticipated, therefore competitive recruitment across sites will continue until 206 participants has been reached and the trial team will monitor recruitment figures to ensure recruitment will be stopped.

Potential participants and/or consultees will be identified by staff members familiar with the trial and the relevant departments in NHS institutions. Identification will utilise paper or electronic hospital records. Staff will check the clinical information and check eligibility criteria against the study criteria. Stroke research nurses and study coordinators will assist in patient recruitment and receiving consent as well as collection of baseline data.

To increase accessibility to the study, poster, leaflets, or audio/video may be used to inform participants of the trial offering a variety of ways to show prospective participants information regarding SIGHT.

Potential participants and/or consultees may be provided with study information either in person or by post/email. All potential participants will be offered the opportunity to discuss the advantages and disadvantages of study participation with a member of the research team and/or their physician before providing consent.

5.3.1.1 Participant selection

There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

Investigators are encouraged to contact the SIGHT Trial Team for guidance in assessing eligibility in relation to exclusion criteria prior to approaching the patient about the trial if required.

5.3.1.2 Participant Inclusion Criteria

- Aged at least 18 years at the time of consent
- Stroke confirmed with clinical brain imaging (CT and/or MRI), not neck or brain vessel imaging (CTA, MRA, DSA)
- Between 1-week and 60-days post-stroke
- Signs of neglect on at least one of the following:
    - Star Cancellation Score ≤51, or
    - BIT line bisection score ≤7, or
    - Oxford Cognitive Screen Cancellation accuracy score <42 and either Oxford Cognitive Screen Cancellation Object score >1 or < -1, or Oxford Cognitive Screen Cancellation Space score >3 or < -2
- Able to follow a one-stage command “grasp this pencil/pen with your less affected arm” as demonstrated by another
- Able to sit with or without support in front of a table for 30 continuous minutes

5.3.1.3 Participant Exclusion Criteria

- Being discharged from in-patient hospital facility to home, or to an in-patient hospital facility that is not part of the regional participating hub, within the next 7 days
- Enrolled on another interventional study targeting neglect
- Limited life expectancy due to another illness or chronic condition making the 3-month follow-up difficult (e.g. widespread malignancy)

For mechanistic neuroimaging study only:

- Contraindications to taking part in MRI study as assessed by the local MRI safety questionnaire (e.g., non-MRI compatible pacemaker)

5.3.1.4 Co-enrolment Guidance

Patients enrolled in the SIGHT trial are not permitted to be co-enrolled in other neglect interventional trials. For patients co-enrolled in any other trials considered for participation in SIGHT, or for patients participating in SIGHT considered for co-enrolment in other studies, permission should be sought from the Trial Management Group.

5.3.2 Screening Procedures and Pre-randomisation Investigations

Written informed consent/consultee agreement to enter and be randomised, if appropriate, into the trial must be obtained from participants or consultee in the case of adults lacking capacity to consent, after explanation of the aims, methods, benefits and potential hazards of the trial and **BEFORE** any trial-specific procedures. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as a usual standard of care.

The site staff will maintain a screening and recruitment log. Screening and recruitment data will be shared with the central trial team enabling NCTU to monitor activity and recommend appropriate action in a timely manner to the Trial Management Team.

5.3.2.1 Initial screening activities

Initial screening of potentially eligible participants will include a check of patients notes to confirm:

- evidence of stroke including review of radiology reports to confirm stroke lesion is visible on clinical scan
- patient meets remaining eligibility criteria where information is available
- for sites participating in the mechanistic study only, suitability for MRI (according to local procedures)

Potentially eligible participants will be provided with participant information sheet. All patients pre-screened will be recorded in the screening log.

5.3.2.2 Consent and Eligibility Confirmation

Once initial screening is complete, the following activities will be undertaken:

- Written informed consent or consultee assent will be obtained to participate
- Star Cancellation sub-test of the BIT
- Line bisection sub-test of the BIT
- Cancellation Task of Oxford Cognitive Screen
- For sites participating in the mechanistic study only, if patient is suitable and consents for MRI, complete screening for MRI (according to local procedures)

5.3.2.3 Eligible patient progression to baseline measures

Patients providing consent and meeting the minimum definition for visual neglect (Star Cancellation Score ≤51, or BIT line bisection score ≤7, or Oxford Cognitive Screen Cancellation accuracy score <42 and either Oxford Cognitive Screen Cancellation Object score >1 or < -1, or Oxford Cognitive Screen Cancellation Space score >3 or < -2) will complete the baseline measures and have relevant data collected as listed below before randomisation can occur:

- Clinical and Demographic data
- If baseline measures are not being undertaken on the same day as eligibility confirmation screening measures, repeat these:
    - Star Cancellation sub-test of the BIT
    - Line Bisection sub-test of the BIT
    - Cancellation Task of Oxford Cognitive Screen (CT-OCS)
- Endpoint weightings line bisection task
- Oxford Cognitive Screen (OCS)
- Catherine Bergego Scale KF-NAP (CBS KF-NAP)
- NIH Stroke Scale/Score (NIHSS) extracted from clinical records (most recent only)
- Perception-Grasping Dissociation task
- Visual field assessment sub-test of the Vision Impairment Screening Assessment (VISA) tool
- Gesture Recognition sub-test of the Birmingham Cognitive Screen (BCoS)
- ***Optional:*** Computerised Extrapersonal Neglect Test (CENT)
- Pseudonymised clinical brain imaging scans (CT and/or MRI) uploaded to UEA via *Image Exchange Portal*
- Pseudonymised clinical brain imaging scan (CT and/or MRI) reports uploaded to database
- Confirmation yes/no of lesion in the Intraparietal Sulcus (IPS)
- MRI eligible patients at sites participating in mechanistic study will have the following MRI neuroimaging sequences before baseline measures are obtained:
    - Localisation/setup scans
    - T1-weighted whole brain scan
    - T2 FLAIR
    - Diffusion weighted imaging scan (DTI)
    - Resting-state functional MRI (rsfMRI)

5.4 Interventions

There are two trial arms:

Arm A –Standard care, treatment as usual (TAU)

Arm B – SIGHT Intervention + TAU

5.4.1 Arm A – Standard care, treatment as usual

Participants allocated to Arm A will only receive TAU according to NICE guidelines [42] as provided routinely in their clinical centre. TAU will be recorded for each patient and at site level.

5.4.2 Arm B – SIGHT Intervention + treatment as usual (TAU)

Participants allocated to Arm B will receive SIGHT for 7 days (30min/day) in addition to TAU over a 10-day period.

The staff delivering SIGHT will set-up the intervention in a separate room to reduce contamination (e.g., patients in Arm A being unblinded). The daily location of therapy delivery will be recorded in the CRF.

The SIGHT therapy involves repeated grasping and moving rods using the less affected arm. Three black lightweight wooden rods are used in different repetitions according to a pre-specified checklist. The therapist simply informs the participant about instructions following a pre-specified checklist and records the number of repetitions completed in each repetition and session.

5.4.2.1 Dose Interruptions and Discontinuations

In cases where participants are unable to complete the 7 sessions within the 10-day window (e.g., due to illness), the intervention team can administer additional therapy sessions to replace the missed sessions. Efficacy measures will still be undertaken between day 11 and day 16 even if intervention delivery is delayed. Therapists delivering intervention will not communicate delays in intervention delivery to blinded assessors undertaking the outcome measures at T1 and T2.

Consistent with intention to treat analysis, patients who decline to continue the intervention (i.e. discontinuations) but who agree to completion of follow-up measures will remain in the trial.

5.4.3 Accountability

Database checks will be built in to notify NCTU operations and relevant site staff of participants allocated to the intervention arm and when follow up assessments are due.

5.4.4 Compliance and Adherence

Therapists will be trained to deliver the intervention therapy during face-to-face training sessions. Additional online support for therapists will be provided during additional face-to-face training where requested and considered necessary by the intervention team. There will also be regular check-in meetings with SIGHT trained therapists and blinded assessors, separately, to monitor progress and address queries. Most therapy staff are rotational so it is highly likely that the staff who are originally trained will rotate during the duration of the study. As noted above we will use a train the trainer approach and lead site therapist will train any new staff joining the study to deliver the SIGHT intervention and randomly check this is done according to protocol.

Intervention **ADHERENCE** and **FIDELITY** will be monitored closely by the staff delivering the therapy using our existing checklists [16] during the first and last therapy sessions [17;56]. This data will be uploaded to the REDCap database at the University of East Anglia (UEA) and used to measure fidelity with SIGHT instructions and set-up. This will also capture the patient's level of engagement and fatigue.

5.4.5 Concomitant Care

All participants will receive treatment as usual for their care regardless of randomisation into this trial.

5.4.6 Protocol Treatment Discontinuation

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. However, an individual participant may stop treatment early or be stopped early for any of the following reasons:

- A new diagnosis of a pathology or adverse event that impacts the participant's ability to take part in the trial or confounds response to SIGHT, e.g., cancer, upper limb fracture.
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment.
- Withdrawal of consent for treatment by the participant.
- Participant moves out of catchment area of clinical centre (acute or community).
- Death

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Data collected up to the date of withdrawal will be retained and included in data analysis.

5.5 Outcomes

5.5.1 Primary Outcomes

The primary outcome measure is the **Star Cancellation sub-test of the Behavioural Inattention Test** [43]. This is a quick 5-min sensitive paper-and-pencil measure of neglect [46-47] that is clinically meaningful and has been sufficiently validated in the stroke population thus being suitable as a primary outcome measure of neglect reduction. This test was also used in our proof-of-concept study [16], informed the sample size calculation of the proposed RCT, as it is the most widely used test for neglect assessment in clinical practice [49] and is recommended as a primary neglect assessment by the European Academy of Neurology [50]. The test has excellent test-retest reliability [66], correlates well with the Barthel Index [64] and was found to be the best predictor of functional outcome when compared to other neglect tests as measured by the modified Barthel Index of Self-Care [48].

5.5.2 Secondary Outcomes

5.5.2.1. Efficacy measures

Following recommendations from the European Academy of Neurology [50], our three secondary outcomes will measure the impact of SIGHT on everyday life ability, using the CBS KF-NAP [30min; 51, 88-89], and on other neglect tests, including endpoint weightings line bisection task [5min; 78-79] and egocentric and allocentric neglect measured with the OCS Cancellation task [3min; 45]. Moreover, at 12 weeks follow-up, we will also collect the SIS [20min;83] to capture therapy effects on functional independence and mood to inform a phase III effectiveness trial.

- **The endpoint weightings line bisection (LB) task** [78-79] is a quick (5min) paper-and-pencil measure involving participants marking the middle of lines presented centrally (**aligned with** patients' midline) or shifted to the left or right of the patient's

midline. A bias to the side of the brain lesion is interpreted as a symptom of neglect. In our proof-of-concept study of SIGHT, LB was sensitive to therapy effects [16]. LB will be administered at baseline, T1 and T2.

- The **CBS KF-NAP** is a scale completed by a clinician that measures neglect during everyday-life activities (30min; 51, 88-89). The clinician observes the patient perform a list of 10 self-care activities that involve movements with upper and lower limbs in various positions (e.g., dressing, eating). The CBS KF-NAP was recommended by our PPI group and Occupational Therapist co-applicant as a clinically relevant measure of neglect in everyday life and judged by our PPI group as an important outcome for this trial. The CBS KF-NAP has excellent internal consistency [68], is sensitive to neglect [65], has excellent inter-rater reliability [67] and shows excellent correlation with Barthel index [51]. CBS KF-NAP will be administered at baseline, T1 and T2.
- The **OCS Cancellation task** is a quick (3min) paper-and-pencil sub-test of the OCS sensitive to neglect and with good test-retest reliability [45] and, in contrast to the other measures included, can distinguish between egocentric (space-centred) and allocentric (object-centred) sub-types of neglect. This measure will be administered at baseline, T1 and T2. There are two parallel versions of this test, and these will be alternated to reduce learning effects.
- The **SIS** (20min; at T2 only) is a stroke-specific patient reported outcome measure which assesses multidimensional stroke outcomes [83]. We have previously administered this scale to stroke survivors with neglect in our proof-of-concept and feasibility studies [16,17]. The SIS has been shown to have excellent internal consistency, excellent concurrent validity with SIS scores significantly correlating with the Barthel Index, the Functional Independence Measure and Fugl-Meyer Assessment [83]. The SIS includes a domain on emotion (9 items) which specifically enquires about feelings, mood, and ability to control emotions. Importantly, the emotion domain of the SIS shows excellent correlations with the Geriatric Depression Scale and the SD-36 Mental Health [83]. To reduce patient burden, we propose collecting the SIS at T2 only, and as in our c-SIGHT trial, via post [16]. Mail administration of the SIS has been shown to be feasible with missing items low [84]. As in our c-SIGHT trial, the blinded assessor will check its completion during the T2 visit and administer the scale or any missing items if incomplete.

5.5.2.2 Mechanistic measures (baseline only)

The mechanistic measures of determinants of response to therapy (Fig.2) will be acquired at baseline (T0) only, and include for all participants the NIHSS, a perception-grasping dissociation task (5min), the visual field VISA sub-test (5min), the OCS (15min), the Gesture Recognition sub-test of the BCoS (5 min), the (optional) CENT (5min) and the stroke lesion location (extracted from clinical scans and reports). For those who are able and consent to MRI we will also acquire a multimodal neuroimaging protocol (30min) measuring structural and functional IPS connectivity.

- **NIHSS** will be extracted from participants medical files and used as measure of stroke severity as recommended [31].
- The **perception-grasping dissociation task** (5min) consists of asking patients to either point to centre of a rod or reach for the rod using a pincer grip, as if to lift the rod so it would be balanced. [19-20, 80]. The rods are placed on a mat with their

centre shifted into the patient's affected hemispace. The deviation from the centre is recorded by therapist in eCRF. The task was adapted from studies showing that neglect is reduced when participants reach to grasp the centre of rods to balance them compared with when they point to the perceived centre [19-20, 80]. We hypothesize that patients who present smaller dissociations between the two tasks may benefit less from SIGHT.

- The **VISA visual field sub-tes**t (5min) is an 'aphasia friendly' and stroke validated measure of visual field deficits (e.g., hemianopia quadrantanopia) [44]. It involves a 5-minute test, where an examiner moves a target inward from the visual field peripheries to determine visual field deficits, finger counting in each visual field quadrant and a qualitative response from the patient of whether the sides of the examiner's face are seen equally e.g. is one side of the face more blurred.
- The **OCS** is an established quick (15min) cognitive screen consisting of 10 tasks encompassing five cognitive domains: attention and executive function, language, memory, number processing, and praxis [45]. The OCS was devised to be inclusive and un-confounded by aphasia and neglect. The OCS offers advantages over other screening tools in terms of ease of completion and feasibility for stroke survivors with physical, language or visuospatial impairments [69]. Moreover, the OCS is more sensitive than the Mini Mental State Examination at detecting cognitive deficits post-stroke [70] and assesses stroke-specific cognitive deficits not assessed by the Montreal Cognitive Assessment or the Addenbrookes Cognitive Examination [71].
- The **gesture recognition sub-test of the BCoS** (5min) will be used to provide quick and valid way to detect apraxia using procedures designed to be inclusive for patients with aphasia and/or spatial neglect [76]. Participants will view familiar gestures (object and non-object related) and asked to choose their meaning. As we are recruiting both right, left and bilateral hemisphere strokes this will help examine whether those with apraxia in our sample are able to benefit from SIGHT.
- **CENT** (5min) is a sensitive computerised 'aphasia friendly' measure of neglect of far space (or extrapersonal neglect) that has been validated in stroke and shown to predict stroke recovery and ADL deficits [77,87]. Participants are asked to use a mouse to click on targets on a screen. The scores are automatically generated.
- The **clinical brain imaging scans (CT and/or MRI) and their reports** will be extracted and used to map the stroke lesion location. Lesions will be manually delineated by UEA team on the structural scan using open-source cross-platform medical image viewers such as MRICROn 72]. Then, the checked lesion maps will be normalized to stereotaxic space using the age-specific template within the Statistical Parametric Mapping Software (SPM) clinical toolbox developed for stroke lesion-symptom mapping studies [73]. Routine clinical brain scans have been demonstrated to be of sufficient quality for lesion mapping research [74-75] and will ensure that lesion mapping can be performed for the full sample (N=206), instead of only those who complete the MRI (N=80), giving us sufficient power (minimum recommended N=100 [75]) for determining the lesion locations significantly associated with lower therapy response.
- **Mechanistic neuroimaging MRI** measures will be acquired at sites who are participating in this sub-study and will cover structural, diffusion and functional brain imaging. Patients who consent and have no MRI-contraindications will be transported to the 3T MRI facility within the hospital they are in. The entire neuroimaging protocol

will be completed within approximately 30min, but 1hr has been allocated to allow patient positioning and removal from the scanner which can take longer in disabled patients. Earplugs and cushions will be provided for comfort. Patients will be given a squeeze emergency ball in their spared hand to alt the scanning and asked to relax while keeping their head still. Head motion will be monitored throughout data acquisition and feedback provided as necessary via the intercom. The neuroimaging modalities selected are feasible in stroke survivors with neglect [28-30] and are recommended for inclusion in stroke trials [31]. Their combination will provide the richest and largest neuroimaging dataset in neglect post-stroke (leading samples published in separate studies to date: structural MRI=68 [53]; structural DTI=38 [54]; rsfMRI=25 [28]). The neuroimaging mechanistic measures will include a series of scan sequences:

- T1-weighted whole brain scan for alignment to normalised space of remaining neuroimaging data (7min). The scan will be a 3D scan with resolution of 1x1x1 mm3 and provide good WM/GM contrast
- T2 FLAIR (5min). The scan will have a resolution of approximately 1x1x3 mm3, it should provide good lesion contrast.
- Diffusion weighted imaging scan (DWIDTI; 8min) for white matter tractography. The sequence should have approximately 60 gradient directions and 3-5 b=0 scans, resolution should be approximately 2x2x2 mm3. It is likely to require some form of parallel imaging to meet the timing requirements. The plan is to do a single shell of b=1000 s/mm2, however if all sites are able then a multi-shell sequence with a second, larger, b-value will be considered.
- Resting-state functional MRI (rsfMRI; 10min) to measure changes in blood oxygenation associated with intrinsic brain activity (i.e., in the absence of an explicit task or stimulus). Again, the resolution should be approximately 2x2x2 mm2, with approximately 250-300 volumes.

Anonymised neuroimaging data will be sent to UEA research team via the Image Exchange Portal and processed using specialist software such as SPM and FSL. We will use well-established pre-processing routines for motion-correction, co-registration, smoothing and temporal filtering, and standardised pipelines that facilitate comparisons across studies (e.g., fMRIprep). Regions of interest (ROIs) will be manually identified in each participant in left and right IPS (seed regions) by visual inspection of the T1 using established anatomical landmarks and then centring a sphere closest to the peak coordinates associated with neglect improvement [28]. ROIs overlapping with lesion will be excluded from analysis.

5.5.2.3 Safety measures

The following safety outcome measures will be collected:

- duration of hospital admission associated with the index stroke (comprising associated acute and community inpatient stays where appropriate)
- death, and cause of death where known,
- readmissions to hospital and primary cause of readmission,

5.5.2.4 Measures of Treatment As Usual (TAU)

TAU will be captured in two ways.

At **site level**, the **profile of TAU** (e.g., average neglect therapy time, frequency, type of therapy and location) will be recorded by the senior stroke occupational therapist at each centre at start of recruitment when the site opens, during the recruitment period, and at end of recruitment.

At **individual patient level**, the therapy delivery staff will record the frequency, duration, location, and overall content (e.g., visual and scanning therapies) of each TAU session the participant receives during the 10-day period of intervention using a study-specific therapy booklet placed in the patient's bedside developed with clinical teams and adapted from our c-SIGHT and SPATIAL feasibility studies.

5.6 Participant Timeline

Figure 3. Schedule of SIGHT enrolment, baseline assessments, allocation to treatment arm, intervention treatment period, and post-intervention assessments.

	STUDY PERIOD					
	Enrolment	Baseline	Allocation	Intervention	Post- Treatment	
TIMEPOINT	t_{-1}	T_0			T_1	T_2
Initial screen	X					
Informed consent	X					
MRI Screening	X					
Star Cancellation BIT	X	X**			X	X
BIT Line Bisection	X	X**				
OCS Cancellation	X	X**			X	X
Endpoint Weightings Line Bisection		X			X	X
Catherine Bergego Scale KF-NAP		X			X	X
Safety outcome measures		X		X	X	X
Stroke Impact Scale						X
Demographics		X				
Clinical Data		X				
Full OCS		X				
NIHSS		X				
VISA visual fields		X				

*CENT****		X				
Gesture recognition BCoS		X				
T1 Structural Weighted Scan		X*				
T2 FLAIR		X*				
Diffusion Weighted Imaging Scan		X*				
Resting-state Functional MRI		X*				
Allocation			X			
[Arm A – Treatment as Usual TAU]				X		
[Arm B – SIGHT Intervention + TAU]				X		

*Mechanistic neuroimaging measures only for participants who are suitable and consent at sites that have an available 3T MRI scanner.

** These measures may be recorded at screening/eligibility confirmation and should be repeated at Baseline (T0) unless screening/eligibility confirmation and T0 are done on the same day

*** Optional measure for sites that have the appropriate equipment

5.6.1 Patient Assessments

5.6.1.1 Screening and Consent

All the screening and consent procedures should be completed within the 1-week to 60 days post-stroke window. Once initial screening has been completed, informed consent to enter and be randomised into the trial must be obtained from the potentially eligible participants or their consultee after explanation of the aims, methods, benefits and potential hazards of the trial and before any trial specific procedures. In addition, if the participant agrees, a letter will be sent to the participant's GP detailing their involvement in the trial. The only procedures that may be performed in advance of consent being obtained are those that would be performed on all patients in the same situation as a usual standard of care.

5.6.1.2 Baseline (T0)

Once the participant or consultee has given informed consent/assent and eligibility has been confirmed (signs of neglect on at least one of the following: Star Cancellation ≤51; or BIT Line bisection score ≤7; or Oxford Cognitive Screen cancellation accuracy <42 as well as either Oxford Cognitive Screen Cancellation Object score >1 or < -1, or Oxford Cognitive Screen Cancellation Space score >3 or < -2), local site staff will collect the baseline measures consisting of: demographic and clinical data; Star Cancellation sub-test of the BIT; Line Bisection sub-test of the BIT; cancellation task of the OCS; endpoint weightings line bisection; the Catherine Bergego Scale KF-NAP (CBS KF-NAP); NIHSS; Perception-Grasping dissociation task; visual field assessment sub-test of the VISA tool; the Oxford Cognitive Screen (OCS), Gesture Recognition sub-test of Birmingham Cognitive Screen (BCoS) and the **optional** Computerised Extrapersonal neglect test (CENT). To account for patient fatigue, these measures can be grouped together and done at different times or on different days to allow for a rest period.

5.6.1.3 Randomisation – Day 0

The completion and submission of the baseline measures will enable the database randomisation notifying the trial team and local SIGHT intervention delivery staff of the patient's trial arm. Randomisation stratification will use trial site, age of patient, neglect severity (according to the Star Cancellation) and whether a lesion is present or not on the Intraparietal Sulcus (IPS).

5.6.1.4 Intervention and treatment as usual – within 10 Days Post-Randomisation

If a patient is allocated to the intervention arm, the SIGHT trained staff will deliver the SIGHT intervention over a 10-day period following randomisation. Treatment as usual will be recorded during this 10-day period for all patients on both arms of the trial.

5.6.1.5 Follow Up (T1) Efficacy Measures – Day 11 (+5 days)

All participants will have a visit from a blinded assessor on Day 11 (+5 days) post-randomisation. The blinded assessor will collect the efficacy measures: Star Cancellation test; endpoint weighting line bisection, OCS and the Catherine Bergego Scale KF-NAP.

5.6.1.6 Follow Up (T2) Efficacy Measures – 12 Weeks (±10 days)

All participants will have a visit from a blinded assessor at 12 weeks (±10 days) post-randomisation. The blinded assessor will collect the efficacy measures: Star Cancellation test; endpoint weighting line bisection, OCS; the Catherine Bergego Scale KF-NAP and the Stroke Impact Scale (SIS).

5.6.2 Early Stopping of Follow-up

If a participant chooses to discontinue their trial treatment, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer take the trial treatment. If, however, the participant exercises the view that they no longer wish to be followed up, this view must be respected and the participant withdrawn entirely from the trial. NCTU should be informed of the withdrawal using the appropriate SIGHT trial documentation as soon as possible. Deaths should also be reported as a withdrawal. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early.

Randomised participants who stop trial follow-up early will not be replaced. Recruitment will be monitored by DMEC and if recruitment is below expected due to drop-outs trial team may seek approvals to increase sample size.

5.6.3 Participant Transfers

If a participant moves from a consenting acute hospital setting to a linked community hospital setting making continued trial procedures at their consenting acute centre not possible, every effort should be made for them to continue the trial at the new location. Established communication and links between delegated sites will ensure patients flowing from acute to community will continue to receive the trial as expected through the duration of their participation. However, should a patient move from a consenting acute hospital to a site not participating in SIGHT, the patient will be withdrawn.

5.6.4 Loss to Follow-up

Every effort will be made by the research teams at sites to establish rapport with participants and/or consultees to emphasise the importance of trial procedures and follow up. Where patients may be discharged to a known community hospital setting, every attempt will be made to continue the trial with the participant and assessors will travel to patients' for follow up appointments at T1 and T2 if necessary.

5.6.5 Trial Closure

The end of the trial is defined as 6 months following the last follow-up visit of the last participant randomised, to allow for data entry and data cleaning activities to be completed.

5.7 Sample Size

The efficacy study is powered to detect a significant change from baseline to T1 between the intervention and control groups for the primary outcome of the Star Cancellation sub-test of the BIT [43]. Our sample size calculation is directly informed by our published proof-of-concept study [16] which found that the SIGHT+TAU group (N=10) had significantly greater neglect improvement on the BIT than the SHAM+TAU group (N=10; $F_{(1,18)}$=6.7, *p*=0.018, partial n^2_p=0.27; see Fig.1). Specifically, informed by this data we have assumed an effect of size of 0.6 (equivalent to partial n^2_p=0.27 [16]). Stroke (and neglect) recovery takes place most rapidly over the first 7 days post-stroke and has been shown to decrease at around 3 months post-stroke [32]. Early after stroke, it has been reported that between 2-days and 9-days post-stroke, 33% of patients with neglect significantly improve in the Star Cancellation Test (median Star Cancellation score at 2 days=31 and 9 days=47; cut-off=51; max=54), with 67% showing poor recovery (median Star Cancellation score at 2 days=26 and 9 days=35). The c-SIGHT feasibility trial data [17] shows that at 3-months post-stroke, 42% of neglect patients have recovered on the Star Cancellation Test (median score at 3 months=53) in line with a recent meta-analysis of 12 studies (N=262 patients, [85]). Thus, to accommodate the additional 10-15% natural recovery rate between 1-week and 3-months post-stroke, we reduced our effect size from 0.6 (estimated from PoC data at 3 months post-stroke [16]) by 15% to 0.51, which with 90% power at the 5% level of significance using a two-sample t-test requires 206 participants (103 per group), including a 20% dropout. The effect size of 0.51 represents a difference of approximately 6.1 points on the Star Cancellation sub-test assuming a SD of approximately 12 obtained from our previous studies [16,17]. As the proposed trial compares SIGHT+TAU and TAU alone we expect our effect size to be larger than the one found in our proof-of-concept study [16]. Natural recovery is further accounted for in the design as some neglect improvement will occur in both experimental and control groups in a similar way since they are balanced for neglect severity - a strong predictor of stroke recovery [38; see randomisation strata]. The intervention effect is additional to natural recovery. The 20% dropout rate is based on our feasibility trials in post-stroke neglect with an average of 17.5% dropout in experimental arm at the 12-week post-intervention follow-up (15% [17] and 20% [56]).

Regarding the mechanistic brain imaging, a sample of 40 per group, which includes 20% attrition, will provide greater than 90% power at 2.5% level of significance (as we have 2 correlations the significance level is adjusted) to detect a correlation of 0.58 between IPS structure and function and treatment response in each arm separately. This sample size is directly informed by published data showing that interhemispheric (left-right) functional

connectivity between the IPS and the rest of the brain predicts neglect improvement at 12-weeks post-stroke (r=0.58; *p*<0.001, N=25 neglect patients [28]). Importantly, the total sample size of 80 for the brain imaging study is feasible within our timeframe based on the FAST-Indicate EME stroke trial [55] and the published rates of 45% for MRI attrition in acute stroke [61]. Specifically, we expect that approximately 112 of the 206 recruited participants will be able and consent to undergo MRI and thus our sample size of 80 is achievable.

5.8 Recruitment and Retention

5.8.1 Recruitment

For the efficacy measures, we estimate that active clinical stoke centres will recruit on average 1.2 participants per site per month to reach the required 206 participants. Acute sites that confirm they have access to a 3T MRI facility are expected to recruit 0.6 participants per site per month for the neuroimaging mechanistic measures.

Considering length of acute hospital stay, a proportion of patients are repatriated to the stroke unit in their local community hospital very soon after their stroke, sometimes within 48-72 hours. Therefore, our trial design has considered patient discharge by: 1) adding costs for 8 stroke units in community hospitals so that patients who are discharged quickly from acute to community stroke units can continue taking part; 2) reducing intervention dosage to 7 sessions over 10 days so it is feasible within the average length of hospital stay of neglect patients at our sites, 21 days; 3) not recruiting patients expecting to be discharged to their own homes in the next 7 days. The baseline mechanistic neuroimaging data will be acquired before discharge from acute centres. Remaining baseline measures can be collected in acute or community centres. T1 or T2 measures can be collected in acute and community hospitals as well as outside of hospital settings (e.g., in patients' own homes).

5.8.2 Retention

To maximise retention and minimise loss to follow-up, funding has been allocated for visits at T1 and T2 to be conducted within patients' home where necessary. Also, pre-established relationships between acute and community hospitals will allow the patient data to continue to be collected and intervention sessions to conducted if they transfer between sites.

5.9 Assignment of Intervention

5.9.1 Allocation

5.9.1.1 Sequence generation -

Randomisation will be implemented by a secure web-based service provided by the NCTU after baseline measures are collected. The randomisation sequence will be stratified by clinical centre and will balance the following evidence-based factors across groups: age (18-64 or ≥65), neglect severity (0-25 very severe or 26-51 less severe on Star Cancellation Test [17]) and preservation of the intraparietal sulcus bilaterally (yes or no) as assessed by qualified staff in the routine clinical imaging (CT and/or MRI). Age and neglect severity are included as these have been shown to significantly impact stroke recovery [59;38-39]. IPS lesion is included to balance our groups for the mechanistic analysis. Time after stroke was not included as our inclusion criteria of participants being 'less than 60-days post stroke' will ensure that all participants will complete intervention within the first 90-days post-stroke (i.e., early subacute phase [32]), which is the recommended period for all stroke recovery trials as it is a critical time for neural plasticity [31-33]. In a similar vein, participants will also be 'at

least 1-week post-stroke' thus avoiding the inclusion of the 30% of patients that show rapid neglect recovery in the first week post-stroke [86].

5.9.1.2 Allocation concealment mechanism
Web-based. Will happen after completing the baseline measures.

5.9.1.3 Allocation Implementation
The participants will be allocated to the intervention by a process embedded in the web-based data management system. The randomisation code will be saved in the study database for later decoding. When a patient is randomised, an email will be sent to the appropriate assigned research team members for the patient, to alert the research team to the start of the intervention if allocated to Arm B.

5.9.2 Blinding
The research staff delivering therapy at each site will be notified of group allocation via the NCTU secure web-based service. Group allocation will be withheld from the blinded assessors. To reduce the risk of contamination, SIGHT will be delivered in a separate treatment room and onsite monitoring of intervention delivery will review trial progress and discuss the importance of this risk. Blinded assessors will only conduct assessments at follow-up visits T1 and T2.

5.9.3 Unblinding
While every effort will be made to ensure that site staff undertaking the efficacy assessments remain unblinded, these staff will be asked to record any occurrences of unblinding.

5.10 Data Collection, Management and Analysis
5.10.1 Data Collection Methods
Each participant will be given a unique trial Participant IDentification number (PID). Data will be collected at the time-points indicated in the Trial Schedule. Assessment scores should be entered into the REDCap database along with copies of each assessment for monitoring purposes. Baseline and follow-up assessments will be paper based and scored in blinded fashion.

The preferred method of data collection is direct online entry of data onto the central database, stored on servers based at NCTU by members of the SIGHT trial team working within each research site. Data may be entered onto paper Case Record Forms (CRFs) prior to entry onto the database, if paper forms are used, they must be transcribed. Staff will receive training on data collection and use of the online system (see Section 4.2).

Data collection, data entry and queries raised by a member of the SIGHT trial team will be conducted in line with the NCTU and trial specific Data Management Standard Operating Procedure.

Identification logs, screening logs and enrolment logs will be kept at the trial site on a secured computer or in a locked cabinet within a secured room if not incorporated in the database.

Participant identifiable data may be stored in the REDCap database to enable participants to be contacted by site staff for the purpose of trial delivery. There will be a clear logical

separation of participant identifiable data from the trial data which is uploaded to REDCap using restricted permissions.

Where there is a requirement for study materials to be stored and/or shared electronically outside of the study database (e.g. supporting materials shared via OneDrive, SharePoint or similar), the mechanism for achieving this will be appropriate in terms of governance, regulatory and legal compliance, and resource to administer it will be identified.

Clinical trial team members will receive trial protocol training. All data will be handled in accordance with the Data Protection Act 2018.

5.10.2 Data Management

Data will be entered under the participants' PID numbers onto the central database stored on servers based at NCTU. Transfer of all MRI and clinic brain imaging data between sites and UEA will be done via Sectra Image Exchange Portal (SIEP), a secure cloud-based NHS-compliant solution that ensures patient data security. Sites will pseudonymise scans prior to uploading to UEA servers. Access to the database, SIEP and brain imaging files will be via unique, individually assigned (i.e. not generic) usernames and passwords, and only accessible to members of the SIGHT trial team, and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected physically and environmentally in accordance with University of East Anglia's General Information Security Policy 3 (GISP3: Physical and environmental security).

The REDCap database [81-82] and associated code have been developed by NCTU Data Management, in conjunction with the SIGHT trial team. The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

After completion of the trial the UK database will be retained on the servers of NCTU for a period of at least a year after publication of the primary outcome, for on-going secondary analyses, after which the CI or their delegate will initiate a request for the study database to be archived by NCTU. It will then be taken offline and archived as per NCTU_DM WI_4_Electronic Archiving. A copy will be provided to Sponsor for facilitating data requests.

The identification, screening and enrolment logs, linking participant identifiable data to the pseudonymised PID, will be held centrally by NCTU in a database or at site in written form in a locked filing cabinet or electronically in password protected form. After completion of the trial the identification, screening and enrolment logs will be stored securely for 10 years and then securely deleted.

5.10.3 Non-Adherence and Non-Retention

Reasons for non-adherence will be recorded where possible. Primary outcome data will be recorded for all those randomised.

5.10.4 Statistical Methods

5.10.4.1 Outcomes

Analysis will be conducted according to random group allocation (intention-to-treat principle). Baseline characteristics of the participants will be summarised using descriptive statistics by groups, n (%) for binary and categorical variables and mean (SD)/median (QIR) for continuous variables. Flow of the participants through the trial will be reported using the CONSORT flow diagram. A descriptive summary of the treatment received as well as adherence and fidelity measures will be given. A full statistical analysis plan will be pre-registered prior to completion of data collection, thus adhering to open and replicable research practices.

The clinical efficacy analysis will compare continuous outcome variables between treatment groups, using a general linear model at each time-point separately adjusting for stratification factors. To account for potential TAU variability across sites, clinical centre will be used as a co-variate. The effect of treatment will be summarised using the adjusted mean difference and 95% confidence interval. Dependent variables will include: Star Cancellation score (primary), CBS KF-NAP score, line bisection error and OCS Hearts overall, ego- and all centric scores and SIS scores in each domain.

The evaluation of mechanistic determinants of response to therapy will be modelled using a general linear model using the following baseline data: structural connectivity as per fractional anisotropy of fibres connecting IPS seed-regions and defined areas in the rest of the brain; inter-hemispheric (left-right) functional connectivity as per time course correlations between IPS seed-regions and rest of the brain; perception-grasping score computed from difference in deviation from rod centre between grasping and perception; stroke severity; visual field VISA sub-test score; and, OCS domain scores. To determine if treatment effect is modified by these mechanistic variables, we will correlate change scores (from baseline to T1, i.e. therapy response; Fig.2) and each of these measures while regressing out lesion volume (computed from the lesion map) as lesion size correlates with stroke recovery [28]. Each data will be included separately and then data reduction methods will be applied so that all the measures can be included in a single model. The study investigating IPS will test effects in each arm separately as well as test for an interaction to see if the association is different in the two arms. In addition, to determine if lesion location predicts treatment response (hypothesis 2), we will use lesion-symptom mapping analysis and test if specific lesion sites are associated with smaller change scores/therapy response.

If patients receive less than 70% of the intervention, they will be included in the intention-to-treat efficacy analysis and T1 and T2 measures will still be collected and included in the mechanistic analysis to predict overall neglect recovery. An additional per-protocol analysis will be conducted in which these individuals will be excluded so that we can differentiate the effect of being allocated to the intervention (the intention-to-treat analysis) and the effect of the intervention if the participant, and therapist, adhere (the per-protocol analysis).

Site will be used as strata for the randomisation; this should remove any potential confounding for TAU variation across sites. In the analysis we will report the ‘dose’ given to the participants. We will carry out a per-protocol analysis including individuals who have received an appropriate dose of SIGHT (>70%). In the intervention group, we will correlate the amount of therapy received against the change in the primary outcome measure.

Missing data will be excluded in the primary analysis. However, the sensitivity of the missing data on the outcomes will be assessed by carrying out multiple imputation assuming that the data is missing at random. If we have reason to believe that the data is not missing at random, then pattern mixture models will be used to assess sensitivity.

Adverse events will be recorded including falls and classified in terms of seriousness and relatedness and a between group analysis will be conducted for those related to the study and overall to examine if therapy has an impact on number of falls.

5.10.4.2 Statistical Analysis Plan

A full statistical analysis plan will be drafted and approved by the trial's governance, .

5.10.4.5 Missing Data

Missing data will be excluded in the primary analysis. However, the sensitivity of the missing data on the outcomes will be assessed by carrying out multiple imputation assuming that the data is missing at random. If we have reason to believe that the data is not missing at random, then pattern mixture models will be used to assess sensitivity.

5.11 Safety

5.11.1 Data Monitoring for harm

The intervention being evaluated is a neurorehabilitation therapy for spatial neglect arising from stroke. In view of the nature of the population, which are all expected to be inpatients at the time of consent, and at risk complications arising from stroke leading to extended hospital stay, readmission to hospital following discharge and subsequent stroke, the intervention being a low risk neurorehabilitation therapy comprising of lifting, grasping and moving rods in a coordinated manner directed by a therapist and which has no additional risk over usual care (as confirmed in a pilot study), and the trial primary, secondary and safety outcomes we do not intend to collect any additional safety endpoints.

5.11.2 Safety reporting

Adverse events (serious and non-serious) will not be collected in this study.

This is a low-risk intervention. No specific risks, untoward incidents or adverse events related to the intervention were reported during development, testing and pilot work. Nine adverse events unrelated to the intervention were reported in the pilot including three deaths; five hospital admissions (due to new stroke event, infection, fall, progressive disease); and one participant was referred to end of life care'. The SIGHT neurorehabilitation intervention therapy is delivered to participants by trained therapists. If participants encounter issues with the materials provided, these will be reported by the therapist to the research team where they will be collated into an Incident Log. The participant has the right to decline any intervention at any time.

At the time of recruitment, all participants will be inpatients in acute or community hospitals. The occurrence of common complications arising from stroke, including: 1) clinical complications such as pneumonia, urinary tract infection, pressure damage and deep vein thrombosis; and 2) neurological complications such as malignant ischemic stroke and symptomatic haemorrhagic transformation, would not be influenced by intervention, although these complications may impact the delivery of the intervention. Reasons for an intervention session not being delivered as anticipated or stopped early will be recorded in the database.

However, as stroke and complications arising from the stroke, is associated with increased risk of death, increased duration of hospital stay (acute and community settings as appropriate), and readmissions, the following safety data will be collected during the study:

- death (and cause)
- length of hospital stay (comprising of total of acute and community inpatient settings as appropriate)
- readmissions to hospital (including reason)

Reasons for withdrawal will also be used to ascertain any potential safety issues, including referral to end of life care.

5.12 Data Monitoring

5.12.1 Data Monitoring Committee

Further details of the roles and responsibilities of the Data Monitoring Committee (DMC), including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the SIGHT DMC Terms of Reference (ToR).

5.12.2 Progression Criteria

Trial progress, including recruitment data collection and attrition rates, will be overseen by the Trial Management Group (TMG) consisting of the CI, co-applicants, NCTU staff and at least one PPI representative from the PPI Advisory Panel. Site and participant recruitment, randomisation, and intervention delivery and data collection will be monitored by NCTU and overseen by the trial team and Trial Management Group on an ongoing basis throughout the trial.

Potential mitigation(s) will be identified and implemented and may include replacing or adding additional sites to address site drop out or under-recruitment (tentative discussions with additional sites have been started) and addressing barriers or challenges to intervention delivery and/or data collection issues. Should any of the stop/go criteria fall into amber or red, progress, including mitigations implemented and planned will be discussed with, and advice sought from, the Trial Steering Committee. NIHR will also be approached to discuss feasibility to continue the trial should the stop/go criteria fall into amber or red.

STOP/GO CRITERIA			
By end of month 12 (6 months recruitment):	Green	Amber	Red
Sites open (target 6)	6	5	3
Patients randomised (target 206)	≥20%	≥12.5% and <20%	<12.5%
Median % Intervention sessions completed	≥75%	≥40% and <75%	<40%

(100% = 7 per patient)			
Primary outcome data completeness (T1)	>90%	≥80% and 90%	<80%

The wider PPI Advisory Panel will also meet every 4 months and once per year outreach drop-in sessions will be carried out in community settings to ensure views from a diverse pool of members of the public are incorporated into the trial. Trial Steering (TSC) and Data Monitoring Committees will be responsible for the provision of independent oversight of the trial. The TSC will be chaired by a clinical trialist and comprise two statisticians. There will be non-voting representation from the trial team and sponsor. The conduct of the oversight committees will follow the NCTU TSC/DMC terms of reference.

5.12.3 Quality Assurance and Control

5.12.3.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the SIGHT trial are based on the standard NCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

5.12.3.2 Central Monitoring at NCTU

NCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The trial database may also be programmed to generate reports on errors. Essential trial issues, events and outputs, including defined key data points, will be detailed in this Protocol and the SIGHT Quality Management and Monitoring Plan (QMMP).

5.12.3.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the SIGHT QMMP. The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority, NCTU must be notified as soon as possible.

5.12.3.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related

documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

5.12.3.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent trial oversight complies with the NCTU trial oversight policy.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the SIGHT Quality Management and Monitoring Plan.

5.12.3.4.1 Trial Management Team

The Trial Management Team (TMT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMT terms of reference.

5.12.3.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

5.12.3.4.3 Independent Trial Steering Committee

The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial to safeguard the interests of trial participants. The TSC provides advice to the CI, NCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

5.12.3.4.4 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to unblinded accumulating comparative data. The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the IDMC terms of reference. The IDMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

5.12.3.4.5 Trial Sponsor

The University of East Anglia (UEA) is the trial sponsor. The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. The Sponsor is responsible for ensuring that the study meets the relevant standards and makes sure that arrangements are put and kept in place for management, monitoring and reporting.

The UEA has delegated some Sponsor's activities to the CI and NCTU, these are documented in the SIGHT delegation of responsibilities.

6 Ethics and Dissemination

6.1 Research Ethics and Health Research Authority Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC and to HRA for approval. Any subsequent amendments to these documents will be submitted for further approval.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

6.3 Other Approvals

Documentation will need to be submitted to the R&D Department at each NHS Site in order to gain confirmation of capacity and capability prior to the study being initiated at that site. Confirmation from the site will take the form of a site agreement signed by both the Sponsor/NCTU and the relevant site.

A copy of the local R&D approval and of the Participant Information Sheet (PIS) and consent form on local headed paper must be forwarded to the co-ordinating centre before participants are randomised to the trial.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the NCTU Protocol Review Committee.

6.4 Amendments

Amendments to the Protocol and other documents (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) will be agreed by the TMG. Such amendments will be forwarded to the Sponsor for confirmation as to whether it is either substantial or non-substantial and will then be submitted to the Health Research Authority or Ethics Committee for categorisation and approval. Once the amendment has been categorised it will be sent to relevant sites for consideration in accordance with standard HRA processes and timescales. Amendments must not be implemented until HRA approval is received and sites have either confirmed acceptance or, no objection has been received within the defined timescale. Notification will be sent by NCTU to trial personnel to confirm when an amendment can be implemented.

6.5 Consent or Assent

Potential participants will be provided with a Participant Information Sheet (PIS) and given time to read it fully. For patients lacking capacity to consent, a consultee will be approached, provided a Consultee PIS and given time to read it fully. Following a discussion with a medical qualified investigator or suitable trained and authorised delegate, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent or consultee declaration will be obtained. During the consent process it will be

made completely and unambiguously clear that the participant or consultee on the participant's behalf is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

The PIS contains information about joining the Neurolab Future Research database, this is an existing database, whereby those on the database are contacted regarding research happening in the Neurolab and asked if they would like to participate. Joining the Neurolab Future Research database is optional, this is clearly stated within the PIS. The consent form/consultee declaration form contains a section where the participant/consultee can indicate whether the participant would like to join the database. Those on the database will not be contacted regarding future research opportunities until their participation in the SIGHT trial has finished.

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the participant information sheets and the participant or consultee will be asked to sign an updated consent/declaration form. These will be approved by the ethics committee prior to their use.

If a participant without capacity at the time of consent and for whom a consultee has given assent, regains capacity, consent will be sought.

A copy of the approved consent or declaration form is available from the NCTU trial team.

6.6 Confidentiality

Any paper copies of personal trial data will be kept at the participating site in a secure location with restricted access. Following consent, identifiable data will be kept on the trial database to allow authorised members of the trial team to contact participants to arrange appointments/assessments. Only authorised trial team members will have password access to this part of the database. This information will be securely destroyed 5 years after the end of the trial.

Confidentiality of participant's personal data is ensured by not collecting participant names on CRFs and limiting access to personal information held on the database at NCTU. At trial enrolment the participant will be issued a participant identification number, and this will be the primary identifier for the participant, with secondary identifiers of month and year of birth and initials.

It is possible that participants may disclose personal or sensitive information to the research team, RDN or local staff. This will be kept confidential, unless such information indicates harm to themselves or someone else. Additionally, if there are any unexpected results (e.g. an 'incidental finding' of signs of spatial neglect in those not suspected to have spatial neglect, or very low mood score), the participant will be informed. With the participant's consent, their GP will be informed in writing and take any further action they see necessary.

The participant's consent form will carry their name and signature. These will be kept on a database (for example eConsent) or at trial site, with a copy sent to NCTU (if held at site) for monitoring purposes. If a copy is kept at site, the copy at NCTU will be destroyed once checks are complete. Consent forms will not be kept with any additional participant data.

6.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

6.8 Indemnity

The University of East Anglia (UEA) hold insurances to cover participants for injury caused by their participation in clinical trials. Participants may be able to claim compensation if they can prove that UEA has been negligent. However, as the SIGHT trial is being carried out in NHS clinics, the clinics continue to have a duty of care to the participants in the trial. UEA does not accept liability for any breach in the NHS clinic's duty of care, or any negligence on the part of clinic employees, applying whether the clinic is an NHS trust or not. The does not affect the participants' rights to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UEA or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim the UEA's insurer, via the Sponsor's office.

NHS clinics selected to participant in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to UEA upon request.

6.9 Finance

This project NIHR159047 is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the MRC, NIHR or the Department of Health and Social Care.

6.10 Archiving

The Sponsor agrees to archive and/or arrange for secure storage of SIGHT trial materials and records for 10 years after the close of the trial unless otherwise advised by the NCTU. Sponsor retains responsibility for confirming when trial materials and records (including data) should be archived.

6.11 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG/TSC. Considerations for approving access are documented in the TMG/TSC Terms of Reference. Upon completion of the trial, all anonymised data will be made open access.

6.12 Ancillary and Post-trial Care

Following trial completion, all participants will continue their usual care in the acute or community hospitals or at home according to the stroke pathways in each area. No additional care or support is expected to be provided by the SIGHT trial.

6.13 Publication Policy

6.13.1 Trial Results

The results of the trial will be disseminated regardless of the direction of effect whilst the ownership of the data arising from the study resides with the SIGHT trial team. The publication policy will be in line with the rules of the International Committee of Medical Journal Editors and the Trial Management Group will decide on authorship with any difficulties being resolved by the Steering Committee.

6.13.2 Authorship

The Trial Management Group (TMG) will nominate a writing group, which will consist of members of the TMG and will be responsible for drafting the manuscript(s) for publication alongside other researchers involved in the specific work being written-up. The members of the writing group will be named on final publications.

6.13.3 Open and Reproducible Research

The full trial protocol, statistical analysis plan and anonymised datasets will be published in an open online repository.

6.14 Patient and Public Involvement

The core idea for SIGHT and this trial stems from discussions with, and suggestions from, stroke survivors, their unpaid carers, and clinicians. Recurring themes of the PPI events were that “there is not enough support available for people with neglect” and that there is a significant need for developing “therapies for neglect that patients can actually do”. “You shouldn’t underestimate just how significant of an advantage this would be to someone who had just had a stroke”.

We previously adopted an iterative co-design approach to ensure that SIGHT is user-friendly and acceptable for stroke survivors (Morse et al. 2022). We embraced user-centred design principles and incorporated feedback of stroke survivors (N=7), their unpaid carers (N=3) and stroke clinicians (N=6) in SIGHT design, set-up, materials, instructions, and dosage (Morse et al. 2022). The following are some examples of changes made to SIGHT based on PPI feedback: reduced the length of daily SIGHT training from one hour [16] to half-an-hour (maximum) since “it’s concentration that’s a killer”; simplified SIGHT instructions so they are understandable to people with language deficits; changed the colour of the SIGHT rods from light brown [16] to black to increase visibility.

Following these changes, we carried out a feasibility trial with interviews with 11 stroke survivors who completed the new version of SIGHT. All stroke survivors were able to complete SIGHT with some noting: ‘they’re the sort of things I enjoy … playing games’, ‘this movement has improved the situation of the left’, ‘the research gave me my life back and I can now drive again’.

The protocol proposed here has been shaped through an additional PPI consultation with stroke survivors (N=4), their unpaid carers (N=2), stroke clinicians with experience of neglect rehabilitation (N=5), our PPI co-applicant who is a stroke survivor, the clinical co-applicants, and the stroke teams at each recruiting site. During these meetings we discussed aspects of this trial including design, inclusion criteria, recruitment, outcome measures, involvement, and dissemination. Here are some examples of the changes incorporated:

- It was requested that we use the term ‘spatial inattention’ instead of ‘neglect’ in lay summary as the word ‘neglect’ has a negative connotation.
- It was requested that SIGHT efficacy is tested in hospital settings so that ‘rehabilitation is targeted to the patients who need it the most’ and given that “patients usually spend most of their day in hospital beds but should be doing more rehabilitation to increase their recovery”.
- It was requested that we include trial delivery costs for community sites to allow inclusion of stroke survivors discharged from acute settings before SIGHT completion.
- Stroke survivors requested that we add internet and printing costs for our PPI panel.
- It was requested that we include translation costs for participant facing materials including SIGHT instructions.
- It was requested that we add costings for portable picnic tables for SIGHT delivery (used in our feasibility study) so intervention can be administered without the need for desks.
- It was requested that we only include the VISA visual field sub-test (rather than the full VISA) to reduce session duration.
- It was requested that blinded assessors are costed at Band 7 given the expertise required to deliver the cognitive, visual and neglect assessments.

We will follow the NIHR-INCLUDE framework [60] to guide trial set-up and delivery, including recruitment and retention strategies. Our inclusive and diverse study-specific PPI advisory panel, led by a stroke survivor, will advise our approach. This panel will be supplemented by community outreach activities and advice from trusted community champions including stroke survivors from groups under-served in health and care research.

Bamford, Woodward-Nutt and Bowen will use an inclusive model of PCPI to reach out to communities that have been historically underrepresented and obtain their input into the study (see Fig. 4). This model has proved successful in engaging with individuals and groups in recent stroke studies in which we have been involved. We have developed close links with “community connectors” and a range of groups and organisations supporting and/or providing services for minoritised groups in Greater Manchester and will develop these links for SIGHT. We will consult with these groups either through direct outreach or through community connectors and will offer individual contact to anyone preferring this to group engagement.

6.14.1 Direct outreach (to groups):

We have links with several groups (including faith groups, stroke groups and local community groups) representing people from diverse backgrounds. Bamford and Woodward-Nutt will attend these to seek members of the advisory group, discuss the research, and obtain feedback on specific parts of the project outside of the advisory group.

6.14.2 Direct outreach (to individuals):

We recognise that some people find it difficult to engage in group settings therefore we will consult with stroke survivors, informal carers, and members of the public from diverse background in person and/or using remote technologies.

6.14.3 Community connectors:

Where community groups prefer to engage via a trusted person from their own community, Bamford and Woodward-Nutt will work with key members of these communities (community connectors) to explore how they can support us to engage with and obtain feedback from their communities.

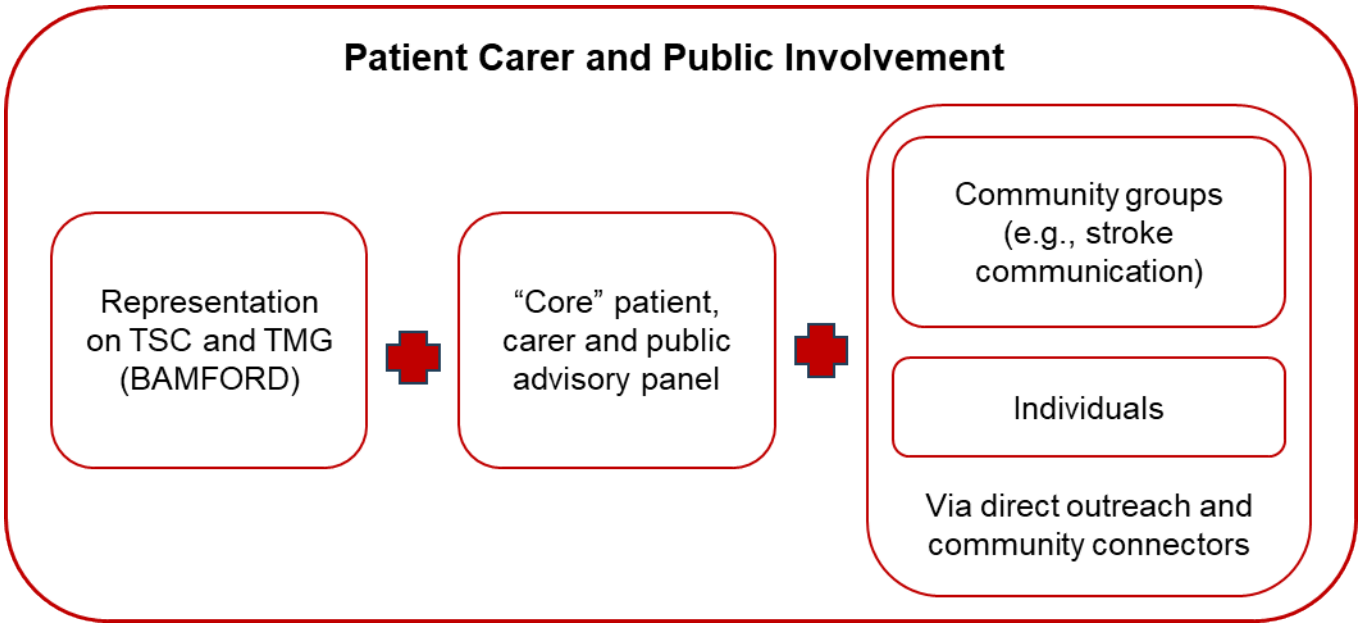
PCPI Advisory panel: Bamford and Woodward-Nutt will proactively recruit stroke survivors/ informal carers of stroke survivors from diverse backgrounds, including minoritised ethnic groups and cultural backgrounds, to the advisory panel utilising existing contacts across Greater Manchester and the wider research team's contacts. Should these strategies lead to an insufficiently diverse panel they may involve individuals from minoritised groups who have interest in, but do not necessarily have first-hand experience of stroke.

Membership of trial steering committee and trial management group: Bamford will be a member of both groups. She will feed information into and out of these groups from the advisory group, from the advisory panel and from outreach and community connectors.

Every effort will be made to ensure that all people eligible for inclusion in this trial, including under-served groups, will be offered the same opportunity to take part. We are in a great position to achieve this, having just completed our feasibility study on SIGHT with similar inclusion criteria and consent procedures and having a PPI lead with vast experience working with under-served groups. Recruiting centres will be reminded of the need to give that opportunity to all who meet the eligibility criteria for this trial. Training will be provided to site staff on inclusivity and ways in which they can facilitate, through partnership with carers or friends, inclusion of patients who have traditionally been excluded from research (e.g., those with vision, hearing loss, language impairments or significant cognitive issues).

Bamford will join all TMG meetings (PPI lead and stroke survivor) and two stroke survivors will be invited to attend all TSC meetings. The wider PPI Advisory Panel will meet every 4 months and once per year outreach drop-in sessions will be carried out in community settings to ensure views from a diverse pool of members of the public are incorporated into the trial. The PPI panel will advise on reducing barriers to participation.

Figure 4. Inclusive PCPI model



7 Ancillary Studies

8 Protocol Amendments

This is the first version. There are no previous versions.

9 References

1. Chan, A., Tetzlaff, J. M., Altman, D. G., Laupacis, A., Gøtzsche, P. C., Krleža-Jerić, K., Hróbjartsson, A., Mann, H., Dickersin, K., Berlin, J. A., Doré, C. J., Parulekar, W. R., Summerskill, W. S., Groves, T., Schulz, K. F., Sox, H. C., Rockhold, F. W., Rennie, D., & Moher, D. (2013). SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Annals of Internal Medicine*, *158*(3), 200. https://doi.org/10.7326/0003-4819-158-3-201302050-00583

2. Chan, A. W., Tetzlaff, J. M., Gøtzsche, P. C., Altman, D. G., Mann, H., Berlin, J. A., Dickersin, K., Hróbjartsson, A., Schulz, K. F., Parulekar, W. R., Krleza-Jeric, K., Laupacis, A., & Moher, D. (2013). SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ (Clinical research ed.)*, *346*, e7586. https://doi.org/10.1136/bmj.e7586

3. The United Kingdom Acquired Brain Injury Forum (UKABIF; 2018). *Acquired brain Injury and neurorehabilitation Time for change. All-party parliamentary group on acquired brain injury report.* United Kingdom Acquired Brain Injury Forum. https://ukabif.org.uk/page/time-for-change

4. Department of Health (DH; 2022). National Stroke Strategy. Department of Health. https://www.hse.ie/eng/services/publications/clinical-strategy-and-programmes/national-stroke-strategy-2022-2027.pdf

5. The Stroke Association, James Lind Alliance (2021). *Shaping stroke research to rebuild lives.* Stroke Association. https://www.stroke.org.uk/sites/default/files/research/stroke_priority_setting_partnership_full_report.pdf

6. NHS England and NHS Improvement (2022). *Research Demand Signalling: National Stroke Programme* (Report No. PAR687) . NHS England. https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2022/03/B0687-research-demand-signalling-national-stroke-progeamme.pdf

7. Appelros, P., Karlsson, G. M., Seiger, A., & Nydevik, I. (2002). Neglect and anosognosia after first-ever stroke: incidence and relationship to disability. *Journal of rehabilitation medicine*, *34*(5), 215–220. https://doi.org/10.1080/165019702760279206

8. Buxbaum, L. J., Ferraro, M. K., Veramonti, T., Farne, A., Whyte, J., Ladavas, E., Frassinetti, F., & Coslett, H. B. (2004). Hemispatial neglect: Subtypes, neuroanatomy, and disability. *Neurology*, *62*(5), 749–756. https://doi.org/10.1212/01.wnl.0000113730.73031.f4

9. Nijboer, T. C., Kollen, B. J., & Kwakkel, G. (2013). Time course of visuospatial neglect early after stroke: a longitudinal cohort study. *Cortex*, *49*(8), 2021–2027. https://doi.org/10.1016/j.cortex.2012.11.006

10. Rengachary, J., He, B. J., Shulman, G. L., & Corbetta, M. (2011). A behavioral analysis of spatial neglect and its recovery after stroke. *Frontiers in human neuroscience*, *5*, 29. https://doi.org/10.3389/fnhum.2011.00029

11. Della Sala, S., Beschin, N., & Cubelli, R. (2018). Persistent neglect in everyday life. *Cortex, 103*, 382–384. https://doi.org/10.1016/j.cortex.2017.09.010

12. Karnath, H., Rennig, J., Johannsen, L., & Rorden, C. (2011). The anatomy underlying acute versus chronic spatial neglect: a longitudinal study. *Brain*, *134*(3), 903–912. https://doi.org/10.1093/brain/awq355

13. Rowe, F. (2014) *Care provision and unmet need for post stroke visual impairment.* Stroke Association and Thomas Pocklington Trust. https://www.stroke.org.uk/sites/default/files/final_report_unmet_need_2013.pdf

14. Bowen, A., Hazelton, C., Pollock, A., & Lincoln, N. B. (2013). Cognitive rehabilitation for spatial neglect following stroke. *The Cochrane database of systematic reviews*, *2013*(7), CD003586. https://doi.org/10.1002/14651858.CD003586.pub3

15. Longley, V., Hazelton, C., Heal, C., Pollock, A., Woodward-Nutt, K., Mitchell, C., Pobric, G., Vail, A., & Bowen, A. (2021). Non-pharmacological interventions for spatial neglect or inattention following stroke and other non-progressive brain injury. *The Cochrane database of systematic reviews*, *7*(7), CD003586. https://doi.org/10.1002/14651858.CD003586.pub4

16. Rossit, S., Benwell, C. S. Y., Szymanek, L., Learmonth, G., McKernan-Ward, L., Corrigan, E., Muir, K., Reeves, I., Duncan, G., Birschel, P., Roberts, M., Livingstone, K., Jackson, H., Castle, P., & Harvey, M. (2019). Efficacy of home-based visuomotor feedback training in stroke patients with chronic hemispatial neglect. *Neuropsychological rehabilitation*, *29*(2), 251–272. https://doi.org/10.1080/09602011.2016.1273119

17. Morse, H., Pomeroy, V., Clark, A., & Rossit, S. (2021). A feasibility randomised controlled trial of a computerised spatial inattention grasping home-based therapy (C-Sight) for spatial neglect post-stroke: Trial update. *International Journal of Stroke*, *16*, 42. https://doi.org/10.1177/17474930211059996

18. Edwards, M. G., & Humphreys, G. W. (1999). Pointing and grasping in unilateral visual neglect: effect of on-line visual feedback in grasping. *Neuropsychologia*, *37*(8), 959–973. https://doi.org/10.1016/s0028-3932(98)00132-8

19. Robertson, I. H., Nico, D., & Hood, B. M. (1997). Believing what you feel: Using proprioceptive feedback to reduce unilateral neglect. *Neuropsychology*, *11*(1), 53–58. https://doi.org/10.1037/0894-4105.11.1.53

20. Robertson, I. H., Nico, D., & Hood, B. M. (1995). The intention to act improves unilateral left neglect: two demonstrations. *Neuroreport*, *7*(1), 246–248. https://doi.org/10.1097/00001756-199512290-00059

21. Harvey, M., & Rossit, S. (2012). Visuospatial neglect in action. *Neuropsychologia*, *50*(6), 1018–1028. https://doi.org/10.1016/j.neuropsychologia.2011.09.030

22. Rossit, S., Fraser, J. A., Teasell, R., Malhotra, P. A., & Goodale, M. A. (2011). Impaired delayed but preserved immediate grasping in a neglect patient with parieto-occipital lesions. *Neuropsychologia*, *49*(9), 2498–2504. https://doi.org/10.1016/j.neuropsychologia.2011.04.030

23. Rossit, S., Malhotra, P., Muir, K., Reeves, I., Duncan, G., & Harvey, M. (2011). The Role of Right Temporal Lobe Structures in Off-line Action: Evidence from Lesion-Behavior Mapping in Stroke Patients. *Cerebral Cortex*, *21*(12), 2751–2761. https://doi.org/10.1093/cercor/bhr073

24. Rossit, S., Malhotra, P., Muir, K., Reeves, I., Duncan, G., Livingstone, K., Jackson, H., Hogg, C., Castle, P., Learmonth, G., & Harvey, M. (2009). No Neglect-Specific deficits in reaching tasks. *Cerebral Cortex*, *19*(11), 2616–2624. https://doi.org/10.1093/cercor/bhp016

25. Milner, D. & Goodale, M. (2006) *The visual brain in action*. (2nd ed.) Oxford University Press.

26. Knights, E., Mansfield, C., Tonin, D., Saada, J., Smith, F. W., & Rossit, S. (2021). Hand-Selective Visual Regions Represent How to Grasp 3D Tools: Brain Decoding during Real Actions. *Journal of Neuroscience*, *41*(24), 5263–5273. https://doi.org/10.1523/jneurosci.0083-21.2021

27. Rossit, S., McAdam, T., Mclean, D. A., Goodale, M. A., & Culham, J. C. (2013). fMRI reveals a lower visual field preference for hand actions in human superior parieto-occipital cortex (SPOC) and precuneus. *Cortex*, *49*(9), 2525–2541. https://doi.org/10.1016/j.cortex.2012.12.014

28. Ramsey, L. E., Siegel, J. S., Baldassarre, A., Metcalf, N. V., Zinn, K., Shulman, G. L., & Corbetta, M. (2016). Normalization of network connectivity in hemispatial neglect recovery. *Annals of Neurology*, *80*(1), 127–141. https://doi.org/10.1002/ana.24690

29. Machner, B., von der Gablentz, J., Göttlich, M., Heide, W., Helmchen, C., Sprenger, A., & Münte, T. F. (2020). Behavioral deficits in left hemispatial neglect are related to a reduction of spontaneous neuronal activity in the right superior parietal lobule. *Neuropsychologia*, *138*, 107356. https://doi.org/10.1016/j.neuropsychologia.2020.107356

30. Wåhlin, A., Fordell, H., Ekman, U., Lenfeldt, N., & Malm, J. (2018). Rehabilitation in chronic spatial neglect strengthens resting-state connectivity. *Acta Neurologica Scandinavica*, *139*(3), 254–259. https://doi.org/10.1111/ane.13048

31. Boyd, L. A., Hayward, K. S., Ward, N. S., Stinear, C. M., Rosso, C., Fisher, R. J., Carter, A. R., Leff, A. P., Copland, D. A., Carey, L. M., Cohen, L. G., Basso, D. M., Maguire, J. M., & Cramer, S. C. (2017). Biomarkers of stroke recovery: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. *International Journal of Stroke*, *12*(5), 480–493. https://doi.org/10.1177/1747493017714176

32. Bernhardt, J., Hayward, K. S., Dancause, N., Lannin, N. A., Ward, N. S., Nudo, R. J., Farrin, A., Churilov, L., Boyd, L. A., Jones, T. A., Carmichael, S. T., Corbett, D., & Cramer, S. C. (2019). A stroke recovery trial development framework: Consensus-based core recommendations from the Second Stroke Recovery and Rehabilitation Roundtable. *International Journal of Stroke*, *14*(8), 792–802. https://doi.org/10.1177/1747493019879657

33. Cramer, S. C. (2010). Stratifying patients with stroke in trials that target brain repair. *Stroke*, *41*. https://doi.org/10.1161/strokeaha.110.595165

34. Pollock, A., St George, B., Fenton, M., & Firkins, L. (2014). Top 10 research priorities relating to life after stroke--consensus from stroke survivors, caregivers, and health professionals. *International journal of stroke : official journal of the International Stroke Society*, *9*(3), 313–320. https://doi.org/10.1111/j.1747-4949.2012.00942.x

35. Smith, T. M., Pappadis, M. R., Krishnan, S., & Reistetter, T. A. (2018). Stroke Survivor and Caregiver Perspectives on Post-Stroke Visual Concerns and Long-Term Consequences. *Behavioural neurology*, *2018*, 1463429. https://doi.org/10.1155/2018/1463429

36. Rowe F. J. (2017). Stroke survivors' views and experiences on impact of visual impairment. *Brain and behavior*, *7*(9), e00778. https://doi.org/10.1002/brb3.778

37. Rowe, F., Wormald, R., Cable, R., Acton, M., Bonstein, K., Bowen, M., Bronze, C., Bunce, C., Conroy, D., Cowan, K., Evans, K., Fenton, M., Giles, H., Gordon, I., Halfhide, L., Harper, R., Lightstone, A., Votruba, M., Waterman, H., & Zekite, A. (2014). The Sight Loss and Vision Priority Setting Partnership (SLV-PSP): overview and results of the research prioritisation survey process. *BMJ open*, *4*(7), e004905. https://doi.org/10.1136/bmjopen-2014-004905

38. Luvizutto, G. J., Moliga, A. F., Rizzatti, G. R. S., Fogaroli, M. O., Moura Neto, E., Nunes, H. R. C., Resende, L. A. L., & Bazan, R. (2018). Unilateral spatial neglect in the acute phase of ischemic stroke can predict long-term disability and functional capacity. *Clinics*, *73*, e131. https://doi.org/10.6061/clinics/2018/e131

39. Gillen, R., Tennen, H., & McKee, T. (2005). Unilateral spatial neglect: relation to rehabilitation outcomes in patients with right hemisphere stroke. Archives of physical medicine and rehabilitation, 86(4), 763–767. https://doi.org/10.1016/j.apmr.2004.10.029

40. Oh-Park, M., Hung, C., Chen, P., & Barrett, A. M. (2014). Severity of spatial neglect during acute inpatient rehabilitation predicts community mobility after stroke. *PM & R : the journal of injury, function, and rehabilitation*, *6*(8), 716–722. https://doi.org/10.1016/j.pmrj.2014.01.002

41. Chen, P., Fyffe, D. C., & Hreha, K. (2017). Informal caregivers' burden and stress in caring for stroke survivors with spatial neglect: an exploratory mixed-method study. *Topics in stroke rehabilitation*, *24*(1), 24–33. https://doi.org/10.1080/10749357.2016.1186373

42. Intercollegiate Stroke Working Party (2023). *National Clinical Guideline for Stroke for the United Kingdom and Ireland.* London: Intercollegiate Stroke Working Party www.strokeguideline.org.

43. Wilson, B., Cockburn, J., & Halligan, P. (1987). Behavioural inattention test. Titchfield: Thames Valley Test Company.

44. Rowe, F. J., Hepworth, L. R., Hanna, K. L., & Howard, C. (2018). Visual Impairment Screening Assessment (VISA) tool: pilot validation. *BMJ Open*, *8*(3), e020562. https://doi.org/10.1136/bmjopen-2017-020562

45. Demeyere, N., Riddoch, M. J., Slavkova, E. D., Bickerton, W. L., & Humphreys, G. W. (2015). The Oxford Cognitive Screen (OCS): validation of a stroke-specific short

cognitive screening tool. *Psychological assessment*, *27*(3), 883–894. https://doi.org/10.1037/pas0000082

46. Bailey MJ, Riddoch MJ, Crome P. Evaluation of a test battery for hemineglect in elderly stroke patients for use by therapists in clinical practice. NeuroRehabilitation. 2000;14(3):139-150. doi:10.3233/NRE-2000-14303

47. Halligan, P., Wilson, B., & Cockburn, J. (1990). A short screening test for visual neglect in stroke patients. *International disability studies*, *12*(3), 95–99. https://doi.org/10.3109/03790799009166260

48. Marsh, N. V., & Kersel, D. A. (1993). Screening tests for visual neglect following stroke. *Neuropsychological Rehabilitation*, *3*(3), 245–257. https://doi.org/10.1080/09602019308401439

49. Checketts, M., Mancuso, M., Fordell, H., Chen, P., Hreha, K., Eskes, G. A., Vuilleumier, P., Vail, A., & Bowen, A. (2021). Current clinical practice in the screening and diagnosis of spatial neglect post-stroke: Findings from a multidisciplinary international survey. *Neuropsychological rehabilitation*, *31*(9), 1495–1526. https://doi.org/10.1080/09602011.2020.1782946

50. Moore, M., Milosevich, E., Beisteiner, R., Bowen, A., Checketts, M., Demeyere, N., Fordell, H., Godefroy, O., Laczó, J., Rich, T., Williams, L., Woodward-Nutt, K., & Husain, M. (2022). Rapid screening for neglect following stroke: A systematic search and European Academy of Neurology recommendations. *European journal of neurology*, *29*(9), 2596–2606. https://doi.org/10.1111/ene.15381

51. Azouvi, P. (1996). Functional Consequences and Awareness of Unilateral Neglect: Study of an Evaluation Scale. *Neuropsychological Rehabilitation*, *6*(2), 133–150. https://doi.org/10.1080/713755501

52. Kwakkel, G., Lannin, N. A., Borschmann, K., English, C., Ali, M., Churilov, L., Saposnik, G., Winstein, C., van Wegen, E. E., Wolf, S. L., Krakauer, J. W., & Bernhardt, J. (2017). Standardized measurement of sensorimotor recovery in stroke trials: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. *International journal of stroke : official journal of the International Stroke Society*, *12*(5), 451–461. https://doi.org/10.1177/1747493017711813

53. Karnath, H. O., Fruhmann Berger, M., Küker, W., & Rorden, C. (2004). The anatomy of spatial neglect based on voxelwise statistical analysis: a study of 140 patients. *Cerebral cortex*, *14*(10), 1164–1172. https://doi.org/10.1093/cercor/bhh076

54. Chechlacz, M., Rotshtein, P., Bickerton, W. L., Hansen, P. C., Deb, S., & Humphreys, G. W. (2010). Separating neural correlates of allocentric and egocentric neglect: distinct cortical sites and common white matter disconnections. *Cognitive neuropsychology*, *27*(3), 277–303. https://doi.org/10.1080/02643294.2010.519699

55. Hunter, S. M., Johansen-Berg, H., Ward, N., Kennedy, N. C., Chandler, E., Weir, C. J., Rothwell, J., Wing, A. M., Grey, M. J., Barton, G., Leavey, N. M., Havis, C., Lemon, R. N., Burridge, J., Dymond, A., & Pomeroy, V. M. (2018). Functional Strength Training and

Movement Performance Therapy for Upper Limb Recovery Early Poststroke-Efficacy, Neural Correlates, Predictive Markers, and Cost-Effectiveness: FAST-INdiCATE Trial. *Frontiers in neurology*, *8*, 733. https://doi.org/10.3389/fneur.2017.00733

56. Longley, V., Woodward-Nutt, K., Turton, A. J., Stocking, K., Checketts, M., Bamford, A., Douglass, E., Taylor, J., Woodley, J., Moule, P., Vail, A., & Bowen, A. (2023). A study of prisms and therapy in attention loss after stroke (SPATIAL): A feasibility randomised controlled trial. *Clinical rehabilitation*, *37*(3), 381–393. https://doi.org/10.1177/02692155221134060

57. Cramer, S. C., Richards, L. G., Bernhardt, J., & Duncan, P. (2023). Cognitive Deficits After Stroke. *Stroke*, *54*(1), 5–9. https://doi.org/10.1161/STROKEAHA.122.041775

58. Baldassarre, A., Ramsey, L., Hacker, C. L., Callejas, A., Astafiev, S. V., Metcalf, N. V., Zinn, K., Rengachary, J., Snyder, A. Z., Carter, A. R., Shulman, G. L., & Corbetta, M. (2014). Large-scale changes in network interactions as a physiological signature of spatial neglect. *Brain : a journal of neurology*, *137*, 3267–3283. https://doi.org/10.1093/brain/awu297

59. Black-Schaffer, R. M., & Winston, C. (2004). Age and functional outcome after stroke. *Topics in stroke rehabilitation*, *11*(2), 23–32. https://doi.org/10.1310/DNJU-9VUH-BXU2-DJYU

60. NIHR (2020) *Improving inclusion of under-served groups in clinical research: Guidance from the NIHR-INCLUDE project.* UK: NIHR. www.nihr.ac.uk/documents/improving-inclusion-of-under-served-groups-in-clinical-research-guidance-from-include-project/25435

61. Hand, P. J., Wardlaw, J. M., Rowat, A. M., Haisma, J. A., Lindley, R. I., & Dennis, M. S. (2005). Magnetic resonance brain imaging in patients with acute stroke: feasibility and patient related difficulties. *Journal of Neurology Neurosurgery & Psychiatry*, *76*(11), 1525–1527. https://doi.org/10.1136/jnnp.2005.062539

62. Stroke Association (SA; 2018). *State of the Nation Stroke Statistics.* London: Stroke Association

63. Patel, A., Berdunov, V., Quayyum, Z., King, D., Knapp, M., & Wittenberg, R. (2020). Estimated societal costs of stroke in the UK based on a discrete event simulation. *Age and ageing*, *49*(2), 270–276. https://doi.org/10.1093/ageing/afz162

64. Agrell, B. M., Dehlin, O. I., & Dahlgren, C. J. (1997). Neglect in elderly stroke patients: a comparison of five tests. *Psychiatry and clinical neurosciences*, *51*(5), 295–300. https://doi.org/10.1111/j.1440-1819.1997.tb03201.x

65. Azouvi, P., Olivier, S., de Montety, G., Samuel, C., Louis-Dreyfus, A., & Tesio, L. (2003). Behavioral assessment of unilateral neglect: study of the psychometric properties of the Catherine Bergego Scale. *Archives of physical medicine and rehabilitation*, *84*(1), 51–57. https://doi.org/10.1053/apmr.2003.50062

66. Bailey, M. J., Riddoch, M. J., & Crome, P. (2004). Test–retest stability of three tests for unilateral visual neglect in patients with stroke: Star Cancellation, Line Bisection, and the

Baking Tray Task. *Neuropsychological Rehabilitation*, *14*(4), 403–419. https://doi.org/10.1080/09602010343000282

67. Bergego, C., Azouvi, P., Samuel, C., Marchal, F., Louis-Dreyfus, A., Jokic, C., Morin, L., Renard, C., Pradat-Diehl, P., & Deloche, G. (1995). Validation d'une échelle d'évaluation fonctionnelle de l'héminégligence dans la vie quotidienne: L'échelle CB. *Annales De Readaptation Et De Medecine Physique, 38,* 183–189. https://doi.org/10.1016/0168-6054(96)89317-2

68. Luukkainen-Markkula, R., Tarkka, I. M., Pitkanen, K., Sivenius, J., & Hamalainen, H. (2011). Comparison of the Behavioural Inattention Test and the Catherine Bergego Scale in assessment of hemispatial neglect. *Neuropsychological rehabilitation*, *21*(1), 103–116. https://doi.org/10.1080/09602011.2010.531619

69. Quinn, T. J., Richard, E., Teuschl, Y., Gattringer, T., Hafdi, M., O'Brien, J. T., Merriman, N., Gillebert, C., Huygelier, H., Verdelho, A., Schmidt, R., Ghaziani, E., Forchammer, H., Pendlebury, S. T., Bruffaerts, R., Mijajlovic, M., Drozdowska, B. A., Ball, E., & Markus, H. S. (2021). European Stroke Organisation and European Academy of Neurology joint guidelines on post-stroke cognitive impairment. *European journal of neurology*, *28*(12), 3883–3920. https://doi.org/10.1111/ene.15068

70. Mancuso, M., Demeyere, N., Abbruzzese, L., Damora, A., Varalta, V., Pirrotta, F., Antonucci, G., Matano, A., Caputo, M., Caruso, M. G., Pontiggia, G. T., Coccia, M., Ciancarelli, I., Zoccolotti, P., & Italian OCS Group (2018). Using the Oxford Cognitive Screen to Detect Cognitive Impairment in Stroke Patients: A Comparison with the Mini-Mental State Examination. *Frontiers in neurology*, *9*, 101. https://doi.org/10.3389/fneur.2018.00101

71. Demeyere, N., Riddoch, M. J., Slavkova, E. D., Jones, K., Reckless, I., Mathieson, P., & Humphreys, G. W. (2015). Domain-specific versus generalized cognitive screening in acute stroke. *Journal of Neurology*, *263*(2), 306–315. https://doi.org/10.1007/s00415-015-7964-4

72. Rorden, C., Karnath, H. O., & Bonilha, L. (2007). Improving lesion-symptom mapping. *Journal of cognitive neuroscience*, *19*(7), 1081–1088. https://doi.org/10.1162/jocn.2007.19.7.1081

73. Rorden, C., Bonilha, L., Fridriksson, J., Bender, B., & Karnath, H. O. (2012). Age-specific CT and MRI templates for spatial normalization. *NeuroImage*, *61*(4), 957–965. https://doi.org/10.1016/j.neuroimage.2012.03.020

74. Moore, M. J., & Demeyere, N. (2022). Lesion symptom mapping of domain-specific cognitive impairments using routine imaging in stroke. *Neuropsychologia*, *167*, 108159. https://doi.org/10.1016/j.neuropsychologia.2022.108159

75. Moore, M. J., Demeyere, N., Rorden, C., & Mattingley, J. B. (2023). Lesion mapping in neuropsychological research: A practical and conceptual guide. *Cortex*, *170*, 38–52. https://doi.org/10.1016/j.cortex.2023.10.001

76. Bickerton, W. L., Riddoch, M. J., Samson, D., Balani, A. B., Mistry, B., & Humphreys, G. W. (2012). Systematic assessment of apraxia and functional predictions from the

Birmingham Cognitive Screen. *Journal of neurology, neurosurgery, and psychiatry*, *83*(5), 513–521. https://doi.org/10.1136/jnnp-2011-300968

77. Rossit, S., Browning, H., Clark, A., Pomeroy, V., & Morse, H. (2023). Impact of aging and stroke on a new computerized test of visual attention in far space. *Journal of Vision, Vision Sciences Society Annual Meeting Abstract*, *23*(9), 4877. https://doi.org/10.1167/jov.23.9.4877

78. McIntosh, R. D., Schindler, I., Birchall, D., & Milner, A. D. (2005). Weights and measures: A new look at bisection behaviour in neglect. *Cognitive Brain Research*, *25*(3), 833–850. https://doi.org/10.1016/j.cogbrainres.2005.09.008

79. McIntosh, R. D., Ietswaart, M., & Milner, A. D. (2017). Weight and see: Line bisection in neglect reliably measures the allocation of attention, but not the perception of length. *Neuropsychologia*, *106*, 146–158. https://doi.org/10.1016/j.neuropsychologia.2017.09.014

80. Edwards, M. G., & Humphreys, G. W. (1999). Pointing and grasping in unilateral visual neglect: effect of on-line visual feedback in grasping. *Neuropsychologia*, *37*(8), 959–973. https://doi.org/10.1016/s0028-3932(98)00132-8

81. Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of biomedical informatics*, *42*(2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010

82. Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neal, L., McLeod, L., Delacqua, G., Delacqua, F., Kirby, J., Duda, S. N., & REDCap Consortium (2019). The REDCap consortium: Building an international community of software platform partners. *Journal of biomedical informatics*, *95*, 103208. https://doi.org/10.1016/j.jbi.2019.103208

83. Duncan, P. W., Wallace, D., Lai, S. M., Johnson, D., Embretson, S., & Laster, L. J. (1999). The stroke impact scale version 2.0. Evaluation of reliability, validity, and sensitivity to change. *Stroke*, *30*(10), 2131–2140. https://doi.org/10.1161/01.str.30.10.2131

84. Duncan, P. W., Reker, D. M., Horner, R. D., Samsa, G. P., Hoenig, H., LaClair, B. J., & Dudley, T. K. (2002). Performance of a mail-administered version of a stroke-specific outcome measure, the Stroke Impact Scale. *Clinical Rehabilitation, 16*(5), 493–505. https://doi.org/10.1191/0269215502cr510oa

85. Overman, M. J., Binns, E., Milosevich, E. T., & Demeyere, N. (2024). The natural recovery of visuospatial neglect: a systematic review and meta-analysis. *medRxiv*. https://doi.org/10.1101/2024.02.05.24302248

86. Umarova, R. M., Nitschke, K., Kaller, C. P., Klöppel, S., Beume, L., Mader, I., Martin, M., Hennig, J., & Weiller, C. (2016). Predictors and signatures of recovery from neglect in acute stroke. *Annals of neurology*, *79*(4), 673–686. https://doi.org/10.1002/ana.24614

87. Morse, H., Jolly, A. A., Browning, H., Clark, A., Pomeroy, V., & Rossit, S. (2024). Aging effects on extrapersonal (far-space) attention: cancellation and line bisection

performance from 179 healthy adults. *Aging, neuropsychology and cognition*, *31*(4), 605–626. https://doi.org/10.1080/13825585.2023.2223903

88. Chen, P., & Hreha, K. (2023) *Kessler Foundation Neglect Assessment Process KF-NAP 2023 Manual*. Kessler Foundation

89. Chen, P., Chen, C. C., Hreha, K., Goedert, K. M., & Barrett, A. M. (2015). Kessler Foundation Neglect Assessment Process uniquely measures spatial neglect during activities of daily living. *Archives of physical medicine and rehabilitation*, *96*(5), 869–876. https://doi.org/10.1016/j.apmr.2014.10.023

10 Appendices

11 Principal Investigator compliance statement

Principal Investigator agreement to confirm adherence to the protocol, the UK Policy Framework for Health and Social Care Research and GCP.

SIGHT: Spatial Inattention Grasping Therapy for neglect post-stroke

I, [Insert investigator name], confirm:

1. that I am willing and able to comply with the requirements of the SIGHT trial;
2. that I regularly treat the target population and believe the site has the potential for recruiting the required number of suitable subjects within the agreed recruitment period (figures included in the trial recruitment plan);
3. that I have sufficient time to properly conduct and complete the trial within the agreed trial period;
4. that I have supplied an up to date curriculum vitae, GCP certificate and/or other relevant documentation requested by NCTU, to demonstrate that I am qualified by education, training and experience to assume responsibility for the proper conduct of the trial at this study site;
5. that I am thoroughly familiar with the appropriate use of the investigational products as described in the protocol, in the current Investigator Brochure (if applicable), in the product information and in other information sources provided by NCTU;
6. that I have an adequate number of qualified staff and adequate facilities available for the foreseen duration of the trial to conduct the trial properly and safely;
7. that I will maintain a signature and delegation log of appropriately qualified persons to whom I have delegated trial related duties which includes confirmation that each member of staff is appropriately trained (including GCP) for the roles allocated to them, and will ensure this is made available to NCTU in a timely manner on request;
8. a research CV for each member of staff on the delegation log will be stored in the site file according to site policy;
9. that I take responsibility for ensuring all staff delegated trial related duties are adequately informed about the protocol, the investigational product and their trial related duties and functions, and that I will continue to take responsibility for regularly updating them as new information becomes available;
10. that the [insert name of site] site has sufficient resources to manage data generated by the trial to allow prompt and complete data and query return to NCTU;
11. that I am aware of, and will comply with, the principles of GCP as given in the SIGHT protocol compliance statement and the applicable regulatory requirements, and that a record of my GCP training is accessible and described on my current curriculum vitae;
12. that a record of GCP training is accessible for all staff delegated responsibilities in relation to the SIGHT trial and who are named and approved on the site signature and delegation of responsibilities log and that individual training evidence will be saved in the site file, for all staff, according to trust policies;

13. that I will permit routine and for-cause monitoring and auditing by NCTU, and inspection by the appropriate regulatory authorities, including the provision of direct access to source data and other participant notes and files as required; and
14. that I agree to archive and/or arrange for secure storage of SIGHT trial materials and records for a minimum of 10 years after the close of the trial unless otherwise advised by the NCTU.

Agreement: Principal Investigator

Name	[insert name]
Signature	[insert signature]
Date	[insert date]

(Please return a copy of this signed agreement (only pages 61 and 62 to the SIGHT team within the NCTU at sight@uea.ac.uk)